CONTENT OUTLINE

Pediatric Hematology-Oncology

Subspecialty In-Training, Certification, and Maintenance of Certification (MOC) Examinations
INTRODUCTION

This document was prepared by the American Board of Pediatrics Subboard of Pediatric Hematology-Oncology for the purpose of developing in-training, certification, and maintenance of certification examinations. The outline defines the body of knowledge from which the Subboard samples to prepare its examinations. The content specification statements located under each category of the outline are used by item writers to develop questions for the examinations; they broadly address the specific elements of knowledge within each section of the outline.
Each Pediatric Hematology-Oncology exam is built to the same specifications, also known as the blueprint. This blueprint is used to ensure that, for the initial certification and in-training exams, each exam measures the same depth and breadth of content knowledge. Similarly, the blueprint ensures that the same is true for each Maintenance of Certification exam form. The table below shows the percentage of questions from each of the content domains that will appear on an exam. Please note that the percentages are approximate; actual content may vary.

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<thead>
<tr>
<th>Content Categories</th>
<th>Initial Certification and In-Training</th>
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<td>7. Hematopoietic Stem Cell Transplantation</td>
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<td>8. Core Knowledge in Scholarly Activities</td>
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## EXAMINATION BLUEPRINT

### Maintenance of Certification
### Pediatric Hematology-Oncology

**Effective January 2016**

### Form 1: General exam with no specific focus area (Core module followed by Hematology-Oncology module)

<table>
<thead>
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<th>Section</th>
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<th>Hematology-Oncology Module</th>
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### Form 2: Exam with Hematology Focus (Core module followed by Hematology module)

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### Form 3: Exam with Oncology Focus (Core module followed by Oncology module)

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Identical for all examination forms
Hematology Oncology

1. **Erythrocytes, Hemoglobin, Iron Metabolism**
   A. The normal erythron
      1. The mature erythrocytes
         a. Structural features
            1. Know the size, shape, and indices of normal erythrocytes
         b. Membrane
            1. Understand the role of the cytoskeleton in maintaining cell shape
            2. Know the determinants affecting osmotic fragility
         c. Hemoglobin (hgb) structure and function
            1. Understand the physiologic mechanisms affecting blood oxygen affinity
            2. Differentiate hgb A from hgb F with respect to oxygen affinity and alkali resistance
            3. Understand the basis for the altered oxygen affinity of hgb F
         d. Energy metabolism
   2. Erythropoiesis
      a. Stages of erythroid maturation
         1. Recognize the morphologic features of erythroid precursors
         2. Know the sites of fetal and post-natal erythropoietin production
      b. Regulation of erythrocyte production
         1. Erythropoietin
            a. Understand the relationship between erythropoietin production, tissue oxygenation, and anemia
      2. Iron and normal iron metabolism
         a. Iron absorption
            1. Identify the foods that are good sources of iron
            2. Understand the factors that affect iron absorption
            3. Know how iron absorption from human milk differs from that in cow milk
         b. Cellular metabolism of iron
            1. Understand the site of iron absorption and the regulation of iron absorption, transport, and storage
         c. Developmental aspects
            1. Know the determinants of body iron at birth
      3. Folate, vitamin B12
         a. Know the dietary sources of folate and vitamin B12
         b. Know the site of intestinal absorption of folic acid and B12
   3. Erythrocyte destruction
      a. Life span of erythrocytes; erythrokinetics
         1. Be familiar with the differences in the normal erythrocyte survival of infants and older children
      b. Mechanisms of erythrocyte destruction
1. Know the laboratory basis for differentiating intravascular from extravascular erythrocyte destruction

c. Hemoglobin catabolism
   1. Understand the biologic activity and clinical alterations of hemopexin and haptoglobin

4. The erythron in the fetal and postnatal periods
   a. Embryonic hgb and characteristics of hgb switching
      1. Know the globin chain composition of embryonic, fetal, and adult hgb’s
      2. Know the relative concentrations of embryonic, fetal, and adult hgb’s in a newborn infant and variations in pathologic states
   b. Distinctive features of the neonatal erythrocyte
      1. Know the characteristics that differentiate the erythrocytes of newborn infants from those of adults
   c. Postnatal changes in erythropoiesis
      1. Know the changes that occur during the postnatal period in hgb concentration, reticulocytes, and bone marrow erythroblasts
   d. The anemia of prematurity
      1. Understand the pathophysiologic basis for the anemia of prematurity
      2. Understand the variable treatment modalities for the anemia of prematurity

B. Anemias
   1. General principles
      a. Definitions and recognition of anemia
         1. Define normal ranges of hgb concentrations and erythrocyte indices at birth and throughout childhood and adolescence
      b. Classification of anemia: morphologic, kinetic
         1. Correlate erythrocyte morphology with clinical syndromes
         2. Know the origin of various erythroid inclusions seen on blood smears
         3. Know how to classify anemias according to altered erythrocyte production, increased erythrocyte destruction, and blood loss
         4. Understand and interpret results of reticulocyte counts
         5. Know that classification of anemias based on cell size is also age-dependent
         6. Know the differential diagnosis of macrocytic anemia
         7. Know the differential diagnosis of microcytic anemia
         8. Know the differential diagnosis of normocytic anemia
      c. Physiologic adaptations to anemia
         1. Understand the physiologic adaptation of erythrocyte 2,3-DPG concentration in response to anemia

2. Disorders of iron metabolism
   a. Iron deficiency anemia
      1. Pathogenesis
         a. Recognize the syndrome of milk-induced gastrointestinal bleeding and understand its laboratory evaluation
         b. Recognize the clinical and laboratory manifestations of pulmonary hemosiderosis and know the appropriate diagnostic approach
         c. Recognize the factors in medical history that predispose pediatric patients to iron deficiency
d. Recognize the association between occult blood loss and iron deficiency anemia

2. Clinical and laboratory features
   a. Know the effect of iron deficiency on erythrocyte morphology, serum iron concentration, total iron-binding capacity, ferritin, free erythrocyte protoporphyrin, and soluble transferrin receptor concentration
   b. Know the order of appearance of laboratory abnormalities as iron deficiency develops
   c. Know the association of pica and iron deficiency
   d. Know the effects on growth and development of iron deficiency

3. Diagnosis
   a. Know the laboratory studies that differentiate the anemia of lead poisoning from that of iron deficiency
   b. Understand the laboratory studies that distinguish iron deficiency anemia from other causes of microcytic anemia

4. Treatment
   a. Determine the proper place for dietary changes, oral iron, parenteral iron, and erythrocyte transfusion in the treatment of iron deficiency

5. Prevention
   a. Know the indications for and types of iron supplementation
   b. Iron overload
      1. Consequences
         a. Understand the relationship between chronic iron overload and clinical organ dysfunction (ie, cardiac, endocrine, liver, pancreas)
      2. Diagnosis
         a. Be able to estimate the amount of iron in a volume of erythrocytes
         b. Understand laboratory tests and other studies, including imaging techniques, used to diagnose and monitor iron overload
         c. Know the genetics and appropriate biochemical and molecular testing for hereditary hemochromatosis
      3. Treatment
         a. Know the principles for prevention and treatment, including treatment regimens (eg, phlebotomy, iron chelators, erythrocytapheresis) of transfusional iron overload and hereditary hemochromatosis
         b. Know the toxicity of iron chelators and appropriate monitoring of therapy
   c. Lead intoxication
      1. Recognize the hematologic features of lead poisoning

3. Anemia of chronic disease and secondary anemias
   a. Recognize the clinical and laboratory findings in the anemia associated with chronic disease and how this differs from iron deficiency
   b. Recognize the effect of acute infection on hgb concentration
   c. Know the indications for and appropriate use of recombinant human erythropoietin in the treatment of secondary anemia such as anemia of renal disease or anemia of chemotherapy
   d. Know the characteristics of anemia associated with hypothyroidism
   e. Know the mechanism of production of abnormal erythrocytes in liver disease
f. Know the relationship between parvovirus B19 infection and anemia, including recognition of the clinical scenario and site of action of the infection and the potential impact of the immunocompromised state

g. Understand the pathogenesis of anemia of chronic disease

4. Anemias due to bone marrow failure
   a. Acquired aplastic anemia (see also section 7.B)
      1. Recognize viral infections, drugs, toxins, megaloblastic anemias, and autoimmune diseases as causes of acquired aplastic anemia
      2. Understand the rationale for use and toxicity of immune modulation in the treatment of acquired aplastic anemia
      3. Know the indications for HSCT in acquired aplastic anemia
      4. Understand the relationship between aplastic anemia, paroxysmal nocturnal hemoglobinuria, and malignant transformation
      5. Know the typical hematologic findings at presentation in patients with aplastic anemia
   b. Fanconi anemia
      1. Know the clinical and molecular features, laboratory findings, and chromosomal abnormalities in Fanconi anemia
      2. Recognize the association between Fanconi anemia and acute leukemia and other malignancies
      3. Know the complications of androgen therapy, including peliosis hepatis, adenoma, and carcinoma, in Fanconi anemia
      4. Know the therapeutic options for Fanconi anemia, and their effectiveness
   c. Diamond-Blackfan syndrome
      1. Recognize the clinical, molecular, and laboratory manifestations of Diamond-Blackfan syndrome
      2. Know the clinical and laboratory parameters that differentiate transient erythroblastopenia of childhood from Diamond-Blackfan syndrome
      3. Know the clinical and laboratory features that distinguish an aplastic crisis of a hemolytic anemia from transient erythroblastopenia of childhood and Diamond-Blackfan syndrome
      4. Know the various treatment modalities and their effectiveness in Diamond-Blackfan syndrome
   d. Transient erythroblastopenia of childhood
      1. Recognize the clinical syndrome of transient erythroblastopenia of childhood and know how to treat it appropriately
   e. Dyskeratosis congenita
      1. Know the clinical presentation, molecular biology, genetics, laboratory findings, and therapy in a patient with dyskeratosis congenita
   f. Pearson syndrome
      1. Know the clinical and laboratory features and underlying defects of Pearson syndrome

5. Hereditary hemolytic anemias
   a. General principles
      1. Know that Rh null phenotype is associated with a hereditary hemolytic anemia
2. Know the relationship between parvovirus infection and aplastic crisis in congenital hemolytic anemias
3. Recognize the role of folate supplementation in patients with hemolytic anemia
   b. Inherited disorders of the erythrocyte membrane
      1. Hereditary spherocytosis
         a. Genetics
            1. Recognize the differences in the phenotypes of the autosomal dominant and autosomal recessive variants of hereditary spherocytosis
         b. Pathophysiology
            1. Know the cytoskeletal defects associated with hereditary spherocytosis
         c. Evaluation
            1. Understand the clinical and laboratory diagnosis of hereditary spherocytosis
            2. Know the basis for and pattern of abnormal osmotic fragility in hereditary spherocytosis
            3. Distinguish between hereditary spherocytosis and autoimmune hemolytic anemia
         d. Management
            1. Know the rationale for and hematologic sequelae of splenectomy in hereditary spherocytosis
         e. Complications
            1. Understand the complications seen in hereditary spherocytosis before and after splenectomy
      2. Hereditary elliptocytosis and pyropoikilocytosis
         a. Genetics
            1. Know the mode of inheritance of hereditary elliptocytosis and pyropoikilocytosis
         b. Pathophysiology
            1. Know the cytoskeletal defects associated with hereditary elliptocytosis and hereditary pyropoikilocytosis
         c. Clinical features
            1. Recognize hemolytic and non-hemolytic variants of hereditary elliptocytosis
            2. Know the clinical features of elliptocytosis and pyropoikilocytosis and the clinical problems of distinguishing them in the neonatal period
         d. Laboratory evaluation
            1. Recognize the morphologic characteristics and other laboratory features of hereditary elliptocytosis and hereditary pyropoikilocytosis
         e. Management
            1. Know the effects of splenectomy on hereditary elliptocytosis and pyropoikilocytosis
      3. Acanthocytosis
         a. Clinical features
            1. Recognize the clinical and laboratory features associated with the inherited and acquired conditions characterized by acanthocytosis
      4. Other membrane disorders
Clinical and laboratory features
1. Recognize the patterns of inheritance and the clinical and laboratory features of other membrane disorders such as stomatocytosis, xerocytosis, pyknocytosis, ovalocytosis, and Wilson disease

c. Inherited disorders of anaerobic glycolysis
1. Pyruvate kinase deficiency
   a. Genetics
      1. Know the inheritance pattern of pyruvate kinase deficiency
   b. Cellular physiology
      1. Recognize how pyruvate kinase deficiency may lead to impaired erythrocyte metabolism
   c. Clinical and laboratory features
      1. Recognize the clinical and laboratory manifestations of pyruvate kinase deficiency
   d. Management
      1. Know the effects of splenectomy on pyruvate kinase deficiency
   e. Complications
      1. Know that hemolysis and gallstone production may persist following splenectomy

2. Triose phosphate isomerase deficiency
   a. Clinical features
      1. Know the relationship between erythrocyte triose phosphate isomerase deficiency and neuromuscular disease

3. Other enzyme deficiencies
   a. Genetics
      1. Know that phosphoglycerate kinase (pgk) deficiency is an X-linked disorder, while other glycolytic disorders are autosomal recessive
   b. Laboratory evaluation
      1. Know the association of pyrimidine-5’-nucleotidase deficiency with basophilic stippling

d. Inherited disorders of the pentose phosphate pathway
1. Glucose-6-phosphate dehydrogenase deficiency (G6PD)
   a. Genetics
      1. Recognize that G6PD deficiency is X-linked
   b. Cellular physiology
      1. Understand the pathophysiology whereby oxidant damage causes hemolysis in G6PD deficiency
   c. Clinical features
      1. Know the association of favism with the Mediterranean and Chinese forms of G6PD deficiency
      2. Know the association of intermittent jaundice with G6PD deficiency
      3. Recognize the clinical and laboratory differences between the major G6PD variants (eg, A-Mediterranean)
      4. Recognize the etiologic role of infection and drugs in hemolytic episodes associated with G6PD deficiency
   d. Laboratory evaluation
1. Recognize the difficulty in making diagnosis in A-variant G6PD deficiency during an acute hemolytic episode
2. Recognize the erythrocyte morphologic abnormalities during an episode of hemolysis in G6PD-deficient individuals

e. Structural disorders of hgb synthesis
1. Hgb S and the sickling syndromes
   a. Genetics
      1. Know the genetic basis for the sickling syndromes
   b. Molecular and pathophysiological mechanisms
      1. Understand the pathophysiology of the sickling phenomenon
      2. Know the characteristics and clinical correlates of irreversibly sickled cells
      3. Understand how polymerization of hgb’s is influenced by other hgb’s (hgb F, A, etc)
      4. Understand the molecular abnormalities in sickle cell syndromes
   c. Clinical features
      1. Recognize the clinical characteristics of sickle-thalassemia syndromes
      2. Know the various clinical manifestations of sickle hemoglobinopathies, including sickle cell trait
      3. Recognize the splenic sequestration syndrome in sickle cell disease
      4. Know the central nervous system complications of sickle cell disease
      5. Know the long-term complications that may occur in patients with hemoglobinopathies (S/S, S/C)
      6. Know the life expectancy in patients who have sickle cell syndromes, including sickle cell trait
      7. Recognize aplastic crisis in sickle cell anemia
      8. Recognize acute chest syndrome in sickle cell anemia
      9. Recognize renal sequelae of sickle cell anemia
   d. Laboratory evaluation
      1. Recognize the laboratory manifestations of sickle cell disease
      2. Understand the utility and limits of various methodologies used to establish the diagnosis of sickle cell syndromes
      3. Understand the way in which DNA analysis can assist in the diagnosis of sickle hemoglobinopathies
      4. Know how to differentiate the homozygous state for hgb S from doubly heterozygous hgb S/hereditary persistence of fetal hgb
      5. Recognize differences in the hgb electrophoretic patterns of sickle cell trait and hgb S/Beta + thalassemia
   e. Management
      1. Understand the risk of infection in sickle cell disease and know the appropriate preventive strategies
      2. Understand the proper therapeutic approach to infection in patients with sickle cell disease
      3. Know the appropriate treatment for a patient with sickle cell disease who has a stroke
      4. Know how to manage acute chest syndrome
5. Know how to manage acute pain crisis in a patient with sickle cell disease
6. Know the indications for and how to plan a transfusion program for a patient with sickle cell disease
7. Know the rationale for using hydroxyurea as a treatment for a patient with sickle cell disease
8. Understand the risk of stroke in sickle cell disease and know the appropriate screening and management strategies
9. Know how to manage priapism
10. Know how to manage aplastic crisis
11. Know how to manage acute sequestration crisis
12. Distinguish the relative advantages and disadvantages of stem cell transplantation and other therapy for sickle cell anemia
13. Understand that extended phenotype matching is necessary in patients with sickle cell disease to avoid erythrocyte alloimmunization

2. Hgb C and hgb SC disease
   a. Genetics
      1. Understand the relative frequency of hgb SC disease compared to other sickling syndromes
      2. Understand the inheritance pattern of patients with hgb SC disease
   b. Molecular mechanisms
      1. Know the chemical and physical differences between hgb C and hgb S
   c. Clinical features
      1. Know the relationship between hgb SC disease and retinopathy
      2. Recognize splenomegaly and spleen infarction as common features in hgb SC disease in older children
      3. Recognize that aseptic necrosis of the femoral head is a common problem in hgb SC disease
      4. Know the clinical and laboratory manifestations of hgb C disease

3. Hgb E
   a. Pathologic and clinical features
      1. Know the inheritance and clinical features of the hgb E syndromes
      2. Understand the proper management of various hgb E syndromes
   b. Laboratory evaluation
      1. Know the laboratory characteristics of each of the hgb E syndromes (hgb AE, hgb EE, and hgb E-beta thalassemia)

4. Unstable hgb’s
   a. Genetics
      1. Understand the inheritance pattern associated with unstable hgb’s
   b. Molecular mechanisms
      1. Understand the molecular and structural abnormalities that lead to hgb instability
   c. Clinical features
      1. Recognize the association of accelerated hemolysis with intercurrent infection or drug exposure in a patient with unstable hemoglobinopathy
   d. Laboratory evaluation
1. Know the laboratory approach to the diagnosis of unstable hgb disease
   e. Management
      1. Know the proper management of patients with unstable hgb’s
   5. Low-affinity hgb’s
      a. Know the relationship of low-oxygen affinity hgb with cyanosis
   f. Quantitative disorders of hgb synthesis
      1. Genetic mechanisms and molecular pathology
         a. Molecular associations
            1. Identify the molecular abnormalities associated with the various types of
               thalassemia syndromes, including alpha, beta, and delta-beta
               thalassemia, hgb E, and hgb Lepore
            2. Understand the pathophysiology of anemia in disorders of globin chain
               synthesis
         b. Alpha-thalassemia
            1. Know the differences in the inheritance of abnormal alpha genes
               between blacks and Asians with alpha-thalassemia
         c. Beta- and delta-beta-thalassemia
            1. Understand the basis for differences in hgb F concentrations in delta-
               beta-thalassemia and hereditary persistence of fetal hgb
            2. Know that absence of delta-chain synthesis is the basis of homozygous
               hereditary persistence of hgb F
      2. Clinical and laboratory features
         a. Alpha-thalassemia
            1. Know the hematologic and hgb electrophoretic manifestations of alpha-
               thalassemia minor
            2. Identify and quantitate the major hgb fractions in alpha-thalassemia
               disorders at birth and in later life
            3. Know the clinical and laboratory features of the alpha-thalassemia
               syndromes, including hgb H and hydrops fetalis
            4. Know the association of hgb Constant Spring with an alpha-thalassemia-
               like syndrome
            5. Know the relationship between genotype and phenotype in alpha-
               thalassemia syndromes
         b. Beta- and delta-beta-thalassemia
            1. Recognize the contribution of ineffective erythropoiesis to the
               pathophysiology of thalassemia
            2. Know the clinical and laboratory features of beta-thalassemia major,
               intermedia, and minor, and the impact of coexistent iron deficiency on
               the ability to diagnose beta-thalassemia minor
            3. Know the clinical and laboratory features of delta-beta-thalassemia
            4. Know how alpha-thalassemia modifies the clinical characteristics of
               beta-thalassemia and hgb E-beta-thalassemia
            5. Understand that iron overload develops in patients with beta-thalassemia
               because of gut hyperabsorption of iron
         c. Hereditary persistence of fetal hgb
1. Know the clinical and laboratory features associated with hereditary persistence of fetal hgb
d. Gamma-thalassemia
   1. Know the transient neonatal hemolytic disorders associated with gamma-thalassemia syndromes
e. Beta-thalassemia/structural hgb variants
   1. Know the clinical and laboratory features of homozygous hgb E and hgb E-beta-thalassemia
3. Diagnosis
   a. Know the indications for and limitations of prenatal diagnosis using chorionic villus sampling
   b. Know the characteristics which differentiate thalassemia from hereditary persistence of hgb F
4. Treatment
   a. Recognize when splenectomy is indicated in thalassemia major
   b. Know the indications for and management of chronic transfusion therapy for thalassemia syndromes
   c. Understand the principles of iron chelation therapy and when to initiate it in a patient with a thalassemia syndrome
   d. Know the beneficial effects and toxicity of ascorbic acid when given to iron-overloaded patients with thalassemia
   e. Distinguish the relative advantages and disadvantages of stem cell transplantation and conventional therapy for thalassemia major
   f. Understand the proper management of thalassemia intermedia
   g. Know the value of different laboratory and imaging studies in the assessment of iron overload
   h. Know the pharmacology of deferoxamine and how this influences drug administration
   i. Know the adverse side effects of deferoxamine (hearing loss, vision changes, growth retardation)
   j. Know the pharmacology of the oral iron chelator deferasirox
   k. Know the adverse side effects of deferasirox
6. Acquired hemolytic anemias
   a. Alloimmune hemolytic anemia; erythroblastosis fetalis
      1. Pathophysiology
         a. Understand the effect of a major blood group incompatibility on Rh sensitization
         b. Know the erythrocyte antigens that most frequently cause erythroblastosis fetalis
      2. Clinical and laboratory features
         a. Recognize the clinical features of erythroblastosis fetalis
         b. Know that transient conjugated hyperbilirubinemia may occur as a complication of severe isoimmune hemolytic disease
      3. Diagnosis
         a. Know the diagnostic criteria for ABO incompatibility
         b. Know the relative predictive value of tests of Rh sensitization
c. Differentiate fetomaternal minor blood group incompatibility from other causes of jaundice in the neonate

d. Understand the appropriate laboratory evaluation of neonatal jaundice secondary to a minor blood group fetomaternal incompatibility

e. Know that maternal anti-Lewis antibodies do not cause hemolytic disease of the newborn

4. Treatment

a. Know when to expect and how to treat the late anemia of isoimmune sensitization

b. Know the indications for exchange transfusion

c. Know what type of blood to use for exchange transfusions and delayed simple transfusions in sensitized infants

5. Prevention

a. Know the indications for the use of anti-D

b. Autoimmune hemolytic anemia

1. Pathophysiology

a. Know the biologic properties and clinical significance of IgG and IgM erythrocyte antibodies

b. Know the mechanism of erythrocyte destruction in IgG-mediated autoimmune hemolytic anemia

c. Know the relationship between the response to corticosteroid therapy and the type of autoantibody

d. Know the direct antiglobulin test results with warm-reactive antibodies, cold agglutinin disease, and paroxysmal cold hemoglobinuria

2. Warm-antibody hemolytic disease

a. Know the antigen specificity (or lack thereof) in warm autoimmune hemolytic anemia

b. Know the clinical presentation and features of idiopathic autoimmune hemolytic anemia of childhood

c. Know of the association of warm-reactive antibodies with other autoimmune disorders

d. Plan the therapy for autoimmune hemolytic anemia

3. Cold agglutinin disease

a. Know the antigen specificity of cold-reactive antibodies

b. Recognize the infections that are associated with cold-reactive antibodies

c. Know the principles of therapy for cold agglutinin disease

4. Paroxysmal cold hemoglobinuria

a. Identify the clinical features of autoimmune hemolytic anemia due to a Donath-Landsteiner antibody

b. Know the characteristics of the Donath-Landsteiner antibody

5. Drug-induced immune hemolytic anemia

6. Know the mechanism of hematologic toxicity of offending drugs

a. Recognize the examples of drug-induced immune hemolysis

c. Anemia due to infection, chemical, physical agents

1. Recognize intravascular hemolysis as a complication of recluse spider bites
2. Know that thermal burns and envenomization may be complicated by acquired spherocytic anemia

d. Erythrocyte fragmentation syndromes
   1. Recognize the pathogenic mechanisms and the clinical and laboratory features of the erythrocyte fragmentation syndromes

e. Paroxysmal nocturnal hemoglobinuria
   1. Recognize the laboratory and clinical manifestations of paroxysmal nocturnal hemoglobinuria
   2. Know the association of paroxysmal nocturnal hemoglobinuria with thrombosis
   3. Understand the molecular and pathophysiologic basis for paroxysmal nocturnal hemoglobinuria

7. Megaloblastic anemias
   a. Vitamin B12 deficiency
      1. Pathophysiology
         a. Recognize anemia due to vitamin B12 deficiency in a breast-fed infant with a vegan mother or a mother with B12 deficiency
         b. Recognize the genetically determined disorders of vitamin B12 malabsorption
         c. Know the association of small-bowel bacterial overgrowth or surgery and megaloblastic anemia
      2. Clinical and laboratory features
         a. Know the clinical and laboratory features of pernicious anemia
         b. Know the association of pernicious anemia with other autoimmune phenomena
         c. Know the clinical and laboratory features of the Imerslund-Grasbeck syndrome
         d. Know the ages at which different disorders of vitamin B12 metabolism are first manifested
         e. Know the morphology of peripheral blood smears and examinations of the bone marrow in megaloblastic anemia
   3. Diagnosis
      a. Know the indications for the Schilling test and how to interpret results of the test
   4. Treatment
      a. Understand the principles of treatment for the vitamin B12 deficiency syndromes
      b. Know the potential of folic acid to correct megaloblastic anemia but not the neuropathy of pernicious anemia
   b. Folate deficiency
      1. Pathophysiology
         a. Understand the biochemical pathway of tetrahydrofolate metabolism that is associated with megaloblastosis
         b. Recognize the association of folic acid deficiency with anticonvulsant therapy
         c. Know that megaloblastic anemia associated with goat milk ingestion is due to folic acid deficiency
d. Know that folate deficiency may be associated with chronic hemolytic disorders

2. Clinical and laboratory features
   a. Understand the progression of laboratory abnormalities in folate deficiency
   b. Recognize the clinical and laboratory characteristics of dietary folate deficiency

3. Diagnosis
   a. Know the limitations of measuring serum folate concentrations in the diagnosis of folate deficiency

4. Treatment

8. Blood loss anemia
   a. Fetomaternal hemorrhage
      1. Recognize the clinical and laboratory characteristics of fetomaternal hemorrhage
   b. Blood loss in the infant and child
      1. Recognize the clinical signs of acute hypovolemia secondary to blood loss and differentiate them from hemolytic anemia
      2. Recognize the need for iron therapy in hemolytic anemias associated with intravascular hemolysis

9. Congenital dyserythropoietic anemias
   a. Recognize the clinical and laboratory manifestations of congenital dyserythropoietic anemia
   b. Know the association of dyserythropoietic anemia type II with multinucleated erythroblasts

10. Congenital sideroblastic anemia
    a. Know the clinical and laboratory manifestations of congenital sideroblastic anemia

C. Other disorders affecting erythrocytes

1. Erythrocytosis
   a. General laboratory principles
      1. Know the laboratory parameters associated with conditions characterized by an increased hgb concentration
   b. Maternal-fetal and fetal-fetal transfusions
      1. Know how to document a maternal-fetal hemorrhage or twin-twin transfusion causing erythrocytosis
      2. Recognize erythrocytosis as a feature of the twin transfusion syndrome
   c. High oxygen affinity hemoglobins
      1. Know the relationship of high oxygen-affinity hgb with erythrocytosis
   d. Other causes of erythrocytosis
      1. Differentiate relative erythrocytosis from erythrocytosis due to an increase in erythrocyte mass
      2. Know the causes of primary and secondary erythrocytosis

2. Methemoglobinemia
   a. Toxic methemoglobinemia
1. Know the basis for the increased vulnerability of infants to methemoglobinemia
2. Know the mechanism for methemoglobin reduction in normal erythrocytes
3. Associate the treatment failure of methemoglobinemia with methylene blue and G6PD deficiency
4. Know that consumption of well water contaminated with nitrates causes methemoglobinemia in infants but not in older children and adults
5. Know the association of methemoglobinemia with diarrhea and acidosis in young infants

b. Congenital cytochrome b5 reductase deficiency
   1. Know how to differentiate methemoglobinemia due to deficient methemoglobin reduction from methemoglobinemia due to increased methemoglobin production

c. Hgb M disorders
   1. Recognize the clinical and laboratory findings of hgb M disease in the newborn infant

3. Porphyrias
   a. Know the differential clinical characteristics of congenital erythropoietic porphyria

2. Leukocytes
   A. Granulocytes
      1. Normal granulocyte characteristics
         a. Know the age- and race-related normal values of granulocytes
         b. Know the life cycle of granulocytes
         c. Know the changes associated with systemic diseases, ie, cell numbers and morphology
         d. Understand and know when to order various tests of neutrophil function
      2. Myelopoiesis
         a. Stage of myeloid maturation
            1. Understand progenitor cell differentiation and maturation
            2. Recognize morphologic features of myeloid precursors
         b. Cytokine stimulation
            1. Understand the action of cytokines on primitive myeloid progenitors and precursors and mature cells
      3. Granules
         a. Recognize the different granulocytic granules and know their content and functions
         b. Know the diseases associated with abnormalities of granule function and morphology
      4. Biochemistry
         a. Understand the various stimulators of biochemical reactions in granulocytes including degranulation, oxidative burst, phagocytosis, and killing
      5. Neutrophil kinetics
         a. Understand the factors that regulate granulopoiesis
      6. Functional properties
         a. Chemotaxis, motility, and ingestion
            1. Know the factors that mediate adherence, movement, and phagocytosis in granulocyte function
         b. Opsonins
1. Know the different opsonins and their role in neutrophil chemotaxis, ingestion, and killing

c. Degranulation
   1. Know the different stimulators and inhibitors of granulocyte degranulation and granular fusion and the mechanism involved in degranulation and granular fusion

d. Killing of ingested microorganisms
   1. Understand the mechanisms of oxygen-dependent and oxygen-independent microbial killing by phagocyte-mediated granulocytes

7. Neutropenia
   a. General
      1. Know the appropriate clinical and laboratory evaluation of childhood neutropenia
      2. Understand and differentiate the childhood presentations of neutropenia
   b. Congenital neutropenia
      1. Severe congenital neutropenia (including Kostmann syndrome)
         a. Know the clinical presentation, molecular biology, genetics, and bone marrow findings in severe congenital neutropenia
         b. Know the treatment options for severe congenital neutropenia
         c. Know the natural history of severe congenital neutropenia
         d. Know the risk of secondary myelodysplasia and leukemia in severe congenital neutropenia and the role of filgrastim (G-CSF) receptor gene mutations
      2. Cyclic neutropenia
         a. Know the clinical presentation, molecular biology, genetics, bone marrow findings, and therapy of cyclic neutropenia
   c. Acquired neutropenia
      1. Isoimmune and alloimmune neutropenia
         a. Know the presentation and pathophysiology of alloimmune neutropenia in newborn infants
         b. Understand the role of specific antigens in alloimmune neutropenia
         c. Know the natural history of, complications of, and therapy for alloimmune neutropenia
      2. Autoimmune neutropenia
         a. Understand the use and limitations of antineutrophil antibodies in the diagnosis and treatment of autoimmune neutropenia
b. Know the natural history of autoimmune neutropenia in infancy

c. Understand the various therapeutic strategies for autoimmune neutropenia

d. Recognize autoimmune neutropenia as a manifestation of autoimmune disorders

e. Know the clinical presentation of autoimmune neutropenia

3. Postinfectious and infection-related neutropenia
   a. Know the viruses commonly associated with infection-related neutropenia
   b. Know the bacteria commonly associated with postinfectious neutropenia
   c. Know the natural history of infection-related neutropenia

4. Drug-induced neutropenia
   a. Know the agents commonly involved in drug-induced neutropenia
   b. Know the mechanisms of bone marrow suppression and peripheral destruction of neutrophils
   c. Understand the therapeutic use of cytokines in drug-induced neutropenia

5. Neutropenia associated with nutritional deficiency
   a. Recognize neutropenia as a feature of copper, B12, or folate deficiency

6. Neutropenia associated with immune defects
   a. Recognize that neutropenia is a feature of immune defects

7. Neutropenia associated with metabolic diseases
   a. Recognize neutropenia as a feature of glycogen storage disease I and other metabolic disorders

8. Neutropenia associated with ECMO and bypass surgery and hemodialysis
   a. Recognize that severe transient neutropenia is associated with extracorporeal membrane oxygenation (ECMO), bypass surgery, and hemodialysis and understand the mechanism

9. Neutropenia associated with hypersplenism
   a. Recognize that hypersplenism can present with neutropenia

8. Neutrophilia
   a. Know the major causes of acute and chronic neutrophilia
   b. Know the significance of neutrophilia in newborn infants

9. Eosinophilia
   a. Know the disorders associated with primary and secondary eosinophilia
   b. Know the correlation of eosinophilia with specific parasitic infestations
   c. Know the clinical consequences of hypereosinophilia

10. Basophils
    a. Know the disorders associated with basophilia

11. Defects of neutrophil function
    a. General
        1. Differentiate the granulocyte functional abnormalities associated with altered killing of microorganisms
        2. Know the clinical features associated with various neutrophil function disorders
    b. Chédiak-Higashi syndrome
        1. Associate the morphologic abnormality of neutrophil granules with the clinical presentation of Chédiak-Higashi syndrome
        2. Know the molecular biology and genetics of Chédiak-Higashi syndrome
3. Know the associated clinical and laboratory findings in Chédiak-Higashi syndrome
4. Understand the immunologic and hemostatic deficits associated with Chediak-Higashi syndrome
c. Leukocyte adhesion deficiency syndromes (LAD types I and II)
   1. Know the genetics, clinical presentation of, and therapy for the various forms of leukocyte adhesion deficiency syndromes
   2. Understand the molecular basis of leukocyte adhesion deficiency syndromes
   3. Know the appropriate laboratory evaluation of leukocyte adhesion deficiency syndromes
   4. Know the complications of leukocyte adhesion deficiency syndromes
d. Chronic granulomatous disease
   1. Know the current approaches to the diagnosis and treatment of chronic granulomatous disease
   2. Know the organisms that are poorly killed by the granulocytes of patients with chronic granulomatous disease
   3. Know the clinical manifestations, molecular biology, and inheritance patterns of chronic granulomatous disease
e. Hyperimmunoglobulinemia E syndrome
   1. Know the clinical manifestations of hyperimmunoglobulin E syndrome
   2. Understand the laboratory evaluation and differential diagnosis of hyperimmunoglobulin E syndrome
f. Myeloperoxidase deficiency
g. Hereditary/morphologic abnormalities of neutrophils
   1. Pelger-Huet anomaly
      a. Recognize the morphologic alteration of neutrophils associated with the Pelger-Huet anomaly
      b. Recognize the conditions associated with Pelger-Huet anomaly
   2. May-Hegglin anomaly
      a. Know the morphologic features that characterize the May-Hegglin anomaly
B. Monocytes, macrophages, and antigen-processing cells
   1. Normal monocyte characteristics
      a. Distinguish monocytes from lymphocytes and granulocytes based on cytochemical reactions
      b. Know the surface markers and membrane antigens that characterize monocyte-macrophages
      c. Know the life cycle of normal monocyte-macrophages
      d. Understand the factors that regulate monocyte production
   2. Function and metabolism
      a. Understand the role of macrophages in the inflammatory response
      b. Know the effects of cytokines on mononuclear phagocytes
   3. Monocytosis
      a. Know the disorders associated with monocytosis
   4. Storage diseases
      a. Know the bone marrow histology of storage disorders
      b. Know that Gaucher disease is diagnosed using the glucocerebrosidase assay
5. Dendritic cells
   a. Know the surface markers and membrane antigens that characterize dendritic cells
   b. Understand the function of dendritic cells

C. Lymphocytes
1. Normal morphology and age-related values
   a. Know the normal age-related circulating blood lymphocyte values
   b. Know the light microscopy and ultrastructure characteristics of lymphocytes and plasma cells
   c. Know the characteristics which differentiate T lymphocytes from B lymphocytes
2. Surface membrane antigens and gene rearrangements
   a. Know the sequence of T-cell receptor gene rearrangement and surface antigen expression during T-cell ontogeny
   b. Know the sequence of immunoglobulin gene rearrangement and surface antigen and immunoglobulin expression during B-cell development
3. Kinetics
   a. Know the life history of lymphocytes
4. Biochemistry
   a. Interleukins
      1. Differentiate the effect of interleukins on T cells, B cells, monocytes, and macrophages
      2. Understand the sequence of events in the activation and replication of lymphocytes
5. Function
   a. B cells
      1. Immunoglobulins
         a. Know the genetics of immunoglobulin production
         b. Know the biological properties of human immunoglobulins
         c. Understand the mechanisms associated with the generation of antibody diversity
   b. T cells
      1. Receptor
         a. Understand the T-cell receptor/CD3 complex
         b. Understand the function of CD4-positive and CD8-positive lymphocytes
      2. Natural killer cells
         a. Know the morphology of natural killer cells
         b. Understand the biology and function of natural killer cells and major histocompatibility complex restriction
      3. Major histocompatibility complex
         a. Differentiate the functions of Class I, II, and III major histocompatibility complex proteins
         b. Understand the process of antigen presentation
6. Lymphocytosis
   a. Know the causes of lymphocytosis
7. Lymphopenia
   a. Know the causes of lymphopenia
   b. Know the relationship between skin test anergy and lymphopenia
8. Alterations in systemic disease
   a. Mononucleosis syndromes
      1. Know the etiology, pathogenesis, and clinical features of mononucleosis syndromes
      2. Recognize the heterophil-negative mononucleosis syndromes
      3. Know how to establish the diagnosis of infectious mononucleosis (Epstein-Barr virus (EBV) infection)
      4. Associate the morphologic abnormalities of lymphocytoses, lymphocyte number, and morphology with the clinical presentation of infectious mononucleosis
   b. Lipid storage disorders
      1. Recognize vacuoles in lymphocytes as a feature of lipid storage disorders

3. Hemostasis
   A. Platelets
      1. Normal platelet characteristics
         a. Normal values
            1. Recognize spurious thrombocytopenia
            2. Know the limitations of electronic platelet counting
            3. Know the normal values for platelet counts in neonates and children
            4. Understand the value of the peripheral blood smear in estimating the platelet count
         b. Platelet production
            1. Know the growth factors which regulate megakaryocyte and platelet production
            2. Know the significance of platelet size
         c. Platelet kinetics
            1. Know the survival of platelets in vivo under normal conditions and in different thrombocytopenic states
            2. Know the mechanism of platelet destruction under normal conditions
            3. Know the normal distribution of platelets between circulation and the spleen
         d. Platelet structure
            1. Know the overall structure of platelets, including the plasma membrane, the canalicular system, and organelles
         e. Platelet function
            1. Know the significance of platelet adhesion and aggregation and their overall relationship to hemostasis
            2. Know the content and function of substances released from platelet granules
            3. Know the relationship of platelet membrane receptors and their associated ligands in platelet aggregation and adhesion
            4. Know the relationship of von Willebrand factor, collagen, and their receptors in platelet adhesion
            5. Know the structural and biochemical changes that occur during platelet activation
            6. Know how prostaglandin metabolism in platelets and endothelial cells differentially affects platelet function
            7. Know the role of cyclic adenosine monophosphate (cAMP) in platelet activation
f. Laboratory assessment of platelet function
1. Know how to interpret the results of platelet aggregation studies
2. Understand the diagnostic utility and limitations of an abnormal result of platelet function screening (PFA) 100 or a prolonged bleeding time
3. Know the relationship between platelet age and function
4. Know how to formulate an approach to the evaluation of a patient with an abnormal result of platelet function screening (PFA 100) or increased bleeding time

2. Thrombocytopenia
a. General considerations
1. Know the general mechanisms and clinical presentation of thrombocytopenia in the setting of impaired production, increased destruction, and abnormal distribution
2. Know the clinical features of bleeding associated with thrombocytopenia as compared to those associated with coagulation factor deficiencies
3. Know the usefulness of the bone marrow aspirate and cytogenetics to differentiate the mechanism of thrombocytopenia

b. Thrombocytopenia in the newborn period
1. General considerations
   a. Know the differential diagnosis of neonatal thrombocytopenia
   b. Know that consumptive thrombocytopenia is seen with conditions such as necrotizing enterocolitis (NEC), or respiratory distress syndrome (RDS)
2. Infection
   a. Know the incidence and course of thrombocytopenia with bacterial sepsis
   b. Know the various congenital infections associated with neonatal thrombocytopenia
3. Neonatal alloimmune thrombocytopenia (NAIT)
   a. Know the major platelet antigens involved in neonatal alloimmune thrombocytopenia
   b. Know the risks and benefits of different therapeutic options and risk factors associated with each option for treating bleeding in neonatal alloimmune thrombocytopenia
   c. Know the clinical and diagnostic features of neonatal alloimmune thrombocytopenia
   d. Know the fetal and maternal management of subsequent pregnancies after an initial child with neonatal alloimmune thrombocytopenia, and the role of paternal platelet typing
   e. Know the influence of ethnicity on the antigens involved in neonatal alloimmune thrombocytopenia
   f. Know the role of human leukocyte antigen (HLA) type and other factors in maternal sensitization to platelet alloantigens
4. Neonatal autoimmune thrombocytopenia
   a. Know the risks and proper management of an infant born to a mother with immune thrombocytopenia
   b. Know the clinical and diagnostic features of neonatal thrombocytopenia due to maternal immune thrombocytopenic purpura
c. Know how to evaluate and manage an infant born to a mother with systemic lupus erythematosus
d. Know the evaluation and management of an infant born to a mother with a history of chronic idiopathic thrombocytopenic purpura

5. Neonatal bone marrow abnormalities
   a. Know the different syndromes associated with decreased platelet production in newborn infants
   b. Know the clinical features, inheritance patterns, treatment, and prognosis of newborn infants with thrombocytopenia-absent-radius syndrome
   c. Know the clinical features, treatment, and prognosis of infants with amegakaryocytic thrombocytopenia
   d. Know the association of thrombocytopenia with other dysmorphic syndromes

6. Neonatal thrombocytopenia due to perinatal drugs
   a. Know how maternal complications and perinatal drugs are associated with decreased platelets in her newborn infant

7. Miscellaneous causes of neonatal thrombocytopenia
   a. Know that neonatal thrombocytopenia may be a manifestation of occult large vessel or catheter thrombosis
   b. Know that neonatal thrombocytopenia can occur secondary to hemangiomas or thrombosis in placental vessels or in the infant
   c. Know that neonatal thrombocytopenia can occur with hemolytic disease of the newborn

   c. Hereditary thrombocytopenia
      1. Know the inborn errors of metabolism associated with neonatal thrombocytopenia
      2. Know that neonatal thrombocytopenia can be a manifestation of certain chromosomal abnormalities
      3. Know the genetics, clinical features, and laboratory characteristics associated with hereditary thrombocytopenia associated with macrothrombocytes or giant platelet syndromes
      4. Know that thrombocytopenia may be the first sign of Fanconi aplastic anemia
      5. Know the clinical features, laboratory findings, immunologic abnormalities, and prognosis in children with Wiskott-Aldrich syndrome
      6. Know the presentation and genetics of X-linked thrombocytopenia and its relationship to Wiskott-Aldrich syndrome

   d. Acquired thrombocytopenic states
      1. Idiopathic thrombocytopenic purpura (ITP)
         a. Know the mechanisms of platelet destruction in acute idiopathic thrombocytopenic purpura
         b. Know the methods to measure antiplatelet antibodies
         c. Know the clinical course, laboratory features, therapeutic options, and complications of therapy in acute idiopathic thrombocytopenic purpura
         d. Understand the management issues and risks of splenectomy in childhood idiopathic thrombocytopenic purpura
e. Know the clinical course, laboratory features, and therapeutic options in chronic idiopathic thrombocytopenic purpura
f. Know the indications for bone marrow examination in idiopathic thrombocytopenic purpura

2. Drug-induced
   a. Know the mechanisms of drug-induced immune thrombocytopenia
   b. Know the treatments (eg, drugs, immunizations) associated with immune thrombocytopenia
   c. Distinguish thrombocytopenia due to immune destruction from thrombocytopenia due to impaired platelet production

3. Infection-related thrombocytopenia
   a. Know the mechanisms of thrombocytopenia in various bacterial and viral infections
   b. Know the viral infections that should be considered as causative factors in children with immune thrombocytopenic purpura

4. Thrombocytopenia associated with intravascular coagulation
   a. Know the presentation, etiology, laboratory findings, and clinical course of thrombocytopenia in hemolytic-uremic syndrome
   b. Know that thrombocytopenia is usually an important feature of disseminated intravascular clotting
   c. Know the clinical presentation, laboratory findings, course of thrombocytopenia, and therapeutic options in acquired acute thrombotic thrombocytopenic purpura (TTP)
   d. Know the clinical presentation, laboratory findings, course of thrombocytopenia, and therapeutic options in the inherited, chronic form of thrombotic thrombocytopenic purpura (TTP)
   e. Know the pathophysiology of thrombotic thrombocytopenic purpura (TTP)
   f. Know the functions of the von Willebrand cleaving protease (ADAMTS13)

5. Thrombocytopenia due to impaired platelet production
   a. Know that thrombocytopenia is a manifestation of aplastic anemia or bone marrow infiltrative disorders

6. Thrombocytopenia due to increased platelet turnover/sequestration
   a. Know the evaluation and management of thrombocytopenia due to hemangioma, Kasabach-Merritt syndrome

7. Thrombocytopenia due to nutritional deficiencies
   a. Know that thrombocytopenia occurs in severe iron, folate, and vitamin B12 deficiencies

8. Thrombocytopenia associated with cardiovascular disorders
   a. Know that cyanotic heart disease may be associated with thrombocytopenia and/or a functional platelet disorder

9. Thrombocytopenia associated with splenomegaly
   a. Know that an enlarged spleen may cause thrombocytopenia due to a shift in the distribution of platelets from the circulation to the splenic pulp

10. Dilutional thrombocytopenia
a. Know that dilutional thrombocytopenia can occur when large volumes of blood are transfused without replacing platelets, including exchange transfusions

11. Post-transfusion purpura
   a. Know the clinical features, pathophysiology, treatment, and incidence of thrombocytopenia due to post-transfusion purpura

12. Thrombocytopenia associated with ECMO
   a. Recognize and know the mechanism of thrombocytopenia associated with extracorporeal circulation

3. Thrombocytosis
   a. Know the disorders associated with reactive thrombocytosis
   b. Know how to differentiate primary thrombocytopenia from reactive thrombocytosis
   c. Know the conditions under which thrombocytosis may be associated with thrombotic complications or hemorrhage
   d. Know how to treat patients with thrombocytosis who have a propensity for thrombosis
   e. Know that thrombocytosis is a sign of asplenia

4. Abnormalities of platelet function
   a. Hereditary disorders of platelet function
      1. Know the molecular basis, clinical characteristics, laboratory features, management, and inheritance pattern associated with Glanzmann thrombasthenia
      2. Know the molecular basis, clinical characteristics, laboratory features, management, and inheritance pattern associated with Bernard-Soulier syndrome
      3. Know the clinical characteristics, laboratory features, management, pathophysiology, and inheritance pattern of adenosine diphosphate storage pool defect
      4. Know the clinical characteristics, laboratory features, management, and inheritance of platelet alpha-granule deficiency
      5. Know the clinical characteristics, laboratory features, management, and inheritance of platelet dense-granule defects
   b. Acquired disorders of platelet function
      1. Drugs
         a. Know the specific effect and duration of the action of aspirin ingestion on platelet function tests
         b. Know the duration of the effect of (nonaspirin) anti-inflammatory drugs on platelet function
         c. Know which commonly used drugs affect platelet function
      2. Uremia
         a. Understand the therapeutic options available for improving platelet function in patients with uremia
         b. Know the possible mechanisms for impaired platelet aggregation in uremia
      3. Other
   c. Treatment of platelet functional disorders
      1. Know the clinical situations which respond to desmopressin therapy
      2. Know the role and risks of platelet transfusions in platelet function disorders
B. Coagulation
   1. Physiology of coagulation, fibrinolysis, and the vessel wall
      a. Contact activation
         1. Know the components of the contact activation system
         2. Know the consequences of deficiencies in the contact activation system on coagulation assays
         3. Know the interaction between the contact activation system and the complement system
         4. Know the function of Factor XI in the coagulation cascade
      b. Factor IX
         1. Know the age-related changes in Factor IX concentrations
         2. Know the site of synthesis of Factor IX
         3. Know the half-life of Factor IX
         4. Know the role of vitamin K in the synthesis and activity of Factor IX and also Factors II (prothrombin), VII, and X
         5. Know the mechanism of activation and the function of Factor IX in the coagulation cascade
         6. Know the consequences of deficiency of Factor IX on the laboratory assessment of hemostasis
      c. Factor VIII
         1. Know that desmopressin increases plasma Factor VIII concentration
         2. Know the natural inhibitors that regulate the activity of Factor VIII
         3. Know the function of Factor VIII in coagulation
         4. Know the consequences of a deficiency of Factor VIII on the laboratory assessment of hemostasis
         5. Know the normal value of Factor VIII in a newborn infant
         6. Know the half-life of Factor VIII
         7. Know that Factor VIII circulates as a complex with von Willebrand factor
      d. Von Willebrand factor
         1. Know the sites of synthesis, storage, and release of von Willebrand factor
         2. Know the platelet aggregation patterns associated with the different types of von Willebrand disease
         3. Know the laboratory methods for measuring the concentration, structure, and function of von Willebrand factor
         4. Know the interaction between von Willebrand factor, platelets, and the vessel wall
         5. Know the consequences of a deficiency of von Willebrand factor on the laboratory assessment of hemostasis
         6. Know the factors that affect the serum concentration of von Willebrand factor
         7. Know the half-life of von Willebrand factor
      e. Factor VII and tissue factor
         1. Know the functions of Factor VII/tissue factor in coagulation
         2. Know the consequences of a deficiency of Factor VII on the laboratory assessment of hemostasis
         3. Know the age-related changes in Factor VII concentration
         4. Know the site of synthesis of Factor VII
5. Know the half-life of Factor VII

f. Factor X
1. Know the mechanism of activation and the function of Factor X in coagulation
2. Know the consequences of a deficiency of Factor X on the laboratory assessment of hemostasis
3. Know that the half-life of Factor X is longer than that of Factor VII and know why this is important when switching anticoagulation from heparin to coumadin

g. Factor V
1. Know the mechanism of activation and the function of Factor V in coagulation
2. Know the consequences of a deficiency of Factor V on the laboratory assessment of hemostasis
3. Know which inhibitors regulate the activity of Factor V

h. Prothrombin and thrombin
1. Know the mechanisms of activation of prothrombin
2. Know the function of prothrombin and thrombin in coagulation, natural anti-coagulation, and fibrinolysis
3. Know the consequences of a deficiency of prothrombin on the laboratory assessment of hemostasis
4. Know the natural inhibitors of thrombin
5. Know the interaction of thrombin with platelets and with the endothelial cells

i. Fibrinogen and fibrin
1. Know the association of fibrinogen concentration and erythrocyte sedimentation rate
2. Know the basic structure of fibrinogen and its gene control
3. Know the function of fibrinogen and fibrin in coagulation
4. Know the consequences of fibrinogen deficiency on the laboratory assessment of hemostasis
5. Know the normal value of fibrinogen in a newborn infant
6. Know the sites of synthesis of fibrinogen
7. Know the half-life of fibrinogen
8. Know the interaction of fibrinogen with platelets
9. Know the screening tests for fibrinogen deficiency and dysfibrinogenemia

j. Factor XIII
1. Know the association of Factor XIII deficiency with poor wound healing
2. Know the consequences of a deficiency of Factor XIII on the laboratory assessment of hemostasis
3. Know the function of Factor XIII in coagulation
4. Know the half-life of Factor XIII
5. Know the sites of synthesis of Factor XIII
6. Know the laboratory test for Factor XIII deficiency

k. Fibrinolysis
1. Know the mechanisms of activation of plasminogen
2. Know the effects of desmopressin on the tissue plasminogen activator
3. Know the natural inhibitors of plasminogen and its activators
4. Know the laboratory tests which measure the fibrinolytic system
5. Know the fibrinolytic and anti-fibrinolytic drugs and their mechanisms of action

1. Blood vessels
   1. Know which connective tissue diseases are associated with bleeding
   2. Know that thrombomodulin is an endothelial cell surface protein which binds thrombin
   3. Know the role of heparan sulfate proteoglycans on the endothelial surface in maintaining a nonthrombogenic surface
   4. Know that endothelial cells synthesize and secrete tissue plasminogen activator
   5. Know that endothelial cells synthesize and secrete plasminogen activator inhibitor
   6. Know that endothelial cells synthesize and secrete protein S

2. Disorders of coagulation (diagnosis and therapy)
   a. General
      1. Understand which components of hemostatic system are measured by screening tests, eg, prothrombin time, partial thromboplastin time, thrombin time, bleeding time, platelet function screen (PFA 100), platelet aggregation studies
      2. Know the effects of specimen collection artifacts on coagulation tests (heparin, polycythemia, inadequate specimen)
      3. Understand the limitations of and the use of preoperative screening tests to rule out bleeding tendencies
      4. Know which coagulation factors are acute phase reactants
   b. Acquired defects
      1. Disseminated intravascular coagulation (DIC) (neonatal and later)
         a. Pathophysiology and clinical features
            1. Recognize the underlying conditions associated with disseminated intravascular coagulation
            2. Recognize and know the pathophysiology of purpura fulminans
            3. Know that disseminated intravascular coagulation does not occur as a primary illness and may occur in severely ill patients without bleeding or thrombosis
            4. Know the triggering events (eg, endotoxin, viruses, procoagulants released from the tissues, toxins) that activate blood coagulation
            5. Know the mechanism by which triggering events lead to disseminated intravascular coagulation
            6. Know which protective mechanisms against disseminated intravascular coagulation are physiologically impaired in sick neonates as compared to older infants and children
            7. Know that the clinical features of disseminated intravascular coagulation can include hemorrhage (localized or diffuse), thrombosis, hemolytic anemia, and organ dysfunction
            8. Know the underlying diseases unique to the neonate that are associated with disseminated intravascular coagulation
         b. Laboratory abnormalities
            1. Know which tests to perform and how to interpret their results in patients with disseminated intravascular coagulation
2. Know that fibrinolysis usually accompanies disseminated intravascular coagulation as a secondary event
3. Know which blood coagulation factors are reduced in the plasma of patients with disseminated intravascular coagulation
4. Know the significance of the measurements of fibrinogen, fibrin production, and degradation (e.g., D-dimer, fibrin monomer, and fibrinopeptides A and B)

**c. Treatment and outcome**
1. Recognize the risks and benefits of the various therapeutic options for disseminated intravascular coagulation
2. Know that control of the primary disorder is the main treatment for disseminated intravascular coagulation

**2. Vitamin K deficiency (neonatal and later)**

**a. Pathophysiology**
1. Know vitamin K is fat soluble
2. Know that vitamin K tissue stores are limited and that patients can become rapidly deficient
3. Know that human milk contains very little vitamin K

**b. Etiology and clinical features**
1. Recognize the hematologic manifestations of cystic fibrosis in an infant
2. Know the clinical conditions associated with vitamin K deficiency
3. Recognize the clinical features of classic vitamin K deficiency in the newborn period (2 to 7 days of age)
4. Recognize the clinical features and the underlying causes of late hemorrhagic disease of the newborn, i.e., occurring between 4 and 12 weeks of age
5. Know that vitamin K deficiency and hemorrhage may occur by 24 hours of age in infants of mothers who have taken anticonvulsant drugs or other vitamin K antagonists

**c. Laboratory findings**
1. Know the laboratory features of vitamin K deficiency (altered coagulation test results, and which specific coagulation proteins are affected)

**d. Treatment and response**
1. Know the efficacy and response time of different vitamin K preparations
2. Know that hemorrhagic disease of the newborn can be prevented by vitamin K shortly after birth

**e. Drug-induced vitamin K deficiency**
1. Know that certain long-acting (super) warfarin-containing rat poisons may cause a severe and prolonged coagulopathy following their ingestion by an infant or young child

**3. Liver disease**

**a. Pathophysiology**
1. Know the multiple mechanisms responsible for excessive bleeding in patients with severe liver disease
2. Know that the liver is the site of synthesis of most clotting factors
b. Laboratory features
   1. Know the laboratory test abnormalities most commonly seen in patients with severe liver disease and clinical bleeding

c. Treatment
   1. Know the treatment options of various therapeutic modalities in patients who are bleeding from liver disease
   2. Know why the use of prothrombin complex concentrates is contraindicated in the treatment of bleeding due to liver disease

4. Blood coagulation inhibitors
   a. Heparins and heparin-like substances (see also section 3.B.2.d)
   b. Inhibitors against specific factors
      1. Recognize that inhibitors against specific blood coagulation factors in a patient without hemophilia are rare during childhood
      2. Know which passively acquired maternal coagulation inhibitors can adversely affect the newborn infant
      3. Know how to differentiate inhibitor from a factor deficiency using conventional coagulation screening tests
   c. Lupus-type anticoagulants
      1. Know what hemostatic defects associated with lupus-type anticoagulants may cause either bleeding or thrombosis
      2. Know the screening and specific laboratory tests to detect the lupus-type anticoagulant, including the 1:1 mixing study
      3. Know that the lupus-type anticoagulant is often transiently observed in healthy children following a viral infection and is one of the most common causes of a prolonged partial thromboplastin time during childhood
      4. Know the management of children and adolescent patients with a lupus-type anticoagulant

5. Miscellaneous acquired bleeding disorders
   a. Know that children with hematophagocytic syndromes may have a severe coagulopathy characterized by marked hypofibrinogenemia
   b. Know the mechanisms by which L-asparaginase affects the coagulation system and the clinical consequences
   c. Know the coagulation abnormalities in patients with nephrotic syndrome and the clinical consequences
   d. Know the coagulation abnormalities in protein-losing enteropathy and their clinical consequences

c. Congenital hemorrhagic disorders
   1. Factors VIII and IX
      a. Clinical features
         1. Know the mode of inheritance for Factor VIII and IX deficiency
         2. Know that some hemophilia carriers are symptomatic
         3. Know the differentiating clinical characteristics of mild, moderate, and severe hemophilia A and B
         4. Recognize the clinical features of retroperitoneal hemorrhage in a patient with hemophilia
5. Understand the relationship between age and the sites and frequency of bleeding episodes in a hemophiliac patient
6. Know the risk factors for inhibitor development
7. Recognize that inhibitors may be transient
8. Know the clinical indications for the use of human recombinant activated Factor VII concentrate
9. Understand the molecular basis for hemophilia

b. Laboratory diagnosis
1. Understand the various tests to prenatally diagnose Factor VIII and IX deficiency
2. Understand the various tests to diagnose the carrier state for Factor VIII or Factor IX deficiency
3. Know the limitations of the partial thromboplastin time in diagnosing plasma concentrations of Factor VIII or Factor IX
4. Understand the Bethesda assay using human Factor VIII
5. Know the differentiating laboratory characteristics of mild, moderate, and severe hemophilia A and B

c. Management
1. Understand the optimum replacement therapy in relation to severity and location of bleeding in a patient with hemophilia
2. Know the indications for and potential complications of desmopressin in patients with hemophilia
3. Know the advantages and disadvantages of specific therapies for Factor VIII deficiency
4. Know the probable causes of therapeutic failure in Factor VIII deficiency
5. Know the therapeutic approaches to a hemophiliac patient with inhibitor
6. Know the management of dental extractions in hemophiliac patients
7. Know the therapeutic approaches to a hemophiliac patient with hematuria
8. Know the advantages and disadvantages of specific therapies for Factor IX deficiency
9. Know the proper management and appropriate pre- and postoperative treatment for a patient with Factor VIII or IX deficiency
10. Understand the indications for prophylaxis in Factor VIII and IX deficiencies
11. Understand the management approaches to chronic arthropathy in a patient with hemophilia
12. Know the diagnostic and therapeutic approaches for a patient with hemophilia
13. Understand the management principles of hemophilia in a neonate or young infant

2. Von Willebrand disease
a. Recognize the clinical features of von Willebrand disease
b. Know the relationship of decreased von Willebrand antigen with von Willebrand disease
c. Correlate the response to desmopressin with various types of von Willebrand disease
d. Know the therapeutic options for the treatment of severe von Willebrand disease
e. Know how to diagnose and treat subtypes of von Willebrand disease
f. Know the inheritance patterns of von Willebrand disease
g. Know the effect of blood type and other factors on von Willebrand antigen concentration

3. Other inherited coagulation disorders
a. Recognize the bleeding patterns in less common coagulation defects (eg, Factors II, V, VII, X, XI)
b. Know the appropriate therapy for Factor XIII deficiency
c. Recognize the clinical features of afibrinogenemias and dysfibrinogenemias
d. Know how to investigate the cause of a prolonged thrombin time
e. Know the appropriate therapy for afibrinogenemia and dysfibrinogenemia
f. Understand that clinical bleeding does not occur with prekallikrein deficiency, high-molecular-weight kininogen deficiency, or Factor XII deficiency
g. Know the inheritance pattern for Factor XIII deficiency
d. Hypercoagulable thrombotic states
1. General
a. Know the important antithrombotic properties of vascular endothelium
b. Know that removal of activated coagulation factors by the liver is important in preventing thrombosis
c. Know that estrogen-containing contraceptives are associated with an increased risk of venous thromboembolism, stroke, and acute myocardial infarction

2. Diagnosis
a. Know how to evaluate a hypercoagulable state
b. For each of the known hereditary thrombotic states, know how to diagnose the defect in infants and older children
c. Understand the clinical manifestations of antithrombin III and proteins C and S deficiencies (homozygous versus heterozygous)
d. Know how to evaluate a child with established deep venous thrombosis of unknown cause (laboratory tests, imaging)
e. Know how the normal concentrations of hemostatic factors in neonates complicates the diagnosis of hypercoagulable states
f. Know the predisposing causes to deep venous thrombosis in infants, children, and adolescents
g. Know the acquired conditions that have been associated with venous and arterial thromboembolism
h. Know the clinical signs and symptoms of venous thrombosis in children
i. Know the clinical signs and symptoms of pulmonary embolism in children
j. Know the laboratory measures important in evaluating a child with venous thrombosis and pulmonary embolism
k. Know the clinical presentation, laboratory features, and epidemiology of activated protein C resistance (Factor V Leiden)
l. Know the problems inherent in diagnosing hypercoagulable states in patients receiving coumadin therapy
m. Know the clinical presentation and laboratory diagnosis of patients with prothrombin mutations

3. Treatment
   a. General considerations
      1. Know the treatment of a hypercoagulable state in a newborn infant
      2. Know the action of anticoagulant drugs used in thrombotic states or in patients with thrombophilia
      3. Know the indications for and treatment of acquired hypercoagulable states
   b. Warfarin
      1. Recognize the embryopathic potential of warfarin therapy
      2. Know the mechanism of action of warfarin and other vitamin K antagonists used as anticoagulants for therapeutic purposes
      3. Recognize the association of skin necrosis with warfarin therapy in patients with heterozygous protein C or protein S deficiency
      4. Know the indications for use of vitamin K antagonists
      5. Know the importance of the international normalized ratio (INR) and its use in monitoring vitamin K antagonists
      6. Recognize that many dietary items and drugs can interact with vitamin K antagonists
   c. Heparin
      1. Recognize the clinical and laboratory correlates of iatrogenic bleeding secondary to heparin administration
      2. Know how to screen blood samples for the presence of heparin
      3. Understand the structure and mechanisms of action of heparin and heparin-like substances
      4. Know the causes of heparin resistance
      5. Recognize the effect of heparin on coagulation assays in specimens from plasma, including those drawn from central catheters
      6. Know the syndrome and treatment of heparin-induced thrombocytopenia, including its association with thrombosis
      7. Know how to monitor heparin and low-molecular-weight heparin therapy
      8. Know the relative advantages and disadvantages of standard heparin vs. low-molecular-weight heparin
   d. Direct anti-thrombin drugs
      1. Know the benefits, pharmacokinetics, and monitoring of direct anti-thrombin drugs
      2. Know the various means to reverse vitamin K antagonists
   e. Fibrinolytic drugs
      1. Know the indications for and risks of using fibrinolytic therapy
      2. Know how to monitor fibrinolytic therapy
4. Pediatric Transfusion Medicine
   A. Collection and storage characteristics
      1. Erythrocytes (liquid storage)
         a. Know the biochemical changes that occur during erythrocyte storage
         b. Know that washed erythrocytes can be stored for up to 24 hours before expiration
         c. Know that erythrocytes can be stored for up to 28 days after irradiation
         d. Know the normal storage time of erythrocytes
      2. Platelets
         a. Recognize the normal storage conditions for platelets (ie, constant agitation, room temperature, maximum length of storage)
         b. Know that single-donor platelets obtained by apheresis have the equivalent of multiple random donor platelet units
      3. Leukocytes
         a. Know the techniques for collecting granulocytes and the shelf-life of granulocytes
      4. Plasma
         a. Understand the process of collection and separation of plasma
         b. Know the different coagulation and anticoagulation proteins present in fresh frozen plasma
      5. Plasma-derived products
         a. Understand the process of manufacturing Factor VIII, prothrombin complex, activated prothrombin complex, coagulation Factor IX, cryoprecipitate, and other factor concentrates
         b. Understand the methods of viral inactivation used in the production of the different plasma-derived products, including heat, solvent-detergent treatment, nanofiltration, and removal of albumin
         c. Know the viruses that are not effectively attenuated or removed by the various methods of treatment of plasma-derived products
         d. Know the factor/factors present in the different plasma-derived products, including cryoprecipitate, prothrombin complex concentrates, activated prothrombin complex concentrates
   B. Typing and crossmatching for transfusion
      1. Erythrocytes
         a. Know why women should be screened early in gestation for minor group antibodies
         b. Be able to interpret the results of direct and indirect antiglobulin tests
         c. Know the common alloantibodies that develop in children with sickle cell disease receiving transfusions
      2. Platelets
         a. Know when platelets should be Rh(D) and ABO-compatible
         b. Understand platelet crossmatching, its indications and limitations
   C. Indications for transfusion
      1. Whole blood
      2. Packed erythrocytes
         a. Recognize that washing erythrocytes causes loss of red cells
b. Know the clinical indications for leukocyte reduction (e.g., decreased risk of HLA sensitization, cytomegalovirus (CMV) transmission, and febrile transfusion reactions)
c. Know the indications for packed erythrocytes

3. Cryopreserved erythrocytes
   a. Know the value of frozen erythrocytes for patients with rare compatibility problems

4. Leukocytes
   a. Know the indications for use of granulocyte concentrates
   b. Know the limitations and risks of using granulocyte concentrates

5. Platelets
   a. Recognize indications for use of HLA-matched platelets and crossmatched platelets
   b. Know the risk for alloimmunization in patients needing repeated platelet transfusions
   c. Know the in vivo recovery and survival of transfused platelets in situations of decreased production and increased destruction
   d. Know the tests and observations required to diagnose alloimmunization
   e. Recognize the indications for platelet transfusion

6. Irradiated blood and blood components
   a. Recognize the immunocompromised conditions in which the use of irradiated blood products is indicated
   b. Know that all blood products for exchange transfusion in a neonate who had an intrauterine transfusion must be irradiated to prevent graft-versus-host disease (GVHD)
   c. Know that blood products from all blood relatives must be irradiated to prevent GVHD, even in immunocompetent recipients
   d. Understand the reasons for irradiation of transfused blood products
   e. Know that leukoreduction does not effectively prevent graft-versus-host disease

7. Plasma
   a. Know the appropriate use of fresh frozen plasma

8. Cryoprecipitate
   a. Know the indications for the transfusion of cryoprecipitate

9. Coagulation factor concentrates
   a. Know the risks of using prothrombin complex concentrate and activated prothrombin concentrates
   b. Know that parvovirus is resistant to solvent detergent and heating methods of inactivation
   c. Know the clinical indications for the use of activated prothrombin complex concentrate

10. Immunoglobulin intravenously
    a. Know the hematologic indications for intravenous administration of immune globulin
    b. Know the side effects of intravenous administration of immune globulin

11. Therapeutic pheresis
    a. Recognize the hematologic indications for therapeutic plasma exchange
b. Know the indications for leukapheresis
c. Know the indications for erythrocyte exchange transfusions

12. Autologous erythrocytes
   a. Recognize the usefulness of autologous erythrocytes in older children scheduled for orthopedic surgery, scoliosis repair, marrow-donor harvest, or other conditions
   b. Recognize the usefulness of autologous erythrocytes for individuals with rare blood groups or compatibility problems

13. Directed donors
   a. Recognize that testing requirements often make it impossible to have directed blood donors in emergent situations
   b. Recognize that relatives should not be used as blood component donors for potential hematopoietic stem cell transplant (HSCT) recipients
   c. Recognize that first-time donors exhibit higher rates of infectious disease markers such as human immunodeficiency virus (HIV), hepatitis B, and hepatitis C than repeat volunteer donors

D. Selection of appropriate blood type
   1. Know the proper approach to elective transfusion in a patient with a known erythrocyte alloantibody
   2. Know the appropriate use of erythrocyte products in patients with autoimmune hemolysis

E. Computation of dose, rate of delivery, modifying conditions
   1. Know the \textit{in vivo} recovery and survival of infused Factor VIII, Factor IX, fibrinogen, and prothrombin
   2. Select and calculate the value of the appropriate erythrocyte product for treating anemia
   3. Calculate the dose of platelet concentrate for transfusion of patients with thrombocytopenia

F. Complications of blood and blood product transfusions
   1. Transfusion-transmitted disease
      a. Know the risk of transmission of HIV-1, hepatitis B, and hepatitis C, in transfusion of single-donor blood components
      b. Recognize the clinical and laboratory manifestations of transfusion-acquired CMV infection
      c. Know that frozen or filtered (leukocyte reduced) erythrocytes will reduce transmission of cytomegalovirus to recipients
      d. Recognize the significance of chronic liver disease following hepatitis C transmission by transfusion
      e. Recognize parvovirus infection in HIV-positive recipients
      f. Know how to identify bacterial contamination of blood products
      g. Know the most frequent pathogens that exist in refrigerated units of packed erythrocytes
   2. Transfusion reactions - acute and delayed
      a. Etiology
         1. Recognize the major factors leading to incompatible blood transfusion
         2. Recognize that febrile reactions in chronically transfused patients may be due to antileukocyte, anti-platelet, or anti-HLA antibodies
3. Know that anaphylactic reaction to blood transfusion is associated with IgA deficiency in the recipient
4. Recognize that a fever may be the first sign of a bacterially contaminated transfusion or an acute hemolytic transfusion reaction
5. Know the cause of allergic transfusion reactions

b. Pathogenesis
1. Recognize that anamnestic antibody production causes delayed hemolytic transfusion reactions and that a compatible crossmatch does not prevent delayed hemolytic transfusion reaction
2. Know the impact of leukoreduction on alloimmunization to random donor platelets
3. Understand the pathogenesis and clinical symptoms of transfusion-related acute lung injury

c. Recognition
1. Recognize an acute hemolytic transfusion reaction
2. Recognize the clinical presentation of a delayed transfusion reaction due to minor blood group incompatibility
3. Recognize the complications of massive blood transfusion

d. Management
1. Know the proper therapeutic approach to a patient refractory to platelet transfusions
2. Know the proper erythrocyte types for patient with delayed hemolytic transfusion reaction
3. Know what to do if an Rh-positive blood product is administered to an Rh-negative female patient of child-bearing age or younger
4. Know what to do if an Rh-positive blood product is administered to an Rh-negative male patient
5. Know the management of acute hemolytic transfusion reaction
6. Know what precautions should be taken when transfusing patients with IgA deficiency

e. Prevention
1. Know various strategies to prevent alloimmunization to platelets

5. Pediatric Oncology
A. General
1. Epidemiology of cancer
   a. Age-related incidence
      1. Know the age distribution of childhood tumors
   b. Race-related incidence
      1. Recognize the differences in childhood cancer based on race and/or ethnic origin
   c. Predisposing factors
      1. Genetic factors
         a. Know the constitutional chromosomal abnormalities associated with specific malignancies
         b. Know the tumors associated with genetic disorders
         c. Know the tumors associated with Beckwith-Wiedemann syndrome
d. Know which tumors are associated with genomic imprinting

e. Know the clinical and molecular genetic features of the Li-Fraumeni syndrome

f. Know which tumors are known to occur in multiple members of a family

g. Know which tumors occur with increased frequency in pediatric patients with neurofibromatosis type I

h. Know which malignancies occur with increased frequency in children with Down syndrome

2. Chemical-related

a. Know the drugs associated with the development of specific malignancies (eg, phenytoin and androgens)

b. Know the relationship between chemical carcinogens and cancer

c. Know the chemotherapy agents used in treating childhood malignancies that can increase the risk for the development of specific second malignancies

3. Environmental

a. Know the association between hepatitis viruses and hepatocellular carcinoma

b. Know which tumors are associated with specific viruses

c. Know which tumors are more common after exposure to ionizing radiation

4. Immunologic

a. Know the relationship between congenital/acquired immunodeficiency or immunosuppressive therapy and malignancy

2. Tumor molecular and cellular biology

a. Understand DNA ploidy and its prognostic significance

b. Understand the use and interpretation of Southern blot

c. Understand lyonization and clonality

d. Understand the role of transcription factors and growth

e. Understand apoptosis

f. Understand the use and interpretation of reverse transcription polymerase chain reaction (RT-PCR)

g. Understand the use and interpretation of fluorescence in situ hybridization (FISH)

h. Know the molecularly characterized fusion genes that correspond to the more common chromosomal abnormalities in childhood leukemias and solid tumors

i. Know the difference between the “two-hit” and sporadic mechanisms of carcinogenesis

3. Oncogenesis and cell growth regulation

a. Know the mechanisms of proto-oncogene activation

b. Understand the concept of gene amplification

c. Know the role of protein kinases in cell growth and transformation

d. Understand the interaction of growth factors and cell surface receptors in growth control

e. Understand the use of clonogenic assays

f. Identify the phases and regulation of the cell cycle

g. Understand principles used to measure cell cycle kinetics

h. Know the mechanism of action of tumor suppressor genes and how activation or deletion can contribute to malignant transformation
i. Know the relationship between defects in DNA repair and oncogenesis
j. Understand clinically important proto-oncogene amplification in tumors of children
k. Know that the molecular abnormality in BCR-ABL leukemia alters the tyrosine kinase gene and that targeted chemotherapy can inhibit this activity

4. Radiation therapy
   a. Principles of radiobiology
      1. Know the effects of hypoxia on tumor and normal tissue sensitivity to radiation
      2. Know the advantages of and indications for using brachytherapy
      3. Know the effects of radiation on cells in different phases
      4. Know which variables influence the response to therapeutic radiation
      5. Know the principles underlying the use of fractionated radiation therapy
      6. Know the tumor characteristics that make it amenable to treatment with stereotactic radiosurgery (such as “gamma knife”)
      7. Know the difference between conformal and conventional radiotherapy
      8. Know which chemotherapy agents act as radiation sensitizers
   b. Complications of radiotherapy
      1. Organ-specific toxicity
         a. Know the early and late effects of varying doses of radiation on normal gonads
         b. Know the early and late effects of varying doses of radiation on the normal thyroid
         c. Know the early and late effects of varying doses and types of radiation on the normal brain, including the impact of age at treatment
         d. Know the early and late effects of varying doses of radiation on the normal heart
         e. Know the clinical, laboratory, and radiologic findings of radiation pneumonitis
         f. Know the early and late effects of varying doses of radiation on normal kidneys
         g. Know the early and late effects of varying doses of radiation on normal skin
         h. Know the early and late effects of varying doses of radiation on the normal liver
         i. Know the long-term effects of varying doses of radiation on normal bones at various ages
         j. Know the early and late effects of varying doses of radiation on normal lungs
         k. Know the early and late effects of varying doses of radiation on the normal gastrointestinal tract
         l. Recognize the marrow toxicity of radiation therapy
         m. Know the effects of varying doses of radiation on normal lungs
   2. Secondary tumors
      a. Know the risks of second malignant neoplasms according to radiation dosage, specific tumors, and combined therapy
      b. Know the frequency of tumor types seen as second malignancies

5. Chemotherapy
   a. Principles of chemotherapy
1. Know the sequence of peripheral blood cell recovery following chemotherapy
2. Know the sites of action, metabolism, and toxicities of chemotherapeutic agents
3. Recognize the effect of hepatic dysfunction on chemotherapeutic drug toxicity and efficacy
4. Recognize the effect of renal dysfunction on chemotherapeutic drug toxicity
5. Understand the principles of tumor cell kill kinetics by chemotherapeutic agent
6. Know the phases of the cell cycle in which specific chemotherapeutic agents exert their effects
7. Know that specific chemotherapeutic agents, as well as pubertal status, increase the risk of infertility
8. Know the age-related physiologic differences that affect drug distribution
9. Understand terms used to define pharmacokinetics (e.g., clearance, half-life, AUC, volume of distribution, bioavailability, and biotransformation)
10. Know the classification of chemotherapeutic agents by mechanism of cytotoxicity
11. Know the drugs capable of causing tissue damage when extravasated and mechanisms of prevention

b. Principles of combination chemotherapy
1. Know the rationale for combination chemotherapy
2. Know the rationale for adjuvant combination chemotherapy
3. Know the rationale for primary or neoadjuvant chemotherapy

c. Principles of drug resistance
1. Know the role of the mdr gene and p-glycoprotein in the development of drug resistance
2. Know mechanisms by which cells develop resistance to anticancer drugs
3. Know strategies to overcome drug resistance

d. Groups of chemotherapy drugs
1. Alkylating drugs
   a. Know which chemotherapy drugs are alkylating drugs
   b. Know the potential short- and long-term toxicities of the chemotherapy alkylating drugs
2. Anti-metabolites
   a. Know which chemotherapy agents used in children with cancer are anti-metabolites
   b. Know the mechanism of action of the cancer drugs that are anti-metabolites
   c. Know that second malignant neoplasms have not been shown to be associated with anti-metabolite therapy
3. Naturally derived drugs
   a. Know the mechanisms of action of the chemotherapy agents that are antibiotics
4. Topoisomerase inhibitors
   a. Know which chemotherapy drugs are topoisomerase inhibitors
   b. Know the potential short- and long-term toxicities of chemotherapy topoisomerase inhibitors
   c. Know the mechanisms of action of chemotherapy topoisomerase inhibitors
5. Mitotic inhibitors
a. Know the potential short- and long-term toxicities of chemotherapy mitotic inhibitors
b. Know the mechanisms of action of chemotherapy mitotic inhibitors
c. Know which chemotherapy drugs are mitotic inhibitors
e. Specific agents
   1. 6-Mercaptopurine
      a. Clinical pharmacology and pharmacokinetics
         1. Understand the mechanism of action of 6-mercaptopurine
         2. Know the effect of allopurinol on bioavailability of 6-mercaptopurine
         3. Understand the pharmacogenetics of 6-mercaptopurine
      b. Complications and their management
         1. Recognize the pattern of hepatic toxicity associated with mercaptopurine
         2. Know the potential toxicities associated with the use of 6-mercaptopurine
   2. 6-Thioguanine
      a. Clinical pharmacology and pharmacokinetics
         1. Know how thioguanine differs from mercaptopurine in metabolism and bioavailability
      b. Complications and their management
         1. Know how thioguanine differs from mercaptopurine in toxicity
   3. Methotrexate (conventional and high-dose)
      a. Clinical pharmacology and pharmacokinetics
         1. Understand the mechanism of action of methotrexate
         2. Know the kinetics and therapeutic principles of high-dose methotrexate with leucovorin rescue
         3. Know that oral methotrexate absorption is highly variable
         4. Know that renal dysfunction delays methotrexate clearance
         5. Know what drugs interfere with methotrexate clearance
         6. Know that methotrexate has little tendency to develop cross-resistance with other drugs
         7. Know the potential differences in methotrexate exposure by dosage, route, and schedule of administration
      b. Complications and their management
         1. Recognize the clinical features of acute methotrexate toxicity
         2. Know the effects of repeated doses of parenteral methotrexate on the brain
   4. Cytarabine
      a. Clinical pharmacology and pharmacokinetics
         1. Understand the mechanism of action of cytarabine
         2. Know the metabolism of cytarabine and impact of organ dysfunction and role of cytidine deaminase
         3. Know the potential differences in cytarabine exposure by dosage, route, and schedule of administration
      b. Complications and their management
         1. Know the toxicities of cytarabine and the impact of organ dysfunction
         2. Know the neurologic toxicity that can occur with high dose cytarabine
c. Clinical use
   1. Know how cytarabine is used in the treatment of childhood malignancy
   2. Know how cytarabine is used in central nervous system (CNS) preventive therapy and in CNS relapse in acute leukemia
   3. Know that intrathecal cytarabine and intravenous high dose cytarabine given in close proximity can cause transverse myelitis

5. Corticosteroids
   a. Clinical pharmacology and pharmacokinetics
      1. Know the mechanism(s) of action of glucocorticoids and the role of glucocorticoid receptors
      2. Understand the pharmacology of different glucocorticoids
      3. Know that systemic dexamethasone achieves higher CNS levels, as compared to prednisone
   b. Complications and their management
      1. Know the acute and delayed toxic effects of corticosteroids and the differences between prednisone and dexamethasone
      2. Know how to manage hyperglycemia associated with corticosteroid administration
      3. Recognize the acute toxicity of corticosteroid therapy, such as mood changes and Cushingoid changes
      4. Know that osteoporosis is a complication of corticosteroid therapy and that schedule of administration influences the likelihood of development of this complication
      5. Know that corticosteroids increase the likelihood of systemic bacterial and fungal infections
      6. Know the difference between potential toxicities of prednisone and dexamethasone
   c. Clinical use
      1. Know the role that systemic corticosteroids play in the treatment of ALL, NHL, Hodgkin lymphoma, and histiocytoses
      2. Know how corticosteroids can be used in managing some of the complications of cancer (ie, nausea and vomiting, increased intracranial pressure, hypercalcemia, and allergic reactions)

6. Hydroxyurea
   a. Understand the mechanism of action, complications, and clinical use of hydroxyurea

7. Anthracyclines
   a. Clinical pharmacology and pharmacokinetics
      1. Understand the mechanism of action of the anthracyclines
      2. Know the metabolism of anthracyclines and the impact of organ dysfunction
      3. Understand the pharmacologic differences of the anthracyclines
   b. Complications and their management
      1. Know the toxicities (acute and long-term) of the anthracyclines and the impact of organ dysfunction
2. Know the risk factors, presentation, evaluation, and management of acute and late anthracycline cardiotoxicity
3. Know that anthracyclines potentiate radiation toxicity
4. Understand the relationship between anthracyclines and second tumors, and be able to distinguish anthracycline-induced acute myeloid leukemia (AML) from other treatment-induced leukemias
5. Know the potential role of dexrazoxane in preventing cardiotoxicity of anthracyclines

c. Clinical use
   1. Know the principal clinical uses for each of the anthracyclines

8. Dactinomycin
   a. Clinical pharmacology and pharmacokinetics
      1. Know the mechanism of action of dactinomycin
      2. Know the metabolism of dactinomycin and the impact of organ dysfunction
   b. Complications and their management
      1. Know the toxicities of dactinomycin
      2. Know that dactinomycin is a radiation sensitizer
      3. Know that infants are at higher risk of dactinomycin toxicity and the appropriate prevention strategies
   c. Clinical uses
      1. Know the primary ways in which dactinomycin is used in the treatment of childhood malignancies

9. Bleomycin
   a. Clinical pharmacology and pharmacokinetics
      1. Know the metabolism of bleomycin and the impact of organ dysfunction
      2. Know the mechanism of action of bleomycin
   b. Complications and their management
      1. Recognize the pulmonary complications of bleomycin and the role of total dose
      2. Know the toxicities of bleomycin and that pulmonary toxicity is related to cumulative dose
   c. Clinical uses
      1. Know how bleomycin is used in the treatment of childhood malignancies

10. Vincristine
    a. Clinical pharmacology and pharmacokinetics
       1. Understand the mechanism of action of vincristine
       2. Know the metabolism of vincristine and the impact of organ dysfunction
    b. Complications and their management
       1. Know the toxicities of vincristine
    c. Clinical use
       1. Understand the use of vincristine in the treatment of various childhood malignancies

11. Vinblastine
    a. Clinical pharmacology and pharmacokinetics
       1. Understand the mechanism of action of vinblastine
2. Know the metabolism of vinblastine
b. Complications and their management
   1. Know that the dose-limiting toxicity of vinblastine is different from that of vincristine
   2. Know the toxicities of vinblastine
c. Clinical use
   1. Understand the clinical use of vinblastine in treating childhood malignancies

12. Cyclophosphamide
   a. Clinical pharmacology and pharmacokinetics
      1. Know the metabolism of cyclophosphamide and the impact of organ dysfunction
      2. Know the mechanism of action of cyclophosphamide
      3. Know that cyclophosphamide is both myelosuppressive and immunosuppressive
      4. Know the potential differences in cyclophosphamide exposure by dosage, route, and schedule of administration
   b. Complications and their management
      1. Know the acute and long-term complications of cyclophosphamide therapy
      2. Know the methods (and their rationale) used to reduce the risk of hemorrhagic cystitis associated with the use of cyclophosphamide
      3. Know the toxicities of cyclophosphamide
c. Clinical use
      1. Understand the clinical use of cyclophosphamide in treating childhood malignancies

13. Ifosfamide
   a. Clinical pharmacology and pharmacokinetics
      1. Understand the mechanism of action of ifosfamide
      2. Know the metabolism of ifosfamide
      3. Know the pharmacologic differences between cyclophosphamide and ifosfamide
   b. Complications and their management
      1. Know how to diagnose and manage renal tubular dysfunction resulting from ifosfamide therapy
      2. Recognize the acute and late toxicities of ifosfamide therapy
      3. Know the diagnosis, causes, and treatment of acute neurotoxicity of ifosfamide therapy
   c. Clinical use
      1. Understand the clinical uses of ifosfamide in treating childhood malignancies

14. Mechlorethamine
   a. Clinical pharmacology and pharmacokinetics
      1. Understand the mechanism of action of mechlorethamine
      2. Understand the history of mechlorethamine in treating childhood malignancies
b. Complications and their management
   1. Know the acute and late toxicities of mechlorethamine therapy
   2. Know the precautions needed for administration of mechlorethamine via peripheral vein

c. Clinical use
   1. Understand the clinical use of mechlorethamine in treating childhood malignancies

15. Carmustine
   a. Clinical pharmacology and pharmacokinetics
      1. Know the metabolism of carmustine
      2. Know the mechanism of action of carmustine
   b. Complications and their management
      1. Know the acute and delayed toxicities of carmustine, including the time course for myelosuppression
      2. Know that prolonged thrombocytopenia can occur with carmustine
   c. Clinical use
      1. Understand the clinical uses of carmustine in the management of childhood malignancies

16. Lomustine
   a. Clinical pharmacology and pharmacokinetics
      1. Know the metabolism of lomustine
      2. Know the mechanism of action of lomustine
   b. Complications and their management
      1. Know the acute and late toxicities of lomustine
      2. Know the relationship between progressive renal atrophy and cumulative doses of lomustine
   c. Clinical use
      1. Understand the clinical uses of lomustine in the management of childhood malignancies

17. Asparaginase (Escherichia coli, Erwinia, PEG-E coli)
   a. Clinical pharmacology and pharmacokinetics
      1. Understand the mechanism of action of asparaginase
      2. Know that asparaginase can be used to modify the toxic effects of methotrexate and cytarabine
      3. Know the different preparations of asparaginase and their pharmacokinetics
      4. Know how PEG asparaginase is made from E. coli asparaginase
   b. Complications and their management
      1. Know the hemostatic complications of asparaginase therapy
      2. Know that asparaginase causes allergic reactions
      3. Know the toxicities of asparaginase
      4. Recognize acute pancreatitis as a complication of asparaginase therapy
      5. Know the treatment options for a patient who is allergic to E. coli, Erwinia, or PEG asparaginase
      6. Recognize hyperglycemia due to decreased insulin production as a complication of asparaginase therapy
      7. Recognize hypoalbuminemia as a complication of asparaginase therapy
   c. Clinical use
1. Know the uses for asparaginase in the treatment of childhood malignancies

18. Cisplatin
   a. Clinical pharmacology and pharmacokinetics
      1. Understand the mechanism of action of cisplatin
      2. Know the metabolism of cisplatin
   b. Complications and their management
      1. Understand the measures to minimize the risk of renal toxicity from cisplatin
      2. Know the toxicities associated with cisplatin therapy
      3. Know the type of hearing loss that occurs with cisplatin and the relationship to cumulative dose
      4. Know that hypomagnesemia is common after cisplatin therapy
   c. Clinical use
      1. Understand the uses of cisplatin in the treatment of childhood malignancies

19. Carboplatin
   a. Clinical pharmacology and pharmacokinetics
      1. Understand the mechanism of action of carboplatin
      2. Understand the metabolism of carboplatin
   b. Complications and their management
      1. Know the toxicities associated with carboplatin
      2. Differentiate carboplatin toxicity from cisplatin toxicity
      3. Know that carboplatin can cause delayed nadirs in platelet counts and absolute granulocyte counts

20. Busulfan
   a. Clinical pharmacology and pharmacokinetics
      1. Understand the mechanism of action of busulfan
      2. Understand the metabolism of busulfan, including the role of age
   b. Complications and their management
      1. Know the toxicities associated with busulfan therapy

21. Epipodophyllotoxins (VP-16, VM-26)
   a. Clinical pharmacology and pharmacokinetics
      1. Understand the mechanism of action of the epipodophyllotoxins
      2. Know the metabolism of the epipodophyllotoxins
   b. Complications and their management
      1. Understand the relationship between epipodophyllotoxins and secondary AML and distinguish it from secondary AML associated with alkylators
      2. Know the acute and late toxicities of epipodophyllotoxins
   c. Clinical use
      1. Know the clinical use of epipodophyllotoxins in the treatment of childhood malignancies

22. Camptothecins (eg, topotecan, irinotecan)
   a. Clinical pharmacology and pharmacokinetics
      1. Understand the mechanism of action of camptothecins
      2. Know the metabolism of the camptothecins
b. Complications and their management
   1. Know the toxicities associated with the camptothecins
   2. Know how to manage the diarrhea that can be associated with irinotecan

c. Clinical use
   1. Know the uses of topotecan and irinotecan in the treatment of pediatric malignancies

23. Temozolomide
   a. Clinical pharmacology and pharmacokinetics
      1. Understand the mechanism of action of temozolomide
      2. Know the metabolism of temozolomide
   b. Complications and their management
      1. Know the toxicities associated with temozolomide
      2. Know that myelosuppression is the dose-limiting toxicity of temozolomide, but is not cumulative
   c. Clinical use
      1. Know how temozolomide is used in the treatment of childhood malignancies

24. Procarbazine
   a. Clinical pharmacology and pharmacokinetics
      1. Know the mechanism of action of procarbazine
      2. Know the toxicities associated with procarbazine
      3. Know the clinical use of procarbazine in the treatment of childhood malignancies

25. Clofarabine
   a. Know the clinical indications for treatment with clofarabine

26. Nelarabine
   a. Know the clinical indications for treatment with nelarabine

6. Biologic response modifiers and immunotherapy
   a. Recognize the common side effects of interferon therapy
   b. Know the mechanism of action, indications, and common side effects of 13-cis-retinoic acid
   c. Know the mechanism of action, indications, and common side effects of all-trans-retinoic acid
   d. Know the mechanism of action, indications, and common side effects of tyrosine kinase inhibitors such as imatinib
   e. Know the mechanism of action, indications, and common side effects of monoclonal antibodies such as rituximab (anti-CD20), gemtuzumab (anti-CD33), and epratuzumab (anti-CD22)

7. Supportive care drugs
   a. Hematologic growth factors
      1. Know the rationale for use, indications, mechanism of action, and toxicity of filgrastim (G-CSF) and sargramostim (GM-CSF) in children receiving chemotherapy
      2. Know the rationale for use, indications, mechanism of action, and toxicity of erythropoietin in children receiving chemotherapy
3. Know the different preparations of filgrastim (G-CSF) and their pharmacokinetics

b. Antiemetics
   1. Know the mechanism of action and side effect profile of various classes of antiemetics (not including serotonin S3 receptor antagonists and neurokinin 1 [NK1] inhibitors)
   2. Know the rationale for use, indications, mechanism of action, and toxicity of the serotonin S3 receptor antagonists
   3. Know the rationale for use, indications, mechanism of action, and toxicity of NK1 inhibitors

c. Miscellaneous
   1. Know the rationale for use, indications, mechanism of action, and potential side effects of rasburicase
   2. Know the rationale for use, indications, mechanism of action, and potential side effects of allopurinol

B. Special diagnostic tests
   1. Bone marrow aspiration and biopsy
      a. Recognize normal marrow osteoclasts or osteoblasts and differentiate from tumor cells
      b. Know that bone marrow aspiration alone is not adequate to rule out involvement of marrow in lymphomas and solid tumors
      c. Know the definitions for M1, M2, and M3 marrow in the acute leukemias
   2. Diagnostic x-ray studies/scans
      a. Know the indications for magnetic resonance imaging compared to computed tomography scan
      b. Know the uses for gallium scans in assessing pediatric malignancies
      c. Know the indications for positron emission tomography (PET) scanning in assessing pediatric malignancies
   3. Examination of the cerebrospinal fluid
      a. Know the risks associated with lumbar puncture for examination of cerebrospinal fluid
      b. Know the definitions of CNS 1, CNS 2, CNS 3 in the acute leukemias
   4. Biochemical markers
      a. Know the biochemical abnormalities that characterize different neoplasms
   5. Immunologic studies
      a. Understand the use of tumor-specific antigens for diagnostic and prognostic purposes

C. Leukemia, general
   1. Incidence and epidemiology
      a. Know the incidence of ALL and acute myelogenous leukemia, and the peak age at which each of these occur
      b. Know the concordance rate of ALL and AML in identical twins
      c. Know the incidence of chronic myelogenous leukemia in children
   2. Leukemogenesis
      a. Know which constitutional and genetic conditions predispose to the development of leukemia
b. Know that Down syndrome is associated with an increased incidence of both acute lymphoblastic and acute myeloid leukemia

c. Know the mechanisms by which immunodeficiency states can have increased risk for leukemia

3. Cell biology
   a. Cytogenetics and oncogenes
      1. Know the non-random chromosomal abnormalities and correlated molecular genetic abnormalities associated with specific phenotypes of ALL and AML
   b. Leukemic cell proliferation \textit{in vitro}
   c. Biologic characterization
      1. Identify the cell morphology of different types of leukemia
      2. Know the immunophenotypic differences between ALL and AML
      3. Know how to identify lymphoid/myeloid mixed lineage ALL and biphenotypic leukemia (by immunophenotyping)

D. Acute lymphoblastic leukemia (ALL)
   1. Clinical and laboratory features
      a. General principles
         1. Know the clinical and laboratory features of B-lineage (non-T, non-B) ALL
         2. Know the epidemiologic, clinical, and laboratory features that characterize B-cell (Burkitt) ALL
         3. Know the epidemiologic, clinical and laboratory features that characterize T-cell lymphoblastic leukemia
         4. Recognize the clinical complications related to the hematologic abnormalities in acute leukemia
         5. Recognize hypereosinophilia as a rare presenting feature of ALL
      b. Pancytopenia
         1. Formulate a differential diagnosis for pancytopenia in childhood
      c. Bone pain
         1. Know that ALL can mimic juvenile idiopathic arthritis at presentation
         2. Recognize the changes on x-ray studies of the skeleton in association with ALL
         3. Know the differential diagnosis of bone pain in a child
      d. Organomegaly
         1. Know the differential diagnosis of hepatosplenomegaly and pancytopenia
      e. Purpura
         1. Recognize how the clinical presentation of leukemia differs from idiopathic thrombocytopenic purpura
      f. Leukocytosis
         1. Recognize the complications associated with hyperleukocytosis
         2. Know the differential diagnosis of an absolute lymphocytosis
      g. Extramedullary leukemia
         1. Know the criteria for the diagnosis of CNS leukemia
         2. Know the clinical manifestations of CNS leukemia
         3. Know the significance of an enlarged testis in ALL
         4. Know the prognostic implications of the duration of first remission for a patient with isolated CNS or testicular relapse
   2. Biologic characterization and classification
a. Morphology
   1. Recognize the morphology of ALL, including the unique morphology of L3 ALL
   2. Know how to distinguish atypical lymphocytes from lymphoblasts
   3. Know how to recognize granular ALL
b. Histochemistry and biochemistry
   1. Know that CD10+ lymphoblasts and T-lymphoblasts both have terminal deoxynucleotidyl transferase activity
c. Immunologic classification
   1. Know how to interpret cell surface markers in the diagnosis and classification of ALL, including CD10+ HLA-DR expression
   2. Know the prognostic significance of biologic markers in ALL
   3. Know the relationship between the expression of surface or cytoplasmic immunoglobulin and specific subsets of leukemia
d. Gene rearrangements
   1. Know the gene rearrangement characteristics of ALL
   2. Know the prognostic significance of the molecular translocations that occur in ALL
3. Prognostic factors
   a. General principles
      1. Know the clinical and laboratory findings that influence prognosis in ALL
      2. Know that the significance of prognostic factors varies among different treatment regimens
      3. Know the National Cancer Institute consensus risk stratification of ALL
   b. Initial leukocyte count
      1. Recognize initial leukocyte count as a risk factor in ALL
   c. Age
      1. Recognize age as a significant risk factor in ALL
      2. Recognize age subgroups as a prognostic factor within infants < 12 months of age at diagnosis
   d. Response to therapy
      1. Know that rapidity of response to chemotherapy in ALL is predictive of outcome
      2. Know the methods that can be used to measure rapidity of response in ALL, including day 8 and day 15 bone marrow examinations and peripheral blood assessments
      3. Know the methods for quantitating minimal residual disease (MRD)
      4. Know the rationale for using minimal residual disease in predicting outcome in ALL
   e. Central nervous system (CNS)
      1. Know which ALL immunophenotypes are most likely to have CNS disease at diagnosis
   f. Cytogenetics
      1. Know the prognostic significance of cytogenetic and molecular diagnostic findings in ALL
2. Know the prognostic significance of hyperploidy (greater than approximately 52 chromosomes) in ALL
3. Know the prognostic significance of Ph chromosome in ALL
4. Know the prognostic significance of DNA index (DI) ploidy, and how it correlates with chromosome count
5. Know that a “normal” leukemic cell karyotype may reflect inadequate growth of tumor cells or an occult translocation
6. Know the prognostic significance of hypodiploidy in ALL
7. Know the cytogenetic/molecular abnormalities most likely to be seen in the leukemic cells of infants less than 12 months old with ALL
8. Know that TEL-AML-1 is the molecular counterpart of t(12;21)
9. Know that the occult t(12;21) is the most common nonrandom cytogenetic abnormality in B-lineage ALL

g. Immunophenotype
1. Know the prognoses of B-precursor, T-cell, and B-cell (Burkitt) ALL, respectively
2. Know the non-random chromosome abnormalities seen in B-precursor, B-cell, and T-cell ALL, respectively

4. Therapy
a. Chemotherapy
1. Identify drugs most valuable for remission induction of ALL
2. Recognize delayed intensification as a useful strategy for standard and high risk ALL
3. Recognize the importance of risk-adjusted therapy for ALL prognostic subgroups
4. Know the principles of treatment for different risk groups of ALL

b. Irradiation
1. Plan the radiation field for prophylactic irradiation of the cranium in ALL
2. Know the complications of intrathecal methotrexate and central nervous system irradiation in a patient with ALL
3. Know that irradiation can be avoided in many patients if any effective central and intrathecal chemotherapy are given

c. Late effects of therapy
1. Recognize the late complications of cranial radiation for ALL
2. Know that brain tumor is a late complication of cranial irradiation for ALL
3. Know the relationship between treatments for acute leukemia and late central nervous system complications
4. Know the effect of age on neuropsychologic function after cranial irradiation in ALL

5. Management and treatment of complications of ALL
a. General principles
1. Know the complications of induction therapy for ALL
2. Plan the management of a patient with pancytopenia during induction therapy for ALL
3. Know the clinical and laboratory features of tumor lysis syndrome and its prophylaxis and management
b. Central nervous system (CNS)
   1. Know the management of central nervous system leukemia that develops after prophylaxis
   2. Plan the management of central nervous system leukemia detected at the time of diagnosis of ALL
   3. Plan the diagnostic evaluation and management of a patient with ALL who has a seizure

c. Testicular
   1. Plan the management of testicular relapse of ALL

d. Bone marrow relapse
   1. Know the importance of the duration of first remission as a prognostic factor after relapse
   2. Know the role of various types of stem cell transplantation in the management of ALL relapse (see also section 7.B)

E. Acute myeloid leukemia (AML)
   1. Clinical and laboratory features
      a. French-American-British (FAB) classifications
         1. Know the clinical presentations and FAB classification of AML
      b. Purpura
         1. Recognize the association of disseminated intravascular coagulation with M3 AML
      c. Leukocytosis
         1. Recognize and manage the myeloproliferative syndrome in infants with Down syndrome and differentiate it from AML
         2. Recognize the potential complications of hyperleukocytosis in AML
         3. Plan the management of hyperleukocytosis in AML
      d. Central nervous system
         1. Recognize that central nervous system leukemia can complicate AML
      e. Extramedullary disease
         1. Recognize that leukemia cutis can be the presenting feature of AML in infants
         2. Recognize chloroma as a manifestation of AML

   2. Biologic characterization and classification
      a. Morphology
         1. Be able to recognize AML subtypes M0 through M7
         2. Know the relationship between myelodysplastic syndromes and AML
      b. Histochemistry, immunologic classification
         1. Recognize the clinical picture, morphologic characteristics, and blast cell surface marker characteristics of acute megakaryocytic leukemia
         2. Know that the M7 subtype is most common in children less than 3 years of age, especially those with Down syndrome
      c. Cytogenetics and molecular genetics
         1. Correlate clinical characteristics with chromosomal abnormalities in AML
         2. Understand the significance of rearrangements of the ATRA receptor gene in M3 AML
         3. Recognize specific clinical syndromes associated with t(8;21), inv(16), t(9;11), t(15;17), and monosomy 7 or 7q- in AML
4. Know the molecular abnormalities with which specific and recurring chromosomal abnormalities are associated in acute nonlymphoblastic leukemia
5. Know the characteristic chromosomal abnormalities and clinical characteristics in secondary AML resulting from topoisomerase II inhibitors and from alkylators, respectively

3. Prognostic factors
   a. Know prognosis of various FAB sub-types of AML
   b. Know the prognostic significance of the non-random cytogenetic abnormalities in AML
   c. Know that therapy is an important prognostic factor in AML
   d. Know the prognostic importance of Down syndrome in acute nonlymphoblastic leukemia

4. Therapy
   a. Chemotherapy
      1. Plan the further chemotherapy of a patient with AML in remission and drug-induced neutropenia and thrombocytopenia
      2. Know the role of all trans-retinoic acid and chemotherapy in the treatment of M3 acute nonlymphoblastic leukemia
      3. Know that high-dose cytarabine is effective in the treatment of AML
      4. Know which drug combinations are most effective in the treatment of AML
      5. Know the role of CNS prophylaxis in the treatment of AML
      6. Know the evidence against the use of extended maintenance therapy for AML
   b. Supportive care
      1. Know the various components of prophylactic and acute supportive care for children with AML receiving treatment
   c. Hematopoietic stem cell transplantation (HSCT) (see also section 7)
      1. Know the indications for allogeneic HSCT in AML

F. Myeloproliferative disorders
   1. Clinical and laboratory features
      a. Know the clinical, laboratory, and prognostic features of adult chronic myeloid leukemia (CML) and juvenile myelomonocytic leukemia (JML)
      b. Know the clinical and laboratory characteristics that differentiate Ph+ CML from Ph+ AML
      c. Recognize priapism as a presenting feature of CML
      d. Recognize the hematologic changes associated with a blast crisis in CML
      e. Know that a blast crisis in CML can involve other cell lines
      f. Know the biologic properties of the malignant cells in JML
      g. Know the criteria for the diagnosis of JML
   2. Biologic characterization and classification
      a. Know the association of bcr-Ab1 oncogene with CML
      b. Know the molecular difference in Ph+ CML and Ph+ ALL in children
   3. Therapy
      a. Chemotherapy
         1. Know the principles of chemotherapy to treat CML
         2. Plan the treatment of a blast crisis in a patient with CML
         3. Know the principles of therapy for JML and for monosomy 7 syndrome
4. Know the principles of using targeted therapy (such as imatinib) in patients with CML

b. Immunotherapy
1. Know the therapeutic effects and side effects of alpha interferon in treatment of CML

b. HSCT (see also section 7)
1. Know the indications for and timing of HSCT in a patient with CML
2. Know the therapeutic options for a patient who has a recurrence of CML after HSCT

G. Lymphomas
1. Hodgkin lymphoma
   a. Epidemiology/predisposing factors/genetics
      1. Know the epidemiologic features of Hodgkin lymphoma in children
      2. Recognize that Hodgkin lymphoma may occur in families
   b. Pathology
      1. Recognize the pathologic subtypes of Hodgkin lymphoma
      2. Know the biologic characteristics of the Reed-Sternberg cell
      3. Know the incidence of each of the pathologic subtypes of Hodgkin lymphoma in children
      4. Recognize the morphologic and immunophenotypic characteristics of Reed-Sternberg cells and of Reed-Sternberg cell variants
   c. Clinical presentation
      1. Recognize the clinical presentation and pattern of spread of Hodgkin lymphoma by anatomic site
      2. Know the differential diagnosis of acute lymphadenopathy and chronic lymphadenopathy simulating malignant lymphoma
      3. Recognize impaired cellular immunity in a patient with Hodgkin lymphoma
      4. Know the most common clinical presentation of Hodgkin lymphoma in children
      5. Know the laboratory abnormalities that may be seen in children with Hodgkin lymphoma at the time of diagnosis
   d. Diagnosis and staging
      1. Utilize imaging modalities appropriately to determine the extent of primary disease and metastatic spread of Hodgkin lymphoma
      2. Know the criteria for Ann Arbor staging in patients with Hodgkin lymphoma
   e. Treatment (see also section 7.B.)
      1. Know the role of radiation therapy in the treatment of Hodgkin lymphoma in children and adolescents
      2. Know the role of chemotherapy in the treatment of Hodgkin lymphoma in children and adolescents
      3. Be able to monitor appropriately the response to treatment of Hodgkin lymphoma
      4. Plan the treatment of a relapse in a patient with Hodgkin lymphoma
      5. Know the principles of treatment for different stages of Hodgkin lymphoma
   f. Prognosis
      1. Know the prognostic features of Hodgkin lymphoma
2. Know the prognosis of Hodgkin lymphoma according to such variables as stage and histology
g. Complications/late effects
1. Evaluate and manage a febrile patient with Hodgkin lymphoma who has previously undergone splenectomy
2. Recognize the radiologic, clinical, and laboratory manifestations of recurrent Hodgkin lymphoma
3. Know the complications and late effects of treatment for Hodgkin lymphoma
4. Recognize the significance of persistent abnormalities revealed by computed tomography after therapy for Hodgkin lymphoma
5. Know the increased risk for and kinds of second malignant neoplasms that are most likely after treatment for Hodgkin lymphoma

2. Non-Hodgkin lymphoma (NHL)
a. Epidemiology/predisposing factors/genetics
1. Know the association of EBV and HIV with NHL
2. Know the cytogenetic and molecular genetic abnormalities associated with NHL
3. Know the chromosomal alterations associated with Burkitt lymphoma
4. Know the gene rearrangement patterns which distinguish monoclonal and polyclonal lymphoproliferative processes
5. Understand the relationship of oncogenes to structural genes in chromosome 8:14 translocation
6. Recognize the clinical and epidemiologic characteristics that distinguish “endemic” from “sporadic” Burkitt lymphoma
7. Know that the inherited and acquired immunodeficiency states predispose to the development of NHL

b. Histopathology and immunophenotype
1. Recognize the pathologic subtypes of NHL in children and adolescents
2. Recognize the pathologic subtypes of NHL relative to primary site and pattern of spread
3. Know the characteristic immunophenotype of Burkitt and Burkitt-like lymphomas
4. Know the relative importance of heavy and light chain immunoglobulin expression in the diagnosis of Burkitt or Burkitt-like lymphomas
5. Know the characteristic immunophenotype of T-cell lymphoblastic NHL
6. Know that, immunophenotypically, Burkitt and Burkitt-like lymphomas are identical to B-cell ALL, and T-cell lymphoblastic lymphomas are identical to T-cell ALL
7. Know the variety of immunophenotypes which may be seen in large cell lymphomas in children

c. Clinical presentation
1. Recognize the clinical presentation of NHL by anatomic site, such as superior vena cava syndrome
2. Know the clinical presentation and laboratory findings of Burkitt lymphoma
3. Recognize when tumor lysis syndrome can be present in NHL
4. Recognize the large B-cell lymphomas that arise in the anterior mediastinum
d. Diagnosis and staging
   1. Utilize appropriate imaging modalities to determine the extent of NHL
   2. Utilize appropriate laboratory studies to determine the extent of NHL
   3. Know that diagnosis of NHL can sometimes be made on pleural effusion or ascitic fluid
   4. Recognize CNS involvement in a patient with NHL
   5. Know how to use the degree of bone marrow involvement to distinguish stage IV NHL and acute leukemia of similar immunophenotype
   6. Recognize that advanced stage T-cell lymphoblastic lymphoma and T-cell ALL represent different stages of the same disease
   7. Recognize that advanced stage Burkitt lymphoma or Burkitt-like NHL and B-cell ALL represent different stages of the same disease

b. Treatment (see also section 7.B.)
   1. Know the role of surgery in the treatment of NHL
   2. Know the role of radiation therapy in the treatment of NHL
   3. Know the role of chemotherapy in the treatment of specific types of NHL
   4. Know the emergency management of a large mediastinal mass in NHL
   5. Know the emergency management of tumor lysis syndrome in NHL
   6. Know the emergency management of spinal cord compression in NHL
   7. Appropriately monitor the response to treatment of NHL
   8. Plan the treatment for a patient with advanced stage Burkitt lymphoma or Burkitt-like NHL
   9. Know the principles of treatment for different stages and histologies of NHL
   10. Plan the treatment for a patient with limited NHL

e. Prognosis
   1. Know the prognostic features of NHL
   2. Know the prognosis of NHL according to such variables as stage, histology, and immunophenotype

g. Complications/late effects
   1. Know the complications and late effects of the treatment of NHL

H. Malignant solid tumors
   1. Bone tumors
      a. Osteosarcoma
         1. Epidemiology/predisposing factors/genetics
            a. Know the cytogenetic and molecular genetic abnormalities associated with osteosarcoma
            b. Know the epidemiology of osteosarcoma
            c. Know that osteosarcoma can occur as a late effect of radiation therapy
            d. Know that patients with hereditary retinoblastoma are at increased risk for osteosarcoma
         2. Pathology
            a. Recognize the pathologic subtypes of osteosarcoma
            b. Know that the histopathologic basis for making the diagnosis of osteosarcoma is finding osteoid-producing malignant cells
         3. Clinical presentation
            a. Recognize the most common skeletal locations for primary osteosarcoma
b. Know the most common metastatic sites in osteosarcoma

4. Diagnosis and staging
   a. Utilize appropriate imaging modalities to determine the extent and metastatic spread of osteosarcoma
   b. Identify the radiologic appearance of osteosarcoma of long bones
   c. Know the differential diagnoses for a primary bone lesion suspected of being osteosarcoma

5. Treatment
   a. Know the role of surgery in the treatment of primary osteosarcoma and in the treatment of metastatic osteosarcoma
   b. Know the role of chemotherapy in the treatment of osteosarcoma
   c. Know the role of neo-adjuvant and post-operative chemotherapy in the treatment of osteosarcoma
   d. Know the available surgical options for treatment of osteosarcoma
   e. Plan the treatment of parosteal and periosteal variants of osteosarcoma
   f. Know the principles of treatment for different stages of osteosarcoma
   g. Be able to monitor appropriately a patient’s response to treatment of osteosarcoma

6. Prognosis
   a. Know the laboratory findings that have prognostic importance in osteosarcoma
   b. Know the prognostic features and prognosis of osteosarcoma, including stage and histology
   c. Know the prognosis of osteosarcoma according to stage and histology
   d. Know how the location of the primary tumor in osteosarcoma influences the prognosis
   e. Know that the histopathologic response (% necrosis) in osteosarcoma to preoperative chemotherapy is of prognostic significance
   f. Know how tumor size at diagnosis of osteosarcoma influences prognosis

7. Complications/late effects
   a. Know the complications and late effects of osteosarcoma
   b. Know the complications and late effects of surgery performed in the treatment of osteosarcoma
   c. Know the complications and late effects of chemotherapy in the treatment of osteosarcoma

b. Ewing sarcoma
1. Epidemiology/predisposing factors/genetics
   a. Know the cytogenetic and molecular genetic abnormalities associated with Ewing sarcoma
   b. Know the association of t(11:22) with both Ewing sarcoma and primitive neuroectodermal tumor

2. Pathology
   a. Formulate a differential diagnosis of small round-cell tumors of bone based on pathologic characteristics
   b. Recognize the pathologic similarities and differences between Ewing sarcoma and primitive neuroectodermal tumor
c. Understand the use of molecular assays in the diagnosis of Ewing sarcoma and primitive neuroectodermal tumor

3. Clinical presentation
   a. Recognize the clinical presentation of Ewing sarcoma by anatomic site and know the most common primary sites
   b. Know the laboratory features of extraosseous Ewing sarcoma

4. Diagnosis and staging
   a. Utilize appropriate imaging modalities to determine the extent and metastatic spread of Ewing sarcoma
   b. Recognize the radiologic findings of Ewing sarcoma

5. Treatment (see also section 7.B)
   a. Know the role of surgery in the treatment of Ewing sarcoma
   b. Know the role of irradiation in the treatment of Ewing sarcoma
   c. Know the role of chemotherapy and preoperative chemotherapy in the treatment of Ewing sarcoma
   d. Be able to appropriately monitor the response to treatment of Ewing sarcoma
   e. Know the principles of treatment for different stages of Ewing sarcoma

6. Prognosis
   a. Understand the prognostic variables in Ewing sarcoma

7. Complications/late effects
   a. Know the complications and late effects of treatment of Ewing sarcoma according to type of therapy
   b. Know the complications and late effects of treatment of Ewing sarcoma according to primary tumor site, eg, pelvis, spine, extremities

2. Retinoblastomas
   a. Epidemiology/predisposing factors/genetics
      1. Understand the inheritance pattern of unilateral and bilateral retinoblastoma
      2. Know the cytogenetic and molecular genetic abnormalities associated with retinoblastoma
      3. Understand the limitations and use of DNA-based diagnoses in genetic counseling of patients with retinoblastoma
   b. Pathology
      1. Recognize the importance of pathologic examination relative to the extent of primary tumor and pattern of spread in retinoblastoma
   c. Clinical presentation
      1. Recognize the clinical presentation of retinoblastoma, including the differences between unilateral and bilateral
      2. Recognize the clinical manifestations of trilateral retinoblastoma
   d. Diagnosis and staging
      1. Know the differential diagnosis of retinoblastoma
      2. Be able to appropriately utilize imaging modalities to determine the extent and metastatic spread of retinoblastoma
      3. Stage retinoblastoma according to the intraocular extent of the tumor
      4. Stage retinoblastoma according to the pathologic findings after enucleation
      5. Know the most common metastatic sites of retinoblastoma
e. Treatment
   1. Know the role of surgery in the treatment of retinoblastoma
   2. Know the role of irradiation in the treatment of retinoblastoma
   3. Know the role of chemotherapy in the treatment of retinoblastoma
   4. Know the role of local surgical techniques, such as photocoagulation, in the treatment of retinoblastoma
   5. Appropriately monitor the response to treatment of retinoblastoma
   6. Plan the treatment according to disease stage of a patient with bilateral retinoblastoma
   7. Know the management of unilateral retinoblastoma
   8. Know the proper follow-up monitoring of an infant who has had enucleation for unilateral retinoblastoma
   9. Know the proper screening and follow-up for children who are siblings of a patient with retinoblastoma
  10. Know the principles of treatment for various stages of retinoblastoma
f. Prognosis
   1. Know the prognostic features and the prognosis of retinoblastoma

h. Complications/late effects
   1. Know the complications and late effects of retinoblastoma and its associated treatment

3. Neuroblastic tumors
   a. Epidemiology/predisposing factors/genetics
      1. Know the cytogenetic and molecular genetic abnormalities associated with neuroblastoma
   b. Pathology
      1. Recognize the characteristic pathologic features of neuroblastomic tumors
      2. Know the relationship of pathologic classification to prognosis and outcome in patients with neuroblastoma
   c. Clinical presentation
      1. Know the association of myoclonic encephalopathy with neuroblastoma
      2. Recognize the clinical and laboratory findings of neuroblastoma
      3. Know the association of intractable secretory diarrhea with neuroblastomic tumors
   d. Diagnosis and staging
      1. Know how to distinguish neuroblastoma in bone marrow from other abnormal cells
      2. Utilize appropriate imaging modalities to determine the extent and metastatic spread of neuroblastoma
      3. Utilize appropriate laboratory studies to determine the extent and metastatic spread of neuroblastoma
   e. Treatment (see also section 7.B.)
      1. Know the principles of treatment for various stages of neuroblastoma
      2. Know the role of surgery in the treatment of neuroblastoma
      3. Know the role of irradiation in the treatment of neuroblastoma
      4. Know the role of chemotherapy in the treatment of neuroblastoma
      5. Know the role of biologic response modifiers in the treatment of neuroblastoma
6. Be able to appropriately monitor the response to treatment of neuroblastoma

f. Prognosis
   1. Know the laboratory, pathologic, and molecular biologic variables of
      prognostic significance (eg, DNA index, MYCN amplification) in patients with
      neuroblastoma
   2. Know the clinical variables (such as age and stage) of prognostic significance
      and their associated prognoses, in patients with neuroblastoma

g. Complications/late effects
   1. Know the complications and late effects of neuroblastoma and its treatment
   2. Know the neurologic complications and late effects of neuroblastoma
      presenting with myoclonic encephalopathy

4. Peripheral neuroectodermal tumors
   a. Clinical presentation
      1. Recognize the clinical presentation of peripheral neuroectodermal tumors by
         anatomic site
   b. Diagnosis and staging
      1. Recognize esthesioneuroblastoma
      2. Utilize appropriate imaging modalities to determine the extent and metastatic
         spread of peripheral neuroectodermal tumors
      3. Utilize appropriate laboratory studies to determine the extent and metastatic
         spread of peripheral neuroectodermal tumors
      4. Know the chromosomal and molecular alterations characteristic of peripheral
         neuroectodermal tumor
   c. Treatment
      1. Know the role of surgery in the treatment of peripheral neuroectodermal tumors
      2. Know the role of irradiation in the treatment of peripheral neuroectodermal
         tumors
      3. Know the role of chemotherapy in the treatment of peripheral neuroectodermal
         tumors
      4. Be able to appropriately monitor the response to treatment of peripheral
         neuroectodermal tumors
      5. Know the principles of treatment for peripheral neuroectodermal tumors
   d. Prognosis
      1. Know the prognostic factors, and their associated prognoses, of primitive
         neuroectodermal tumors
   e. Complications/late effects
      1. Know the complications and late effects of primitive neuroectodermal tumors
         and their treatment

5. Brain tumors
   a. Epidemiology/predisposing factors/genetics
      1. Know the cytogenetic and molecular genetic abnormalities associated with
         brain tumors
      2. Recognize the association between brain tumors and heritable syndromes (eg,
         neurofibromatosis, tuberous sclerosis)
      3. Know the association between pineoblastoma and retinoblastoma
   b. Pathology
1. Recognize the pathologic subtypes of brain tumors such as low-grade glioma, high-grade glioma, medulloblastoma, ependymoma, atypical teratoid rhabdoid tumor, choroid plexus carcinoma, and CNS germ cell tumor
2. Recognize the pathologic subtypes of brain tumors relative to primary tumor site and pattern of spread
3. Recognize the relationship between histologic grade of gliomas and prognosis

**c. Clinical presentation**
1. Recognize the clinical presentation of brain tumors by anatomic site
2. Know the clinical and laboratory manifestations of different central nervous system tumors
3. Know the clinical and laboratory features of medulloblastoma
4. Know the clinical and laboratory features of cerebellar astrocytoma
5. Know the clinical and laboratory features of brain-stem glioma
6. Know the clinical and laboratory features of pineal tumors
7. Know the clinical and laboratory features of ependymoma
8. Know the clinical and laboratory features of primitive neuroectodermal tumors
9. Know the clinical and laboratory features of optic pathway gliomas
10. Recognize the relationship between age and anatomic site in the clinical presentation of brain tumors
11. Know the clinical and laboratory features of hypothalamic tumors
12. Know the clinical and laboratory features of intramedullary spinal cord tumors

**d. Diagnosis and staging**
1. Utilize appropriate imaging modalities to determine the extent and metastatic spread of brain tumors
2. Know which CNS tumors are associated with spinal cord metastases
3. Know the appropriate imaging, CSF, and other laboratory studies to use for staging CNS tumors
4. Know the patterns of metastasis and spread characteristic of CNS tumors

**e. Treatment** (see also section 7.B)
1. Know the role of surgery in the treatment of brain tumors
2. Recognize that surgery alone is curative for cerebellar astrocytoma
3. Know the role of irradiation in the treatment of brain tumors
4. Know the role of chemotherapy in the treatment of brain tumors
5. Monitor the response to treatment of brain tumors using clinical modalities
6. Monitor the response to treatment of brain tumors using imaging modalities
7. Monitor the response to treatment of brain tumors using biochemical markers
8. Know the principles of management for patients with medulloblastoma
9. Know the principles of management for patients with low-grade astrocytoma
10. Know the principles of management for patients with brain-stem glioma
11. Know the principles of management for patients with pineal tumors
12. Know the principles of management for patients with ependymoma
13. Know the principles of management for patients with primitive neuroectodermal tumors
14. Know the principles of management for patients with high-grade gliomas (anaplastic astrocytoma and glioblastoma multiforme)
15. Know the principles of management of patients with CNS germ cell tumors
f. Prognosis
   1. Know the prognostic features (eg, stage and histology), and their associated
      prognoses, of brain tumors
   2. Know the natural history of medulloblastoma
   3. Know the natural history of low-grade astrocytoma
   4. Know the natural history of brain-stem glioma
   5. Know the natural history of pineal-cell tumors
   6. Know the natural history of ependymoma
   7. Know the natural history of central nervous system primitive neuroectodermal
      tumors
   8. Identify the prognostic factors in patients with medulloblastoma
   9. Identify the prognostic factors in patients with astrocytoma
  10. Identify the prognostic factors in patients with brain-stem glioma
  11. Identify the prognostic factors in patients with pineal-cell tumors
  12. Identify the prognostic factors in patients with ependymoma
  13. Identify the prognostic factors in patients with primitive neuroectodermal
      tumors
  14. Know the natural history of high-grade gliomas
  15. Identify the prognostic factors in patients with CNS germ cell tumors

g. Complications/late effects
   1. Know the complications and late effects of brain tumors
   2. Know the late effects of brain tumors and their treatment in patients of various
      ages
   3. Know the secondary malignancies associated with treatment of brain tumors
   4. Know the potential neurologic sequelae of brain tumors and their treatment
   5. Know the potential endocrine sequelae of brain tumors and their treatment
   6. Know the potential intellectual sequelae of brain tumors and their treatment
   7. Know the complications and late effects of surgery performed in the treatment
      of brain tumors
   8. Know the complications and late effects of irradiation in the treatment of brain
      tumors
   9. Know the complications and late effects of chemotherapy in the treatment of
      brain tumors, eg, secondary malignancies

6. Hepatoblastoma and hepatocellular carcinoma
   a. Epidemiology/predisposing factors/genetics
      1. Know the cytogenetic and molecular genetic abnormalities associated with
         hepatoblastoma and hepatocellular carcinoma
      2. Know the association of familial polyposis coli with hepatoblastoma and
         hepatocellular carcinoma
      3. Know which congenital conditions are associated with an increased risk of
         hepatoblastoma
      4. Know the association of hepatocellular carcinoma with inborn errors of
         metabolism causing cirrhosis
   b. Pathology
      1. Recognize the pathologic subtypes of hepatoblastoma and hepatocellular
         carcinoma relative to prognosis and pattern of spread
c. Clinical presentation
   1. Recognize the clinical presentation of hepatoblastoma and hepatocellular carcinoma

d. Diagnosis and staging
   1. Utilize appropriate imaging modalities to determine the extent and metastatic spread of hepatoblastoma and hepatocellular carcinoma
   2. Utilize appropriate laboratory studies to determine the extent and metastatic spread of hepatoblastoma and hepatocellular carcinoma

e. Treatment
   1. Know the role of surgery in the treatment of hepatoblastoma and hepatocellular carcinoma
   2. Know the role of irradiation in the treatment of hepatoblastoma and hepatocellular carcinoma
   3. Know the role of chemotherapy in the treatment of hepatoblastoma and hepatocellular carcinoma
   4. Know the role of liver transplantation in the treatment of hepatoblastoma and hepatocellular carcinoma
   5. Appropriately monitor the response to treatment of hepatoblastoma and hepatocellular carcinoma
   6. Know the principles of management of hepatoblastoma and hepatocellular carcinoma

f. Prognosis
   1. Know the prognostic features, and their associated prognoses, of hepatoblastoma and hepatocellular carcinoma

g. Complications/late effects
   1. Know the complications and late effects of hepatoblastoma and hepatocellular carcinoma and their therapy

7. Renal tumors
a. Epidemiology/predisposing factors/genetics
   1. Know the cytogenetic and molecular genetic abnormalities associated with renal tumors
   2. Know the somatic abnormalities associated with Wilms tumor

b. Pathology
   1. Recognize the pathologic subtypes of renal tumors relative to primary tumor and pattern of spread
   2. Know the relationship between histologic pattern of Wilms tumor and prognosis
   3. Know the significance of the presence of nephroblastomatosis in a patient with Wilms tumor
   4. Know the biologic characteristics and clinical management of mesoblastic nephroma

c. Clinical presentation
   1. Recognize the clinical presentation of renal tumors
   2. Know the congenital anomalies that are associated with an increased risk of Wilms tumor

d. Diagnosis and staging
1. Utilize appropriate imaging modalities to determine the extent metastatic spread of renal tumors
2. Utilize appropriate laboratory studies to determine the extent and metastatic spread of renal tumors
3. Know the procedures necessary to stage Wilms tumor (stages I-V)

 Treatment
1. Know the complications of radiation therapy in patients with Wilms tumor
2. Know the role of surgery in the treatment of renal tumors
3. Plan the management of an infant with a mesoblastic nephroma
4. Know the role of irradiation in the treatment of renal tumors
5. Know the role of chemotherapy in the treatment of renal tumors
6. Be able to appropriately monitor the response to treatment of renal tumors
7. Understand the therapy of pulmonary metastases of Wilms tumor
8. Know the appropriate treatment of Wilms tumor in relation to stage and histologic subtype
9. Plan the management of a patient with recurrent Wilms tumor
10. Know the principles of management of renal tumors

 Prognosis
1. Know the prognostic features, and their associated prognoses, of renal tumors

 Complications/late effects
1. Know the complications and late effects of renal tumors and their treatment

 Rhabdomyosarcoma

 Epidemiology/predisposing factors/genetics
1. Know the cytogenetic and molecular genetic abnormalities associated with rhabdomyosarcoma

 Pathology
1. Recognize how rhabdomyosarcoma is differentiated from similar tumors by immunohistochemical tests
2. Recognize the pathologic subtypes of rhabdomyosarcoma relative to prognosis and patterns of presentation and spread

 Clinical presentation
1. Head/neck (parameningeal vs nonparameningeal)
   a. Recognize the clinical presentation of rhabdomyosarcoma affecting the head and neck (parameningeal versus nonparameningeal)
2. Orbit and nasopharynx
   a. Recognize the clinical presentation of orbital rhabdomyosarcoma
   b. Recognize the clinical presentation of nasopharyngeal rhabdomyosarcoma
3. Trunk
   a. Recognize the clinical presentation of rhabdomyosarcoma affecting the trunk
4. Genitourinary system
   a. Bladder
      1. Recognize the clinical presentation of rhabdomyosarcoma affecting the bladder
   b. Prostate gland
1. Recognize the clinical presentation of rhabdomyosarcoma affecting the prostate gland

c. Vagina
   1. Recognize the clinical presentation of vaginal rhabdomyosarcoma

5. Extremities
   a. Recognize the clinical presentation of rhabdomyosarcoma affecting the extremities

d. Diagnosis and staging
   1. Be able to appropriately utilize imaging and laboratory modalities to determine the extent and metastatic spread of rhabdomyosarcoma

e. Treatment
   1. Know the role of surgery in the treatment of rhabdomyosarcoma
   2. Know the role of irradiation in the treatment of rhabdomyosarcoma
   3. Know the role of chemotherapy in the treatment of rhabdomyosarcoma
   4. Be able to monitor appropriately the response to treatment of rhabdomyosarcoma
   5. Know the principles of management of rhabdomyosarcoma

f. Prognosis
   1. Know the prognostic features, and their associated prognoses, of rhabdomyosarcoma, including the impact of stage and histology, anatomic site of the primary tumor, and site of metastasis
   2. Know the prognostic significance of tumor recurrence in rhabdomyosarcoma

g. Complications/late effects
   1. Know the complications and late effects of rhabdomyosarcoma and its therapy

9. Soft tissue sarcomas other than rhabdomyosarcoma
   a. Epidemiology/predisposing factors/genetics
      1. Recognize the cytogenetic and molecular genetic abnormalities associated with soft tissue sarcomas other than rhabdomyosarcoma

   b. Pathology
      1. Recognize the pathologic subtypes of soft tissue sarcomas other than rhabdomyosarcoma relative to prognosis and pattern of spread

   c. Clinical presentation
      1. Recognize the clinical presentation of soft tissue sarcomas other than rhabdomyosarcoma by anatomic site

   d. Diagnosis and staging
      1. Utilize appropriate imaging modalities and laboratory studies to determine the extent and metastatic spread of soft tissue sarcomas other than rhabdomyosarcoma

   e. Treatment
      1. Know the role of surgery in the treatment of soft tissue sarcomas other than rhabdomyosarcoma
      2. Know the role of irradiation in the treatment of soft tissue sarcomas other than rhabdomyosarcoma
      3. Know the role of chemotherapy in the treatment of soft tissue sarcomas other than rhabdomyosarcoma
4. Appropriately monitor the response to treatment of soft tissue sarcomas other than rhabdomyosarcoma
5. Know the principles of management of soft-tissue sarcomas other than rhabdomyosarcoma

f. Prognosis
   1. Know the prognostic features, and their associated prognoses, of soft-tissue sarcomas other than rhabdomyosarcoma

10. Gonadal/germ cell tumors
    a. Epidemiology/predisposing factors/genetics
       1. Know the cytogenetic and molecular genetic abnormalities associated with gonadal/germ cell tumors
       2. Know the age distribution of patients with gonadal/germ cell tumors
    b. Pathology
       1. Recognize the pathologic subtypes of gonadal/germ cell tumors relative to prognosis and patterns of spread
    c. Clinical presentation
       1. Recognize the clinical presentation of gonadal/germ cell tumors by anatomic site
       2. Know the biologic markers and clinical correlates of germ cell tumors
    d. Diagnosis and staging
       1. Utilize appropriate imaging modalities and laboratory studies to determine the extent and metastatic spread of gonadal/germ cell tumors
    e. Treatment
       1. Know the role of surgery in the treatment of gonadal/germ cell tumors
       2. Know the role of radiation therapy in the treatment of gonadal/germ cell tumors
       3. Know the role of chemotherapy in the treatment of gonadal/germ cell tumors
       4. Be able to monitor appropriately the response to treatment of gonadal/germ cell tumors
       5. Know the principles of management of gonadal/germ cell tumors
    f. Prognosis
       1. Know the prognostic features, and their associated prognoses, of gonadal/germ cell tumors
       2. Know the clinical, radiologic, and prognostic features of sacrococcygeal germ cell tumors
    g. Complications/late effects
       1. Know the complications and late effects of gonadal/germ cell tumors and their treatment

I. Histiocytic disorders
   1. Epidemiology/predisposing factors/genetics
      a. Know the inheritance pattern of familial hemophagocytic lymphohistiocytosis
   2. Pathology
      a. Know the pathologic classification of childhood histiocytosis
      b. Recognize the histopathologic features of histiocytosis
3. Clinical presentation
   a. Recognize the clinical and laboratory features of Langerhans cell histiocytosis
   b. Recognize the clinical and laboratory features of sinus histiocytosis with massive lymphadenopathy
   c. Recognize the clinical and laboratory features of familial hemophagocytic lymphohistiocytosis

4. Diagnosis and staging
   a. Recognize hemophagocytosis in bone marrow
   b. Know the appropriate laboratory and imaging studies to determine the extent of Langerhans cell histiocytosis
   c. Know the appropriate laboratory and imaging studies to determine the extent of hemophagocytic lymphohistiocytosis

5. Treatment
   a. Plan appropriate management of Langerhans cell histiocytosis based on disease effects, location and extent
   b. Plan appropriate management of hemophagocytic lymphohistiocytosis

6. Prognosis
   a. Know the prognostic features, and their associated prognoses, of Langerhans cell histiocytosis
   b. Know the prognostic features, and their associated prognoses, of viral-associated hemophagocytic syndrome and familial erythrophagocytic lymphohistiocytosis
   c. Know the prognostic features, and their associated prognoses, of sinus histiocytosis

7. Complications/late effects
   a. Know the complications of Langerhans cell histiocytosis and its treatment

J. Supportive care
1. Nutrition
   a. Know the nutritional needs of patients of different ages undergoing antineoplastic therapy
   b. Understand the principles and complications of parenteral nutrition
   c. Know the role of nasogastric feeding and gastrostomy in the care of patients

2. Dental care and oral hygiene
   a. Know the importance of dental hygiene in patients receiving antineoplastic treatment and/or HSCT
   b. Know the importance of prophylactic dental treatment in patients receiving radiation therapy to the head and neck
   c. Know how to treat buccal ulceration in a patient receiving antineoplastic therapy

3. Central venous access
   a. Know the indications for and the complications of central venous catheterization
   b. Know the advantages and disadvantages of the different types of central venous access
   c. Know the indications for removing a central venous access

4. Pain control
   a. Know which factors predispose children to narcotic addiction in the management of pain
   b. Understand the principles of pain control, including pain assessment
c. Know the various analgesic and narcotic drugs and their routes of administration and side effects
d. Know the treatment for opioid overdose and the attendant risks of such treatment
e. Understand the management approach to procedural pain
5. Fatal illness and terminal care
   a. Know how to arrange for terminal home care for a child with cancer
   b. Know how to counsel family members at times of diagnosis, relapse, and terminal illness
   c. Know the effect of fatal illness and its treatment on the patient’s family members, including siblings
   d. Know the community resources available to assist the family of a child with cancer
   e. Know the principles and approach to management for a child who is approaching death as a result of terminal illness
6. Antiemetics
   a. Know the principles of management for acute and delayed therapy-induced vomiting
   b. Know how to prevent and treat side effects of a phenothiazine antiemetic
7. Schooling
   a. Know how to achieve appropriate and optimal school re-entry for patients receiving antineoplastic therapy
   b. Know how to utilize community and school-based resources in maintaining educational continuity for the child receiving antineoplastic treatment
8. Immunologic Abnormalities
   A. Infections in immunocompromised patients
      1. Prophylaxis
         a. Bacterial
            1. Indications for antimicrobials
               a. Know the role of prophylactic antibiotics in preventing bacterial infection in an immunocompromised patient
               b. Know the indications for and risks and benefits of trimethoprim with sulfamethoxazole for prophylaxis against bacterial infections in an immunocompromised patient
               c. Know the indications for and benefits of antibiotic prophylaxis for patients with anatomic or functional asplenia
         b. Fungal
            1. Know the indications and alternative topical and systemic methods of achieving antifungal prophylaxis in an immunocompromised patient
         c. Viral
            1. Rubeola
               a. Know the management of rubeola exposure in a nonimmunized immunocompromised patient
               b. Know the clinical manifestations of rubeola in immunocompromised patients
            2. Cytomegalovirus (CMV) (see also section 7.F.1)
               a. Know the association of CMV disease with reduced T-lymphocyte mediated immunity in the post-transplantation period
b. Understand the use of CMV-negative blood products in the prevention of CMV infection
c. Understand the issues surrounding leukocyte depletion by filtration of cellular blood products in prevention of CMV infection in an immunocompromised host
d. Understand that CMV disease may occur by primary infection or reactivation of latent infection, and know the effective strategies for prevention of CMV disease in patients following allogeneic marrow transplantation
e. Know the clinical manifestations of CMV disease in immunocompromised patients
f. Know the laboratory assays that confirm the presence of acute CMV infection
g. Know the modalities for CMV treatment in an immunocompromised patient

3. Herpes zoster, varicella, and herpes simplex
   a. Know the management of varicella exposure in an immunocompromised patient
   b. Understand that prophylaxis can prevent herpes simplex virus and varicella zoster virus reactivation in immunocompromised patients
   c. Understand the risk factors for herpes simplex reactivation in the immunocompromised patient

Pneumocystis jiroveci (carinii)
   1. Know the medications available for prophylaxis against \textit{P. jiroveci (carinii)} in immunosuppressed patients

2. Treatment of infection in immunocompromised patients
   a. Bacterial
      1. Types of bacteria
         a. Know the common and uncommon bacteria causing infections in the immunocompromised host
      2. Indications for antimicrobials
         a. Know the appropriate antimicrobial therapy for treatment of suspected or proven bacterial infection in an immunocompromised patient
         b. Know the evaluation and management of fever in a patient with neutropenia
   3. Complications of antimicrobials
      a. Recognize the interaction of antibiotics and chemotherapeutic agents
   b. Fungal
      1. Know the common and uncommon fungi causing infections in the immunocompromised host
      2. Know the appropriate antimicrobial therapy for treatment of suspected or proven fungal infection in an immunocompromised patient
      3. Know the indications for empiric anti-fungal therapy in the febrile, neutropenic patient
   c. Viral
      1. Know the common and uncommon viruses causing infections in the immunocompromised host
2. Know the appropriate antimicrobial therapy for treatment of suspected or proven viral infection in an immunocompromised patient
3. Know the clinical manifestations of herpes simplex infection in immunocompromised patients
4. Know the risk, presentation, and management of varicella zoster virus dissemination in the immunocompromised host who has chickenpox
d. Protozoal infections
1. Know the common and uncommon protozoans causing infections in the immunocompromised host
2. Know the appropriate antimicrobial therapy for treatment of suspected or proven protozoan infection in an immunocompromised patient
3. Know the approach to diagnosis and modalities of treatment for *P. jiroveci* (*carinii*) infection
e. Other
1. Know the indications for the use of immunoglobulin in the prevention or treatment of infections in an immunocompromised patient

B. Immunodeficiency states (congenital and acquired)
1. Congenital immune deficiencies
   a. Clinical features and inheritance patterns
      1. Know how to evaluate a child with recurrent infections for possible congenital immunodeficiency diseases
   b. Relationship between immunodeficiency and cancer
      1. Understand which immune deficiencies can lead to lymphoproliferative disease
      2. Understand which immunodeficiency states are associated with increased incidence of cancer
      3. Know the mechanisms by which immunodeficiency states can have increased risk for cancer
   c. Specific congenital immune deficiencies
      1. Wiskott-Aldrich syndrome
         a. Know the clinical manifestations, inheritance, and laboratory findings associated with Wiskott-Aldrich syndrome
         b. Know that T-lymphocyte dysfunction is associated with Wiskott-Aldrich syndrome
         c. Know the roles of splenectomy and HSCT in managing thrombocytopenia in Wiskott-Aldrich syndrome
      2. Disorders of immunoglobulin production
         a. Know that disorders of immunoglobulin production can be associated with autoimmune cytopenias such as immune thrombocytopenia and/or hemolytic anemia
      3. Severe combined immune deficiency (SCID)
         a. Recognize the hematological manifestations of various forms of SCID
         b. Know that some patients with SCID may have panhypogammaglobulinemia and increased lymphocyte counts
         c. Know the characteristics of maternal lymphocyte engraftment in SCID
         d. Appreciate the risk of transfusion-associated GVHD in SCID
      4. X-linked lymphoproliferative disease
a. Know the hematologic disorders associated with X-linked lymphoproliferative disease
b. Recognize the importance of a family history of lymphoproliferative disease, bone marrow failure, and immunodeficiency in male maternal relatives
c. Know the abnormal response of patients with X-linked lymphoproliferative disease to EBV

2. Acquired immunodeficiency syndrome (AIDS)
   a. Know the hematologic abnormalities associated with HIV infection and retroviral therapies
   b. Know the malignancies that can occur in patients with HIV infection and when to do HIV testing in children with malignancies

C. Autoimmune lymphoproliferative syndrome (ALPS)
   1. Know the lymph node pathology that occurs in ALPS and the tests used to screen for the diagnosis of ALPS
   2. Know that autoimmune cytopenias and lymphoma are associated with ALPS

7. Hematopoietic Stem Cell Transplantation (HSCT)
   A. Biologic principles
      1. Types of HSCT
         a. Know the definitions of allogeneic, syngeneic, and autologous HSCT
      2. Hematopoietic stem cells for transplantation
         a. Know from which tissues hematopoietic stem cells may be harvested
      3. HLA system
         a. Recognize the difference between class I and class II antigens
         b. Know the laboratory methods currently in use for HLA typing, the results each method provides, and their appropriate uses in evaluation of marrow transplant candidates and donors
         c. Know the inheritance pattern of human HLA antigens and how this pattern applies to selection of allogeneic marrow transplant donors
      4. Graft versus host disease (GVHD)
         a. Recognize that GVHD represents a donor response directed against major and/or minor HLA disparities in the host, causing injury to recipient tissue by donor cells such as t-cells, natural killer cells, and cytokines
      5. Graft rejection
         a. Recognize that allogeneic marrow graft rejection is mediated by residual host T-lymphocytes responding to histocompatibility differences in the donor cells
   B. Indications
      1. Know the role of HSCT for ALL in different disease stages (see also section 5.D.5.c)
      2. Know the role of HSCT in the treatment of Hodgkin lymphoma (see also section 5.G.1.e)
      3. Know the role of HSCT in the treatment of NHL (see also section 5.G.2.e)
      4. Know the possible role of HSCT in the treatment of Ewing sarcoma (see also section 5.H.1.b.)
      5. Know the possible role of HSCT in the treatment of neuroblastoma (see also section 5.H.3.e)
6. Know the possible role of HSCT in the treatment of brain tumors (see also section 5.H.5.e)

7. Recognize the possible indications for HSCT in patients with functional hematologic disorders (eg, sickle cell anemia, thalassemia, chronic granulomatous disease, leukocyte adhesion defects, Glanzmann thrombasthenia)

8. Recognize the possible indications for bone marrow transplantation in patients with metabolic storage diseases (eg, Hurler syndrome)

9. Recognize the possible indications for HSCT in patients with immunodeficiencies (eg, SCIDS)

10. Recognize the possible indications for HSCT in patients with bone marrow failure (eg, aplastic anemia, Diamond-Blackfan syndrome, Kostmann syndrome, amegakaryocytic thrombocytopenia)

11. Know the indications for HSCT in ANLL (see also section 5.E.4)

12. Know the possible role of HSCT in the treatment of Wilms tumor

13. Understand the rationale for HSCT in patients with genetic disorders

14. Know the indications for HSCT in the treatment of other hematologic malignancies such as chronic myelogenous leukemia, JML, and hemophagocytic lymphohistiocytosis

15. Recognize donor or recipient conditions that may preclude HSCT

C. Methods

1. Donor selection
   a. Judge the suitability of a donor-recipient match, given the major and minor HLA class I and II typing
   b. Understand the advantages and disadvantages of allogeneic HSCT as compared with autologous HSCT in various disorders
   c. Know the potential indications for the use of peripheral blood stem cells
   d. Recognize pertinent factors besides HLA typing that should be considered in selection of allogeneic HSCT donors
   e. Understand the advantages and disadvantages of the various available hematopoietic stem cell sources with regard to degree of match, engraftment, and incidence of GVHD
   f. Understand the components of an HSCT donor evaluation
   g. Understand the relative advantages and disadvantages of stem cell source, comparing peripheral blood vs bone marrow vs cord blood

2. Preparative therapy
   a. Recognize the need to adjust preparative regimens for patients with DNA repair defects like Fanconi anemia or dyskeratosis congenita
   b. Understand the rationale for preparative therapy in HSCT for different clinical indications and using different donor types
   c. Understand that preparative therapy may not be necessary in some patients with SCID
   d. Understand the role of submyeloablative therapy in HSCT
   e. Recognize appropriate preparative regimens for common HSCT indicators such as acute leukemia, recurrent lymphoma, or neuroblastoma

3. Hematopoietic stem cell collection
   a. Peripheral blood stem cells
1. Understand the methods of collecting and preserving peripheral blood stem cells
2. Understand the methods available to mobilize peripheral blood stem cells
   b. Umbilical cord stem cells
      1. Understand collection and storage methods of umbilical cord stem cells
c. Stem cell dose
   1. Understand the importance of CD34 quantification on HSCT product preparation and selection
   2. Recognize the appropriate stem cell dose for HSCT
   3. Understand the relationship between cell dose and engraftment
4. Marrow processing
   a. T cell
      1. Understand the risks and benefits of lymphocyte depletion for GVHD prophylaxis
      2. Recognize the methods by which T-lymphocytes can be separated and/or removed from marrow or peripheral blood stem cells
   b. Tumor cell
      1. Know the methods for purging autologous marrow or peripheral blood of malignant cells (positive and negative selection)
D. Outcomes
1. Graft versus host disease
   a. Recognize the clinical and laboratory manifestations of acute GVHD
   b. Recognize the clinical and laboratory manifestations of chronic GVHD
   c. Evaluate a patient who has undergone HSCT and differentiate GVHD from other complications of HSCT
   d. Know which drugs are useful for prevention and/or treatment of GVHD after HSCT
   e. Recognize risk factors for acute GVHD following HSCT
   f. Recognize risk factors for chronic GVHD following HSCT
   g. Recognize which histocompatibility antigens are most influential in the causation of GVHD
2. Graft rejection
   a. Know the factors associated with graft rejection
3. Complications
   a. Infections
      1. Recognize the spectrum, timing, and specific organisms involved in the infectious complications that may occur following HSCT
      2. Know how post-transplant immune reconstitution influences the pattern and frequency of infection
      3. Recognize risk factors for infection following HSCT
      4. Recognize the factors that influence the rate of immune reconstitution following HSCT
      5. Know the microorganisms that cause pneumonia following HSCT
      6. Know the infectious complications and their management following autologous HSCT
      7. Know the strategies available for the prevention of infection following HSCT
b. Non-infectious complications
   1. Early onset
      a. Recognize the unique problems of patients with Fanconi anemia, and other DNA-repair defects, undergoing HSCT
      b. Know what factors increase the risk of post HSCT EBV lymphoproliferative disease
      c. Recognize the causes of interstitial pneumonitis following HSCT
      d. Recognize the signs, symptoms, and diagnostic findings of hepatic veno-occlusive disease following HSCT
      e. Recognize the risk of and factors associated with cardiac failure following HSCT
      f. Recognize the risk of and factors associated with renal dysfunction following HSCT
      g. Know the toxicities associated with hematopoietic stem cell infusion
      h. Know the clinical presentation, laboratory findings, and treatment of thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome associated with HSCT
      i. Recognize the risk of and factors associated with hepatic dysfunction following HSCT
      j. Recognize the risk of and factors associated with neurologic dysfunction following HSCT
      k. Recognize the risk of and factors associated with blood group incompatibility and hemolytic complications
   2. Late sequelae
      a. Know the risk for the development of cataracts in patients who have undergone HSCT
      b. Know the risk of infertility after HSCT
      c. Know the risk for development of endocrinopathies in patients who have undergone HSCT
      d. Know the relationship of the conditioning regimen and the complications of HSCT
      e. Recognize the risk of second malignancies following HSCT
      f. Recognize the risk of and factors associated with chronic lung disease following HSCT
   c. Other
      1. Understand how donor source and degree of match influence the frequency and type of complications after HSCT
      2. Understand the principles and methods for immune modulation to manage relapse after HSCT
   4. Survival
      a. Recognize relapse potential following HSCT for leukemias
      b. Recognize the factors influencing post-transplant survival
      c. Know the anticipated outcome and disease-free survival for HSCT based on donor, source of hematopoietic stem cells, and primary diagnosis
      d. Recognize how donor, stem cell source, recipient disease, and disease status influence mortality after HSCT
8. Core Knowledge in Scholarly Activities
   A. Principles of use of biostatistics in research
      1. Types of variables
         a. Distinguish types of variables (eg, continuous, categorical, ordinal, nominal)
         b. Understand how the type of variable (eg, continuous, categorical, nominal) affects the choice of statistical test
      2. Distribution of data
         a. Understand how distribution of data affects the choice of statistical test
         b. Differentiate normal from skewed distribution of data
         c. Understand the appropriate use of the mean, median, and mode
         d. Understand the appropriate use of standard deviation
         e. Understand the appropriate use of standard error of the mean
      3. Hypothesis testing
         a. Distinguish the null hypothesis from an alternative hypothesis
         b. Interpret the results of hypothesis testing
      4. Statistical tests
         a. Understand when to use and how to interpret the chi square test
         b. Understand when to use and how to interpret tests comparing continuous variables between two groups (eg, t test, Mann Whitney U)
         c. Understand when to use and how to interpret tests comparing continuous variables between three or more groups (eg, ANOVA, Kruskal-Wallis)
         d. Understand when to use paired tests
         e. Understand the appropriate use of parametric versus nonparametric tests
         f. Interpret a p value
         g. Interpret a p value when multiple comparisons have been made
         h. Interpret a confidence interval
         i. Identify a type I error
         j. Identify a type II error
      5. Measurement of association and effect
         a. Understand how to interpret relative risk and absolute risk
         b. Understand how to interpret odds ratio
         c. Understand how to interpret number needed to treat or harm
         d. Understand how to interpret hazard ratio
         e. Understand when to use and how to interpret correlation coefficient
      6. Regression
         a. Understand when to use and how to interpret regression analysis (eg, linear, logistic)
         b. Understand when to use and how to interpret survival analysis (eg, Kaplan Meier)
      7. Diagnostic tests
         a. Recognize the importance of an independent “gold standard” in evaluating a diagnostic test
         b. Interpret sensitivity and specificity
         c. Interpret positive and negative predictive values
         d. Understand how disease prevalence affects the positive and negative predictive value of a test
         e. Interpret a receiver operating characteristic curve
8. Systematic reviews and meta-analysis
   a. Understand the purpose of a systematic review
   b. Understand the advantages of adding a meta-analysis to a systematic review
   c. Interpret the results of a meta-analysis

B. Principles of epidemiology and clinical research design
1. Assessment of study design, performance and analysis (internal validity)
   a. Recognize and understand the strengths and limitations of a cohort study, case
      control study, and randomized controlled clinical trial
   b. Recognize the use and limitations of surrogate endpoints
   c. Understand the use of intent-to-treat analysis
   d. Understand how sample size affects the power of a study
2. Assessment of generalizability (external validity)
   a. Understand how nonrepresentative samples can bias results
   b. Assess how the data source (eg, diaries, billing data, discharge diagnostic code)
      may affect study results
3. Bias and confounding
   a. Identify common strategies in study design to avoid or reduce bias
   b. Identify common strategies in study design to avoid or reduce confounding
4. Causation
   a. Understand the difference between association and causation
5. Incidence and prevalence
   a. Distinguish disease incidence from disease prevalence
6. Screening
   a. Understand factors that affect the rationale for screening for a condition or disease
      (eg, prevalence, test accuracy, risk benefit, disease burden, presence of a
      presymptomatic state)
7. Cost benefit, cost effectiveness, and outcomes
   a. Interpret cost-effectiveness ratios
   b. Distinguish costs from charges
   c. Understand quality-adjusted life years
8. Measurement
   a. Understand the types of validity that relate to measurement (eg, face, construct,
      criterion, predictive, content)
   b. Distinguish accuracy from precision
   c. Understand when to use and how to interpret a kappa coefficient

C. Ethics in research
1. Professionalism and misconduct in research
   a. Identify and manage potential conflicts of interest in the funding, design, and/or
      execution of a research study
   b. Identify various forms of research misconduct (eg, plagiarism, fabrication,
      falsification)
   c. Know how, and to whom, to report concerns of research misconduct
2. Principles of research with human subjects
   a. Understand and contrast the functions of an Institutional Review Board and a Data
      Safety Monitoring Board
b. Recognize the types of protections in designing research that might be afforded to children and other vulnerable populations

c. Understand the federal regulatory definitions regarding which activities are considered research and what constitutes human subjects research

d. Understand the federal regulatory definition of minimal risk and apply this to research involving children

e. Understand the ethical considerations of study design (e.g., placebo, harm of intervention, deception, flawed design)

3. Principles of consent and assent
   a. Understand what constitutes informed consent in research
   b. Distinguish between consent and assent in research involving children

D. Quality improvement
   1. Design of a Project
      a. Understand various models of quality improvement and recognize that all utilize a data-informed, iterative process using tests of change to achieve a stated aim
      b. Understand that the aim of any quality improvement project should be specific, measurable, achievable, realistic, and time-limited
      c. Understand strategies to optimize identification of key drivers and interventions to achieve a specific aim
      d. Understand tools to facilitate completion of quality improvement work, including key driver diagrams and process maps
      e. Understand each phase of a Plan-Do-Study-Act (PDSA) cycle

   2. Data and measurement
      a. Differentiate between process, outcome, and balancing measures
      b. Interpret a run chart and identify shifts, trends, and outliers in data
      c. Differentiate between a run chart and a control chart
      d. Differentiate between common cause and special cause variation