

# CONTENT OUTLINE

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## Pediatric Hematology-Oncology

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**Maintenance of Certification Examination**

**Effective January 2014**

## **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.

**EXAM PERCENTAGES LIST**  
**Modules and Total Examination**  
**Effective January 2014**

**Form 1: General Exam with no specific focus area (Core Module followed by Hematology-Oncology Module)<sup>1</sup>**

	Core Module <sup>2</sup>	Hematology-Oncology Module	General exam with NO Focus Area <sup>1</sup>
I. Erythrocytes, Hemoglobin, Iron Metabolism	8%	11%	19%
II. Leukocytes	2%	3%	5%
III. Hemostasis	7%	11%	18%
IV. Pediatric Transfusion Medicine	5%	--	5%
V. Pediatric Oncology	16%	19%	35%
VI. Immunologic abnormalities	2%	2%	4%
VII. Hematopoietic Stem Cell Transplantation	3%	4%	7%
VIII. Core Knowledge in Scholarly Activities	<u>7%</u>	<u>--</u>	<u>7%</u>
	50%	50%	<b>100%</b>

**Form 2: Exam with Hematology Focus (Core Module followed by Hematology Module)**

	Core Module <sup>2</sup>	Hematology Module	Exam with HEMATOLOGY Focus
I. Erythrocytes, Hemoglobin, Iron Metabolism	8%	22%	30%
II. Leukocytes	2%	5%	7%
III. Hemostasis	7%	20%	27%
IV. Pediatric Transfusion Medicine	5%	--	5%
V. Pediatric Oncology	16%	--	16%
VI. Immunologic abnormalities	2%	2%	4%
VII. Hematopoietic Stem Cell Transplantation	3%	1%	4%
VIII. Core Knowledge in Scholarly Activities	<u>7%</u>	<u>--</u>	<u>7%</u>
	50%	50%	<b>100%</b>

**Form 3: Exam with Oncology Focus (Core Module followed by Oncology Module)**

	Core Module <sup>2</sup>	Oncology Module	Exam with ONCOLOGY Focus
I. Erythrocytes, Hemoglobin, Iron Metabolism	8%	--	8%
II. Leukocytes	2%	--	2%
III. Hemostasis	7%	--	7%
IV. Pediatric Transfusion Medicine	5%	--	5%
V. Pediatric Oncology	16%	44%	60%
VI. Immunologic abnormalities	2%	2%	4%
VII. Hematopoietic Stem Cell Transplantation	3%	4%	7%
VIII. Core Knowledge in Scholarly Activities	<u>7%</u>	<u>--</u>	<u>7%</u>
	50%	50%	<b>100%</b>

<sup>1</sup> equivalent to forms used in the past

<sup>2</sup> identical for all examination forms

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# **I. Erythrocytes, Hemoglobin, Iron Metabolism**

## **A. The normal erythron**

### **1. The mature erythrocytes**

#### **a. Structural features**

Know the size, shape, and indices of normal erythrocytes

#### **b. Membrane**

Understand the role of the cytoskeleton in maintaining cell shape

Know the determinants affecting osmotic fragility

#### **c. Hemoglobin (hgb) structure and function**

Understand the physiologic mechanisms affecting blood oxygen affinity

Differentiate hgb A from hgb F with respect to oxygen affinity and alkali resistance

Understand the basis for the altered oxygen affinity of hgb F

#### **d. Energy metabolism**

### **2. Erythropoiesis**

#### **a. Stages of erythroid maturation**

Recognize the morphologic features of erythroid precursors

Know the sites of fetal and post-natal erythropoietin production

#### **b. Regulation of erythrocyte production**

Understand the relationship between erythropoietin production, tissue oxygenation, and anemia

### **(1). Iron and normal iron metabolism**

#### **(a). Iron absorption**

Identify the foods that are good sources of iron

Understand the factors that affect iron absorption

Know how iron absorption from human milk differs from that in cow milk

**(b). Cellular metabolism of iron**

Understand the site of iron absorption and the regulation of iron absorption, transport, and storage

**(c). Developmental aspects**

Know the determinants of body iron at birth

**(2). Folate, vitamin B12**

Know the dietary sources of folate and vitamin B12

Know the site of intestinal absorption of folic acid and B12

**3. Erythrocyte destruction**

**a. Life span of erythrocytes; erythrokinetics**

Be familiar with the differences in the normal erythrocyte survival of infants and older children

**b. Mechanisms of erythrocyte destruction**

Know the laboratory basis for differentiating intravascular from extravascular erythrocyte destruction

**c. Hemoglobin catabolism**

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**

Know the globin chain composition of embryonic, fetal, and adult hgbs

Know the relative concentrations of embryonic, fetal, and adult hgbs in a newborn infant and variations in pathologic states

**b. Distinctive features of the neonatal erythrocyte**

Know the characteristics that differentiate the erythrocytes of newborn infants from those of adults

**c. Postnatal changes in erythropoiesis**

Know the changes that occur during the postnatal period in hemoglobin concentration, reticulocytes, and bone marrow erythroblasts

**d. The anemia of prematurity**

Understand the pathophysiologic basis for the anemia of prematurity

Understand the variable treatment modalities for the anemia of prematurity

## **B. Anemias**

### **1. General principles**

#### **a. Definitions and recognition of anemia**

Define normal ranges of hgb concentrations and erythrocyte indices at birth and throughout childhood and adolescence

#### **b. Classification of anemia: morphologic, kinetic**

Correlate erythrocyte morphology with clinical syndromes

Know the origin of various erythroid inclusions seen on blood smears

Know how to classify anemias according to altered erythrocyte production, increased erythrocyte destruction, and blood loss

Understand and interpret results of reticulocyte counts

Know that classification of anemias based on cell size is also age-dependent

Know the differential diagnosis of macrocytic anemia

Know the differential diagnosis of microcytic anemia

Know the differential diagnosis of normocytic anemia

#### **c. Physiologic adaptations to anemia**

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**

Recognize the syndrome of milk-induced gastrointestinal bleeding and understand its laboratory evaluation

Recognize the clinical and laboratory manifestations of pulmonary hemosiderosis and know the appropriate diagnostic approach

Recognize the factors in medical history that predispose pediatric patients to iron deficiency

Recognize the association between occult blood loss and iron deficiency anemia

**(2). Clinical and laboratory features**

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

Know the order of appearance of laboratory abnormalities as iron deficiency develops

Know the association of pica and iron deficiency

Know the effects on growth and development of iron deficiency

**(3). Diagnosis**

Know the laboratory studies that differentiate the anemia of lead poisoning from that of iron deficiency

Understand the laboratory studies that distinguish iron deficiency anemia from other causes of microcytic anemia

**(4). Treatment**

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

**(5). Prevention**

Know the indications for and types of iron supplementation

**b. Iron overload**

**(1). Consequences**

Understand the relationship between chronic iron overload and clinical organ dysfunction (ie, cardiac, endocrine, liver, pancreas)

**(2). Diagnosis**

Be able to estimate the amount of iron in a volume of erythrocytes

Understand laboratory tests and other studies, including imaging techniques, used to diagnose and monitor iron overload

Know the genetics and appropriate biochemical and molecular testing for hereditary hemochromatosis

**(3). Treatment**

Know the principles for prevention and treatment, including treatment regimens



(eg, phlebotomy, iron chelators, erythrocytapheresis) of transfusional iron overload and hereditary hemochromatosis

Know the toxicity of iron chelators and appropriate monitoring of therapy

**c. Lead intoxication**

Recognize the hematologic features of lead poisoning

**3. Anemia of chronic disease and secondary anemias**

Recognize the clinical and laboratory findings in the anemia associated with chronic disease and how this differs from iron deficiency

Recognize the effect of acute infection on hgb concentration

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

Know the characteristics of anemia associated with hypothyroidism

Know the mechanism of production of abnormal erythrocytes in liver disease

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

Understand the pathogenesis of anemia of chronic disease

**4. Anemias due to bone marrow failure**

**a. Acquired aplastic anemia (See also VII.B.)**

Recognize viral infections, drugs, toxins, megaloblastic anemias, and autoimmune diseases as causes of acquired aplastic anemia

Understand the rationale for use and toxicity of immune modulation in the treatment of acquired aplastic anemia

Know the indications for HSCT in acquired aplastic anemia

Understand the relationship between aplastic anemia, paroxysmal nocturnal hemoglobinuria, and malignant transformation

Know the typical hematologic findings at presentation in patients with aplastic anemia

**b. Fanconi anemia**

Know the clinical and molecular features, laboratory findings, and chromosomal abnormalities in Fanconi anemia

Recognize the association between Fanconi anemia and acute leukemia and other malignancies

Know the complications of androgen therapy, including peliosis hepatis, adenoma, and carcinoma, in Fanconi anemia

Know the therapeutic options for Fanconi anemia, and their effectiveness

**c. Diamond-Blackfan syndrome**

Recognize the clinical, molecular, and laboratory manifestations of Diamond-Blackfan syndrome

Know the clinical and laboratory parameters that differentiate transient erythroblastopenia of childhood from Diamond-Blackfan syndrome

Know the clinical and laboratory features that distinguish an aplastic crisis of a hemolytic anemia from transient erythroblastopenia of childhood and Diamond-Blackfan syndrome

Know the various treatment modalities and their effectiveness in Diamond-Blackfan syndrome

**d. Transient erythroblastopenia of childhood**

Recognize the clinical syndrome of transient erythroblastopenia of childhood and know how to treat it appropriately

**e. Dyskeratosis congenita**

Know the clinical presentation, molecular biology, genetics, laboratory findings, and therapy in a patient with dyskeratosis congenita

**f. Pearson syndrome**

Know the clinical and laboratory features and underlying defects of Pearson syndrome

**5. Hereditary hemolytic anemias**

Know that Rh null phenotype is associated with a hereditary hemolytic anemia

Know the relationship between parvovirus infection and aplastic crisis in congenital hemolytic anemias

Recognize the role of folate supplementation in patients with hemolytic anemia

**a. Inherited disorders of the erythrocyte membrane**

**(1). Hereditary spherocytosis**

**(a). Genetics**

Recognize the differences in the phenotypes of the autosomal dominant and autosomal recessive variants of hereditary spherocytosis

**(b). Pathophysiology**

Know the cytoskeletal defects associated with hereditary spherocytosis

**(c). Evaluation**

Understand the clinical and laboratory diagnosis of hereditary spherocytosis

Know the basis for and pattern of abnormal osmotic fragility in hereditary spherocytosis

Distinguish between hereditary spherocytosis and autoimmune hemolytic anemia

**(d). Management**

Know the rationale for and hematologic sequelae of splenectomy in hereditary spherocytosis

**(e). Complications**

Understand the complications seen in hereditary spherocytosis before and after splenectomy

**(2). Hereditary elliptocytosis and pyropoikilocytosis**

**(a). Genetics**

Know the mode of inheritance of hereditary elliptocytosis and pyropoikilocytosis

**(b). Pathophysiology**

Know the cytoskeletal defects associated with hereditary elliptocytosis and hereditary pyropoikilocytosis

**(c). Clinical features**

Recognize hemolytic and non-hemolytic variants of hereditary elliptocytosis

Know the clinical features of elliptocytosis and pyropoikilocytosis and the clinical problems of distinguishing them in the neonatal period

**(d). Laboratory evaluation**

Recognize the morphologic characteristics and other laboratory features of hereditary elliptocytosis and hereditary pyropoikilocytosis

**(e). Management**

Know the effects of splenectomy on hereditary elliptocytosis and pyropoikilocytosis

**(3). Acanthocytosis**

**(a). Clinical features**

Recognize the clinical and laboratory features associated with the inherited and acquired conditions characterized by acanthocytosis

**(4). Other membrane disorders**

**(a). Clinical and laboratory features**

Recognize the patterns of inheritance and the clinical and laboratory features of other membrane disorders such as stomatocytosis, xerocytosis, pyknocytosis, ovalocytosis, and Wilson disease

**b. Inherited disorders of anaerobic glycolysis**

**(1). Pyruvate kinase deficiency**

**(a). Genetics**

Know the inheritance pattern of pyruvate kinase deficiency

**(b). Cellular physiology**

Recognize how pyruvate kinase deficiency may lead to impaired erythrocyte metabolism

**(c). Clinical and laboratory features**

Recognize the clinical and laboratory manifestations of pyruvate kinase deficiency

**(d). Management**

Know the effects of splenectomy on pyruvate kinase deficiency

**(e). Complications**

Know that hemolysis and gallstone production may persist following splenectomy

**(2). Triose phosphate isomerase deficiency**

**(a). Clinical features**

Know the relationship between erythrocyte triose phosphate isomerase deficiency and neuromuscular disease

**(3). Other enzyme deficiencies**

**(a). Genetics**

Know that phosphoglycerate kinase (pgk) deficiency is an X-linked disorder, while other glycolytic disorders are autosomal recessive

**(b). Laboratory evaluation**

Know the association of pyrimidine-5'-nucleotidase deficiency with basophilic stippling

**c. Inherited disorders of the pentose phosphate pathway**

**(1). Glucose-6-phosphate dehydrogenase deficiency**

**(a). Genetics**

Recognize that G6PD deficiency is X-linked

**(b). Cellular physiology**

Understand the pathophysiology whereby oxidant damage causes hemolysis in G6PD deficiency

**(c). Clinical features**

Know the association of favism with the Mediterranean and Chinese forms of G6PD deficiency

Know the association of intermittent jaundice with G6PD deficiency

Recognize the clinical and laboratory differences between the major G6PD variants (eg, A-Mediterranean)

Recognize the etiologic role of infection and drugs in hemolytic episodes associated with G6PD deficiency

**(d). Laboratory evaluation**

Recognize the difficulty in making diagnosis in A-variant G6PD deficiency during an acute hemolytic episode

Recognize the erythrocyte morphologic abnormalities during an episode of hemolysis in G6PD-deficient individuals

**d. Structural disorders of hgb synthesis**

**(1). Hgb S and the sickling syndromes**

**(a). Genetics**

Know the genetic basis for the sickling syndromes

**(b). Molecular and pathophysiological mechanisms**

Understand the pathophysiology of the sickling phenomenon

Know the characteristics and clinical correlates of irreversibly sickled cells

Understand how polymerization of hgbs is influenced by other hgbs (hgb F, A, etc)

Understand the molecular abnormalities in sickle cell syndromes

**(c). Clinical features**

Recognize the clinical characteristics of sickle-thalassemia syndromes

Know the various clinical manifestations of sickle hemoglobinopathies, including sickle cell trait

Recognize the splenic sequestration syndrome in sickle cell disease

Know the central nervous system complications of sickle cell disease

Know the long-term complications that may occur in patients with hemoglobinopathies (S/S, S/C)

Know the life expectancy in patients who have sickle cell syndromes, including sickle cell trait

Recognize aplastic crisis in sickle cell anemia

Recognize acute chest syndrome in sickle cell anemia

Recognize renal sequelae of sickle cell anemia

**(d). Laboratory evaluation**

Recognize the laboratory manifestations of sickle cell disease

Understand the utility and limits of various methodologies used to establish the diagnosis of sickle cell syndromes

Understand the way in which DNA analysis can assist in the diagnosis of sickle hemoglobinopathies

Know how to differentiate the homozygous state for hgb S from doubly heterozygous hgb S/hereditary persistence of fetal hemoglobin

Recognize differences in the hemoglobin electrophoretic patterns of sickle cell trait and Hgb S/Beta + thalassemia

**(e). Management**

Understand the risk of infection in sickle cell disease and know the appropriate preventive strategies

Understand the proper therapeutic approach to infection in patients with sickle cell disease

Know the appropriate treatment for a patient with sickle cell disease who has a stroke

Know how to manage acute chest syndrome

Know how to manage acute pain crisis in a patient with sickle cell disease

Know the indications for and how to plan a transfusion program for a patient with sickle cell disease

Know the rationale for using hydroxyurea as a treatment for a patient with sickle cell disease

Understand the risk of stroke in sickle cell disease and know the appropriate screening and management strategies

Know how to manage priapism

Know how to manage aplastic crisis

Know how to manage acute sequestration crisis

Distinguish the relative advantages and disadvantages of stem cell transplantation and other therapy for sickle cell anemia

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**

Understand the relative frequency of hgb SC disease compared to other sickling syndromes

Understand the inheritance pattern of patients with hgb SC disease

**(b). Molecular mechanisms**

Know the chemical and physical differences between hgb C and hgb S

**(c). Clinical features**

Know the relationship between hgb SC disease and retinopathy

Recognize splenomegaly and spleen infarction as common features in hgb SC disease in older children

Recognize that aseptic necrosis of the femoral head is a common problem in hgb SC disease

Know the clinical and laboratory manifestations of hgb C disease

**(3). Hgb E**

**(a). Pathologic and clinical features**

Know the inheritance and clinical features of the hgb E syndromes

Understand the proper management of various hgb E syndromes

**(b). Laboratory evaluation**

Know the laboratory characteristics of each of the hgb E syndromes (hgb AE, hgb EE, and hgb E-beta thalassemia)

**(4). Unstable hgbs**

**(a). Genetics**

Understand the inheritance pattern associated with unstable hgbs

**(b). Molecular mechanisms**

Understand the molecular and structural abnormalities that lead to hgb instability

**(c). Clinical features**

Recognize the association of accelerated hemolysis with intercurrent infection or drug exposure in a patient with unstable hemoglobinopathy

**(d). Laboratory evaluation**

Know the laboratory approach to the diagnosis of unstable hgb disease

**(e). Management**

Know the proper management of patients with unstable hgbs

**(5). Low-affinity hgbs**

Know the relationship of low-oxygen affinity hgb with cyanosis

**e. Quantitative disorders of hgb synthesis**



**(1). Genetic mechanisms and molecular pathology**

Identify the molecular abnormalities associated with the various types of thalassemia syndromes, including alpha, beta, and delta-beta thalassemia, hgb E, and hgb Lepore

Understand the pathophysiology of anemia in disorders of globin chain synthesis

**(a). Alpha-thalassemia**

Know the differences in the inheritance of abnormal alpha genes between blacks and Asians with alpha-thalassemia

**(b). Beta- and delta-beta-thalassemia**

Understand the basis for differences in hgb F concentrations in delta-beta-thalassemia and hereditary persistence of fetal hgb

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**

Know the hematologic and hgb electrophoretic manifestations of alpha-thalassemia minor

Identify and quantitate the major hgb fractions in alpha-thalassemia disorders at birth and in later life

Know the clinical and laboratory features of the alpha-thalassemia syndromes, including hgb H and hydrops fetalis

Know the association of hgb Constant Spring with an alpha-thalassemia-like syndrome

Know the relationship between genotype and phenotype in alpha thalassemia syndromes

**(b). Beta- and delta-beta-thalassemia**

Recognize the contribution of ineffective erythropoiesis to the pathophysiology of thalassemia

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

Know the clinical and laboratory features of delta-beta-thalassemia

Know how alpha-thalassemia modifies the clinical characteristics of

beta-thalassemia and hgb E-beta-thalassemia

Understand that iron overload develops in patients with beta- thalassemia because of gut hyperabsorption of iron

**(c). Hereditary persistence of fetal hgb**

Know the clinical and laboratory features associated with hereditary persistence of fetal hgb

**(d). Gamma-thalassemia**

Know the transient neonatal hemolytic disorders associated with gamma-thalassemia syndromes

**(e). Beta-thalassemia/structural hgb variants**

Know the clinical and laboratory features of homozygous hgb E and hgb E-beta-thalassemia

**(3). Diagnosis**

Know the indications for and limitations of prenatal diagnosis using chorionic villus sampling

**(a). Hereditary persistence of fetal hgb**

Know the characteristics which differentiate thalassemia from hereditary persistence of hgb F

**(4). Treatment**

Recognize when splenectomy is indicated in thalassemia major

Know the indications for and management of chronic transfusion therapy for thalassemia syndromes

Understand the principles of iron chelation therapy and when to initiate it in a patient with a thalassemia syndrome

Know the beneficial effects and toxicity of ascorbic acid when given to iron-overloaded patients with thalassemia

Distinguish the relative advantages and disadvantages of stem cell transplantation and conventional therapy for thalassemia major

Understand the proper management of thalassemia intermedia

Know the value of different laboratory and imaging studies in the assessment of iron overload

Know the pharmacology of deferoxamine and how this influences drug

administration

Know the adverse side effects of deferoxamine (hearing loss, vision changes, growth retardation)

Know the pharmacology of the oral iron chelator deferasirox

Know the adverse side effects of deferasirox

## **6. Acquired hemolytic anemias**

### **a. Alloimmune hemolytic anemia; erythroblastosis fetalis**

#### **(1). Pathophysiology**

Understand the effect of a major blood group incompatibility on Rh sensitization

Know the erythrocyte antigens that most frequently cause erythroblastosis fetalis

#### **(2). Clinical and laboratory features**

Recognize the clinical features of erythroblastosis fetalis

Know that transient conjugated hyperbilirubinemia may occur as a complication of severe isoimmune hemolytic disease

#### **(3). Diagnosis**

Know the diagnostic criteria for ABO incompatibility

Know the relative predictive value of tests of Rh sensitization

Differentiate fetomaternal minor blood group incompatibility from other causes of jaundice in the neonate

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

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

#### **(4). Treatment**

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

Know the indications for exchange transfusion

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

#### **(5). Prevention**

Know the indications for the use of anti-D

**b. Autoimmune hemolytic anemia**

**(1). Pathophysiology**

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

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

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

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

**(2). Warm-antibody hemolytic disease**

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

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

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

Plan the therapy for autoimmune hemolytic anemia

**(3). Cold agglutinin disease**

Know the antigen specificity of cold-reactive antibodies

Recognize the infections that are associated with cold-reactive antibodies

Know the principles of therapy for cold agglutinin disease

**(4). Paroxysmal cold hemoglobinuria**

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

Know the characteristics of the Donath- Landsteiner antibody

**(5). Drug-induced immune hemolytic anemia**

Know the mechanism of hematologic toxicity of offending drugs

Recognize the examples of drug-induced immune hemolysis

**c. Anemia due to infection, chemical, physical agents**

Recognize intravascular hemolysis as a complication of recluse spider bites

Know that thermal burns and envenomization may be complicated by acquired spherocytic anemia

**d. Erythrocyte fragmentation syndromes**

Recognize the pathogenic mechanisms and the clinical and laboratory features of the erythrocyte fragmentation syndromes

**e. Paroxysmal nocturnal hemoglobinuria**

Recognize the laboratory and clinical manifestations of paroxysmal nocturnal hemoglobinuria

Know the association of paroxysmal nocturnal hemoglobinuria with thrombosis

Understand the molecular and pathophysiologic basis for paroxysmal nocturnal hemoglobinuria

**7. Megaloblastic anemias**

**a. Vitamin B12 deficiency**

**(1). Pathophysiology**

Recognize anemia due to vitamin B12 deficiency in a breast-fed infant with a vegan mother or a mother with B12 deficiency

Recognize the genetically determined disorders of vitamin B12 malabsorption

Know the association of small bowel bacterial overgrowth or surgery and megaloblastic anemia

**(2). Clinical and laboratory features**

Know the clinical and laboratory features of pernicious anemia

Know the association of pernicious anemia with other autoimmune phenomena

Know the clinical and laboratory features of the Imerslund-Graesbeck syndrome

Know the ages at which different disorders of vitamin B12 metabolism are first manifested

Know the morphology of peripheral blood smears and examinations of the bone marrow in megaloblastic anemia

**(3). Diagnosis**

Know the indications for the Schilling test and how to interpret results of the test

**(4). Treatment**

Understand the principles of treatment for the vitamin B12 deficiency syndromes

Know the potential of folic acid to correct megaloblastic anemia but not the neuropathy of pernicious anemia

**b. Folate deficiency**

**(1). Pathophysiology**

Understand the biochemical pathway of tetrahydrofolate metabolism that is associated with megaloblastosis

Recognize the association of folic acid deficiency with anticonvulsant therapy

Know that megaloblastic anemia associated with goat milk ingestion is due to folic acid deficiency

Know that folate deficiency may be associated with chronic hemolytic disorders

**(2). Clinical and laboratory features**

Understand the progression of laboratory abnormalities in folate deficiency

Recognize the clinical and laboratory characteristics of dietary folate deficiency

**(3). Diagnosis**

Know the limitations of measuring serum folate concentrations in the diagnosis of folate deficiency

**(4). Treatment**

**c. Other causes of megaloblastosis**

Recognize disorders other than folate or B12 deficiency causing megaloblastosis

**8. Blood loss anemia**

**a. Fetomaternal hemorrhage**

Recognize the clinical and laboratory characteristics of fetomaternal hemorrhage

**b. Blood loss in the infant and child**

Recognize the clinical signs of acute hypovolemia secondary to blood loss and differentiate them from hemolytic anemia

Recognize the need for iron therapy in hemolytic anemias associated with intravascular hemolysis

**9. Congenital dyserythropoietic anemias**

Recognize the clinical and laboratory manifestations of congenital dyserythropoietic anemia

Know the association of dyserythropoietic anemia type II with multinucleated erythroblasts

**10. Congenital sideroblastic anemia**

Know the clinical and laboratory manifestations of congenital sideroblastic anemia

**C. Other disorders affecting erythrocytes**

**1. Erythrocytosis**

Know the laboratory parameters associated with conditions characterized by an increased hgb concentration

Correlate laboratory parameters (Hct, MCV, reticulocyte count) with clinical situations associated with erythrocytosis

**a. Maternal-fetal and fetal-fetal transfusions**

Know how to document a maternal-fetal hemorrhage or twin-twin transfusion causing erythrocytosis

Recognize erythrocytosis as a feature of the twin transfusion syndrome

**b. High oxygen affinity hemoglobins**

Know the relationship of high oxygen-affinity hgb with erythrocytosis

**c. Other causes of erythrocytosis**

Differentiate relative erythrocytosis from erythrocytosis due to an increase in erythrocyte mass

Know the causes of primary and secondary erythrocytosis

**2. Methemoglobinemia**

**a. Toxic methemoglobinemia**

Know the basis for the increased vulnerability of infants to methemoglobinemia

Know the mechanism for methemoglobin reduction in normal erythrocytes

Associate the treatment failure of methemoglobinemia with methylene blue and G6PD deficiency

Know that consumption of well water contaminated with nitrates causes methemoglobinemia in infants but not in older children and adults

Know the association of methemoglobinemia with diarrhea and acidosis in young infants

**b. Congenital cytochrome b5 reductase deficiency**

Know how to differentiate methemoglobinemia due to deficient methemoglobin reduction from methemoglobinemia due to increased methemoglobin production

**c. Hgb M disorders**

Recognize the clinical and laboratory findings of hgb M disease in the newborn infant

**3. Porphyrrias**

Know the differential clinical characteristics of congenital erythropoietic porphyria

**II. Leukocytes**

**A. Granulocytes**

**1. Normal granulocyte characteristics**

Know the age- and race-related normal values of granulocytes

Know the life cycle of granulocytes

Know the changes associated with systemic diseases, ie, cell numbers and morphology

Understand and know when to order various tests of neutrophil function

**2. Myelopoiesis**

**a. Stage of myeloid maturation**

Understand progenitor cell differentiation and maturation

Recognize morphologic features of myeloid precursors

**b. Cytokine stimulation**

Understand the action of cytokines on primitive myeloid progenitors and precursors and mature cells



### **3. Granules**

Recognize the different granulocytic granules and know their content and functions

Know the diseases associated with abnormalities of granule function and morphology

### **4. Biochemistry**

Understand the various stimulators of biochemical reactions in granulocytes including degranulation, oxidative burst, phagocytosis, and killing

### **5. Neutrophil kinetics**

Understand the factors that regulate granulopoiesis

### **6. Functional properties**

#### **a. Chemotaxis, motility, and ingestion**

Know the factors that mediate adherence, movement, and phagocytosis in granulocyte function

#### **b. Opsonins**

Know the different opsonins and their role in neutrophil chemotaxis, ingestion, and killing

#### **c. Degranulation**

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**

Understand the mechanisms of oxygen-dependent and oxygen-independent microbial killing by phagocyte-mediated granulocytes

### **7. Neutropenia**

#### **a. General**

Know the appropriate clinical and laboratory evaluation of childhood neutropenia

Understand and differentiate the childhood presentations of neutropenia

#### **b. Congenital neutropenia**

##### **(1). Severe congenital neutropenia (including Kostmann syndrome)**

Know the clinical presentation, molecular biology, genetics, and bone marrow findings in severe congenital neutropenia

Know the treatment options for severe congenital neutropenia

Know the natural history of severe congenital neutropenia

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**

Know the clinical presentation, molecular biology, genetics, bone marrow findings, and therapy of cyclic neutropenia

**(3). Shwachman-Diamond syndrome**

Know the clinical presentation, molecular biology, genetics, bone marrow findings, and therapy of Shwachman-Diamond syndrome

**(4). Benign congenital neutropenia**

Know the clinical presentation, genetics, laboratory findings, and therapy of benign congenital neutropenia

**(5). Myelokathexis/WHIM syndrome**

Know the clinical presentation, laboratory findings, genetics, and treatment for the myelokathexis (WHIM) syndrome

**(6). Dyskeratosis congenita (see I.B.4.e)**

**c. Acquired neutropenia**

**(1). Isoimmune and alloimmune neutropenia**

Know the presentation and pathophysiology of alloimmune neutropenia in newborn infants

Understand the role of specific antigens in alloimmune neutropenia

Know the natural history of, complications of, and therapy for alloimmune neutropenia

**(2). Autoimmune neutropenia**

Understand the use and limitations of antineutrophil antibodies in the diagnosis and treatment of autoimmune neutropenia

Know the natural history of autoimmune neutropenia in infancy

Understand the various therapeutic strategies for autoimmune neutropenia

Recognize autoimmune neutropenia as a manifestation of autoimmune disorders

Know the clinical presentation of autoimmune neutropenia

**(3). Postinfectious and infection-related neutropenia**

Know the viruses commonly associated with infection-related neutropenia

Know the bacteria commonly associated with postinfectious neutropenia

Know the natural history of infection-related neutropenia

**(4). Drug-induced neutropenia**

Know the agents commonly involved in drug-induced neutropenia

Know the mechanisms of bone marrow suppression and peripheral destruction of neutrophils

Understand the therapeutic use of cytokines in drug-induced neutropenia

**(5). Neutropenia associated with nutritional deficiency**

Recognize neutropenia as a feature of copper, B12, or folate deficiency

**(6). Neutropenia associated with immune defects**

Recognize that neutropenia is a feature of immune defects

**(7). Neutropenia associated with metabolic diseases**

Recognize neutropenia as a feature of glycogen storage disease I and other metabolic disorders

**(8). Neutropenia associated with ECMO and bypass surgery and hemodialysis**

Recognize that severe transient neutropenia is associated with ECMO, bypass surgery, and hemodialysis and understand the mechanism

**(9). Neutropenia associated with hypersplenism**

Recognize that hypersplenism can present with neutropenia

**8. Neutrophilia**

Know the effect of glucocorticoids on the absolute neutrophil count

Know the major causes of acute and chronic neutrophilia

Know the significance of neutrophilia in newborn infants

## **9. Eosinophilia**

Know the disorders associated with primary and secondary eosinophilia

Know the correlation of eosinophilia with specific parasitic infestations

Know the clinical consequences of hypereosinophilia

## **10. Basophils**

Know the disorders associated with basophilia

## **11. Defects of neutrophil function**

### **a. General**

Differentiate the granulocyte functional abnormalities associated with altered killing of microorganisms

Know the clinical features associated with various neutrophil function disorders

### **b. Chédiak-Higashi syndrome**

Associate the morphologic abnormality of neutrophil granules with the clinical presentation of Chédiak-Higashi syndrome

Know the molecular biology and genetics of Chédiak-Higashi syndrome

Know the associated clinical and laboratory findings in Chédiak-Higashi syndrome

Understand the immunologic and hemostatic deficits associated with Chédiak-Higashi syndrome

### **c. Leukocyte adhesion deficiency syndromes (LAD types I and II)**

Know the genetics, clinical presentation of, and therapy for the various forms of leukocyte adhesion deficiency syndromes

Understand the molecular basis of leukocyte adhesion deficiency syndromes

Know the appropriate laboratory evaluation of leukocyte adhesion deficiency syndromes

Know the complications of leukocyte adhesion deficiency syndromes

### **d. Chronic granulomatous disease**

Know the current approaches to the diagnosis and treatment of chronic granulomatous disease

Know the organisms that are poorly killed by the granulocytes of patients with chronic granulomatous disease

Know the clinical manifestations, molecular biology, and inheritance patterns of chronic granulomatous disease

**e. Hyperimmunoglobulinemia E syndrome**

Know the clinical manifestations of hyperimmunoglobulin E syndrome

Understand the laboratory evaluation and differential diagnosis of hyperimmunoglobulin E syndrome

**f. Myeloperoxidase deficiency**

Know the genetics, clinical presentation, and laboratory evaluation of neutrophil myeloperoxidase deficiency

**g. Hereditary/morphologic abnormalities of neutrophils**

**(1). Pelger-Huet anomaly**

Recognize the morphologic alteration of neutrophils associated with the Pelger-Huet anomaly

Recognize the conditions associated with Pelger-Huet anomaly

**(2). May-Hegglin anomaly**

Know the morphologic features that characterize the May-Hegglin anomaly

**B. Monocytes, macrophages, and antigen-processing cells**

**1. Normal monocyte characteristics**

Distinguish monocytes from lymphocytes and granulocytes based on cytochemical reactions

Know the surface markers and membrane antigens that characterize monocyte-macrophages

Know the life cycle of normal monocyte-macrophages

Understand the factors that regulate monocyte production

**2. Function and metabolism**

Understand the role of macrophages in the inflammatory response

Know the effects of cytokines on mononuclear phagocytes

**3. Monocytosis**

Know the disorders associated with monocytosis

#### **4. Storage diseases**

Know the bone marrow histology of storage disorders

Know that Gaucher disease is diagnosed using the glucocerebrosidase assay

#### **5. Dendritic cells**

Know the surface markers and membrane antigens that characterize dendritic cells

Understand the function of dendritic cells

### **C. Lymphocytes**

#### **1. Normal morphology and age-related values**

Know the normal age-related circulating blood lymphocyte values

Know the light microscopy and ultrastructure characteristics of lymphocytes and plasma cells

Know the characteristics which differentiate T lymphocytes from B lymphocytes

#### **2. Surface membrane antigens and gene rearrangements**

Know the sequence of T-cell receptor gene rearrangement and surface antigen expression during T-cell ontogeny

Know the sequence of immunoglobulin gene rearrangement and surface antigen and immunoglobulin expression during B-cell development

#### **3. Kinetics**

Know the life history of lymphocytes

#### **4. Biochemistry**

##### **a. Interleukins**

Differentiate the effect of interleukins on T cells, B cells, monocytes, and macrophages

Understand the sequence of events in the activation and replication of lymphocytes

#### **5. Function**

##### **a. B cells**

**(1). Immunoglobulins**

Know the genetics of immunoglobulin production

Know the biological properties of human immunoglobulins

Understand the mechanisms associated with the generation of antibody diversity

**b. T cells**

**(1). Receptor**

Understand the T-cell receptor/CD3 complex

Understand the function of CD4-positive and CD8-positive lymphocytes

**(2). Natural killer cells**

Know the morphology of natural killer cells

Understand the biology and function of natural killer cells and major histocompatibility complex restriction

**(3). Major histocompatibility complex**

Differentiate the functions of Class I, II, and III major histocompatibility complex proteins

Understand the process of antigen presentation

**6. Lymphocytosis**

Know the causes of lymphocytosis

**7. Lymphopenia**

Know the causes of lymphopenia

Know the relationship between skin test anergy and lymphopenia

**8. Alterations in systemic disease**

**a. Mononucleosis syndromes**

Know the etiology, pathogenesis, and clinical features of mononucleosis syndromes

Recognize the heterophil-negative mononucleosis syndromes

Know how to establish the diagnosis of infectious mononucleosis (Epstein-Barr virus infection)

Associate the morphologic abnormalities of lymphocytoses, lymphocyte number, and morphology with the clinical presentation of infectious mononucleosis

**b. Lipid storage disorders**

Recognize vacuoles in lymphocytes as a feature of lipid storage disorders

**III. Hemostasis**

**A. Platelets**

**1. Normal platelet characteristics**

**a. Normal values**

Recognize spurious thrombocytopenia

Know the limitations of electronic platelet counting

Know the normal values for platelet counts in neonates and children

Understand the value of the peripheral blood smear in estimating the platelet count

**b. Platelet production**

Know the growth factors which regulate megakaryocyte and platelet production

Know the significance of platelet size

**c. Platelet kinetics**

Know the survival of platelets in vivo under normal conditions and in different thrombocytopenic states

Know the mechanism of platelet destruction under normal conditions

Know the normal distribution of platelets between circulation and the spleen

**d. Platelet structure**

Know the overall structure of platelets, including the plasma membrane, the canalicular system, and organelles

**e. Platelet function**

Know the significance of platelet adhesion and aggregation and their overall relationship to hemostasis

Know the content and function of substances released from platelet granules

Know the relationship of platelet membrane receptors and their associated



ligands in platelet aggregation and adhesion

Know the relationship of von Willebrand factor, collagen, and their receptors in platelet adhesion

Know the structural and biochemical changes that occur during platelet activation

Know how prostaglandin metabolism in platelets and endothelial cells differentially affects platelet function

Know the role of cyclic adenosine monophosphate (cAMP) in platelet activation

**f. Laboratory assessment of platelet function**

Know how to interpret the results of platelet aggregation studies

Understand the diagnostic utility and limitations of an abnormal result of platelet function screening (PFA 100) or a prolonged bleeding time

Know the relationship between platelet age and function

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**

Know the general mechanisms and clinical presentation of thrombocytopenia in the setting of impaired production, increased destruction, and abnormal distribution

Know the clinical features of bleeding associated with thrombocytopenia as compared to those associated with coagulation factor deficiencies

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**

Know the differential diagnosis of neonatal thrombocytopenia

Know that consumptive thrombocytopenia is seen with conditions such as necrotizing enterocolitis (NEC), or respiratory distress syndrome (RDS)

**(2). Infection**

Know the incidence and course of thrombocytopenia with bacterial sepsis

Know the various congenital infections associated with neonatal thrombocytopenia

**(3). Neonatal alloimmune thrombocytopenia (NAIT)**

Know the major platelet antigens involved in neonatal alloimmune thrombocytopenia

Know the risks and benefits of different therapeutic options and risk factors associated with each option for treating bleeding in neonatal alloimmune thrombocytopenia

Know the clinical and diagnostic features of neonatal alloimmune thrombocytopenia

Know the fetal and maternal management of subsequent pregnancies after an initial child with neonatal alloimmune thrombocytopenia, and the role of paternal platelet typing

Know the influence of ethnicity on the antigens involved in neonatal alloimmune thrombocytopenia

Know the role of HLA type and other factors in maternal sensitization to platelet alloantigens

**(4). Neonatal autoimmune thrombocytopenia**

Know the risks and proper management of an infant born to a mother with immune thrombocytopenia

Know the clinical and diagnostic features of neonatal thrombocytopenia due to maternal immune thrombocytopenic purpura

Know how to evaluate and manage an infant born to a mother with systemic lupus erythematosus

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**

Know the different syndromes associated with decreased platelet production in newborn infants

Know the clinical features, inheritance patterns, treatment, and prognosis of newborn infants with thrombocytopenia-absent-radius syndrome

Know the clinical features, treatment, and prognosis of infants with amegakaryocytic thrombocytopenia

Know the association of thrombocytopenia with other dysmorphic syndromes

**(6). Neonatal thrombocytopenia due to perinatal drugs**

Know how maternal complications and perinatal drugs are associated with decreased platelets in her newborn infant

**(7). Miscellaneous causes of neonatal thrombocytopenia**

Know that neonatal thrombocytopenia may be a manifestation of occult large vessel or catheter thrombosis

Know that neonatal thrombocytopenia can occur secondary to hemangiomas or thrombosis in placental vessels or in the infant

Know that neonatal thrombocytopenia can occur with hemolytic disease of the newborn

**c. Hereditary thrombocytopenia**

Know the inborn errors of metabolism associated with neonatal thrombocytopenia

Know that neonatal thrombocytopenia can be a manifestation of certain chromosomal abnormalities

Know the genetics, clinical features, and laboratory characteristics associated with hereditary thrombocytopenia associated with macrothrombocytes or giant platelet syndromes

Know that thrombocytopenia may be the first sign of Fanconi aplastic anemia

Know the clinical features, laboratory findings, immunologic abnormalities, and prognosis in children with Wiskott-Aldrich syndrome

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)**

Know the mechanisms of platelet destruction in acute idiopathic thrombocytopenic purpura

Know the methods to measure antiplatelet antibodies

Know the clinical course, laboratory features, therapeutic options, and complications of therapy in acute idiopathic thrombocytopenic purpura

Understand the management issues and risks of splenectomy in childhood idiopathic thrombocytopenic purpura

Know the clinical course, laboratory features, and therapeutic options in chronic

idiopathic thrombocytopenic purpura

Know the indications for bone marrow examination in idiopathic thrombocytopenic purpura

**(2). Drug-induced**

Know the mechanisms of drug-induced immune thrombocytopenia

Know the treatments (eg, drugs, immunizations) associated with immune thrombocytopenia

Distinguish thrombocytopenia due to immune destruction from thrombocytopenia due to impaired platelet production

**(3). Infection-related thrombocytopenia**

Know the mechanisms of thrombocytopenia in various bacterial and viral infections

Know the viral infections that should be considered as causative factors in children with immune thrombocytopenic purpura

**(4). Thrombocytopenia associated with intravascular coagulation**

Know the presentation, etiology, laboratory findings, and clinical course of thrombocytopenia in hemolytic-uremic syndrome

Know that thrombocytopenia is usually an important feature of disseminated intravascular clotting

Know the clinical presentation, laboratory findings, course of thrombocytopenia, and therapeutic options in acquired acute thrombotic thrombocytopenic purpura (TTP)

Know the clinical presentation, laboratory findings, course of thrombocytopenia, and therapeutic options in the inherited, chronic form of thrombotic thrombocytopenic purpura (TTP)

Know the pathophysiology of thrombotic thrombocytopenic purpura (TTP)

Know the functions of the von Willebrand cleaving protease (ADAMTS13)

**(5). Thrombocytopenia due to impaired platelet production**

Know that thrombocytopenia is a manifestation of aplastic anemia or bone marrow infiltrative disorders

**(6). Thrombocytopenia due to increased platelet turnover/sequestration**

Know the evaluation and management of thrombocytopenia due to hemangioma,

Kasabach-Merritt syndrome

**(7). Thrombocytopenia due to nutritional deficiencies**

Know that thrombocytopenia occurs in severe iron, folate, and vitamin B12 deficiencies

**(8). Thrombocytopenia associated with cardiovascular disorders**

Know that cyanotic heart disease may be associated with thrombocytopenia and/or a functional platelet disorder

**(9). Thrombocytopenia associated with splenomegaly**

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**

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

**(11). Post-transfusion purpura**

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

**(12). Thrombocytopenia associated with ECMO**

Recognize and know the mechanism of thrombocytopenia associated with extracorporeal circulation

**3. Thrombocytosis**

Know the disorders associated with reactive thrombocytosis

Know how to differentiate primary thrombocythemia from reactive thrombocytosis

Know the conditions under which thrombocytosis may be associated with thrombotic complications or hemorrhage

Know how to treat patients with thrombocytosis who have a propensity for thrombosis

Know that thrombocytosis is a sign of asplenia

**4. Abnormalities of platelet function**

**a. Hereditary disorders of platelet function**

Know the molecular basis, clinical characteristics, laboratory features,

management, and inheritance pattern associated with Glanzmann thrombasthenia

Know the molecular basis, clinical characteristics, laboratory features, management, and inheritance pattern associated with Bernard-Soulier syndrome

Know the clinical characteristics, laboratory features, management, pathophysiology, and inheritance pattern of adenosine diphosphate storage pool defect

Know the clinical characteristics, laboratory features, management, and inheritance of platelet alpha-granule deficiency

Know the clinical characteristics, laboratory features, management, and inheritance of platelet dense-granule defects

## **b. Acquired disorders of platelet function**

### **(1). Drugs**

Know the specific effect and duration of the action of aspirin ingestion on platelet function tests

Know the duration of the effect of (nonaspirin) anti-inflammatory drugs on platelet function

Know which commonly used drugs affect platelet function

### **(2). Uremia**

Understand the therapeutic options available for improving platelet function in patients with uremia

Know the possible mechanisms for impaired platelet aggregation in uremia

### **(3). Other**

## **c. Treatment of platelet functional disorders**

Know the clinical situations which respond to DDAVP therapy

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**

Know the components of the contact activation system

Know the consequences of deficiencies in the contact activation system on coagulation assays

Know the interaction between the contact activation system and the complement system

Know the function of Factor XI in the coagulation cascade

**b. Factor IX**

Know the age-related changes in Factor IX concentrations

Know the site of synthesis of Factor IX

Know the half-life of Factor IX

Know the role of vitamin K in the synthesis and activity of Factor IX and also Factors II (prothrombin), VII, and X

Know the mechanism of activation and the function of Factor IX in the coagulation cascade

Know the consequences of deficiency of Factor IX on the laboratory assessment of hemostasis

**c. Factor VIII**

Know that DDAVP increases plasma Factor VIII concentration

Know the natural inhibitors that regulate the activity of Factor VIII

Know the function of Factor VIII in coagulation

Know the consequences of a deficiency of Factor VIII on the laboratory assessment of hemostasis

Know the normal value of Factor VIII in a newborn infant

Know the half-life of Factor VIII

Know that Factor VIII circulates as a complex with von Willebrand factor

**d. Von Willebrand factor**

Know the sites of synthesis, storage, and release of von Willebrand factor

Know the platelet aggregation patterns associated with the different types of von Willebrand disease

Know the laboratory methods for measuring the concentration, structure, and function of von Willebrand factor

Know the interaction between von Willebrand factor, platelets, and the vessel wall

Know the consequences of a deficiency of von Willebrand factor on the laboratory assessment of hemostasis

Know the factors that affect the serum concentration of von Willebrand factor

Know the half-life of von Willebrand factor

**e. Factor VII and tissue factor**

Know the functions of Factor VII/tissue factor in coagulation

Know the consequences of a deficiency of Factor VII on the laboratory assessment of hemostasis

Know the age-related changes in Factor VII concentration

Know the site of synthesis of Factor VII

Know the half-life of Factor VII

**f. Factor X**

Know the mechanism of activation and the function of Factor X in coagulation

Know the consequences of a deficiency of Factor X on the laboratory assessment of hemostasis

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**

Know the mechanism of activation and the function of Factor V in coagulation

Know the consequences of a deficiency of Factor V on the laboratory assessment of hemostasis

Know which inhibitors regulate the activity of Factor V

**h. Prothrombin and thrombin**

Know the mechanisms of activation of prothrombin

Know the function of prothrombin and thrombin in coagulation, natural anti-coagulation, and fibrinolysis

Know the consequences of a deficiency of prothrombin on the laboratory assessment of hemostasis

Know the natural inhibitors of thrombin



Know the interaction of thrombin with platelets and with the endothelial cells

**i. Fibrinogen and fibrin**

Know the association of fibrinogen concentration and erythrocyte sedimentation rate

Know the basic structure of fibrinogen and its gene control

Know the function of fibrinogen and fibrin in coagulation

Know the consequences of fibrinogen deficiency on the laboratory assessment of hemostasis

Know the normal value of fibrinogen in a newborn infant

Know the sites of synthesis of fibrinogen

Know the half-life of fibrinogen

Know the interaction of fibrinogen with platelets

Know the screening tests for fibrinogen deficiency and dysfibrinogenemia

**j. Factor XIII**

Know the association of Factor XIII deficiency with poor wound healing

Know the consequences of a deficiency of Factor XIII on the laboratory assessment of hemostasis

Know the function of Factor XIII in coagulation

Know the half-life of Factor XIII

Know the sites of synthesis of Factor XIII

Know the laboratory test for Factor XIII deficiency

**k. Fibrinolysis**

Know the mechanisms of activation of plasminogen

Know the effects of DDAVP on the tissue plasminogen activator

Know the natural inhibitors of plasminogen and its activators

Know the laboratory tests which measure the fibrinolytic system

Know the fibrinolytic and anti-fibrinolytic drugs and their mechanisms of action

**l. Blood vessels**

Know which connective tissue diseases are associated with bleeding

Know that thrombomodulin is an endothelial cell surface protein which binds thrombin

Know the role of heparan sulfate proteoglycans on the endothelial surface in maintaining a nonthrombogenic surface

Know that endothelial cells synthesize and secrete tissue plasminogen activator

Know that endothelial cells synthesize and secrete plasminogen activator inhibitor

Know that endothelial cells synthesize and secrete protein S

## **2. Disorders of coagulation (diagnosis and therapy)**

### **a. General**

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

Know the effects of specimen collection artifacts on coagulation tests (heparin, polycythemia, inadequate specimen)

Understand the limitations of and the use of preoperative screening tests to rule out bleeding tendencies

Know which coagulation factors are acute phase reactants

### **b. Acquired defects**

#### **(1). Disseminated intravascular coagulation (DIC) (neonatal and later)**

##### **(a). Pathophysiology and clinical features**

Recognize the underlying conditions associated with disseminated intravascular coagulation

Recognize and know pathophysiology of purpura fulminans

Know that disseminated intravascular coagulation does not occur as a primary illness and may occur in severely ill patients without bleeding or thrombosis

Know the triggering events (eg, endotoxin, viruses, procoagulants released from the tissues, toxins) that activate blood coagulation

Know the mechanism by which triggering events lead to disseminated intravascular coagulation

Know which protective mechanisms against disseminated intravascular coagulation are physiologically impaired in sick neonates as compared to older infants and children

Know that the clinical features of disseminated intravascular coagulation can include hemorrhage (localized or diffuse), thrombosis, hemolytic anemia, and organ dysfunction

Know the underlying diseases unique to the neonate that are associated with disseminated intravascular coagulation

**(b). Laboratory abnormalities**

Know which tests to perform and how to interpret their results in patients with disseminated intravascular coagulation

Know that fibrinolysis usually accompanies disseminated intravascular coagulation as a secondary event

Know which blood coagulation factors are reduced in the plasma of patients with disseminated intravascular coagulation

Know the significance of the measurements of fibrinogen, fibrin production, and degradation (eg, D-dimer, fibrin monomer, and fibrinopeptides A and B)

**(c). Treatment and outcome**

Recognize the risks and benefits of the various therapeutic options for disseminated intravascular coagulation

Know that control of the primary disorder is the main treatment for disseminated intravascular coagulation

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

**(a). Pathophysiology**

Know vitamin K is fat soluble

Know that vitamin K tissue stores are limited and that patients can become rapidly deficient

Know that human milk contains very little vitamin K

**(b). Etiology and clinical features**

Recognize the hematologic manifestations of cystic fibrosis in an infant

Know the clinical conditions associated with vitamin K deficiency

Recognize the clinical features of classic vitamin K deficiency in the newborn

period (2 to 7 days of age)

Recognize the clinical features and the underlying causes of late hemorrhagic disease of the newborn, ie, occurring between 4 and 12 weeks of age

Know that vitamin K deficiency and hemorrhage may occur by 24 hours of age in infants of mothers who have taken anti-convulsant drugs or other vitamin K antagonists

**(c). Laboratory findings**

Know the laboratory features of vitamin K deficiency (altered coagulation test results, and which specific coagulation proteins are affected)

**(d). Treatment and response**

Know the efficacy and response time of different vitamin K preparations

Know that hemorrhagic disease of the newborn can be prevented by vitamin K shortly after birth

**(e). Drug-induced vitamin K deficiency**

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**

Know the multiple mechanisms responsible for excessive bleeding in patients with severe liver disease

Know that the liver is the site of synthesis of most clotting factors

**(b). Laboratory features**

Know the laboratory test abnormalities most commonly seen in patients with severe liver disease and clinical bleeding

**(c). Treatment**

Know the treatment options of various therapeutic modalities in patients who are bleeding from liver disease

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**

### **III.B.2.d.(3)(c)**

#### **(b). Inhibitors against specific factors**

Recognize that inhibitors against specific blood coagulation factors in a patient without hemophilia are rare during childhood

Know which passively acquired maternal coagulation inhibitors can adversely affect the newborn infant

Know how to differentiate inhibitor from a factor deficiency using conventional coagulation screening tests

#### **(c). Lupus-type anticoagulants**

Know what hemostatic defects associated with lupus-type anticoagulants may cause either bleeding or thrombosis

Know the screening and specific laboratory tests to detect the lupus-type anticoagulant, including the 1:1 mixing study

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

Know the management of children and adolescent patients with a lupus-type anticoagulant

#### **(5). Miscellaneous acquired bleeding disorders**

Know that children with hematophagocytic syndromes may have a severe coagulopathy characterized by marked hypofibrinogenemia

Know the mechanisms by which L-asparaginase effects the coagulation system and the clinical consequences

Know the coagulation abnormalities in patients with nephrotic syndrome and the clinical consequences

Know the coagulation abnormalities in protein-losing enteropathy and their clinical consequences

### **c. Congenital hemorrhagic disorders**

#### **(1). Factors VIII and IX**

##### **(a). Clinical features**

Know the mode of inheritance for Factor VIII and IX deficiency

Know that some hemophilia carriers are symptomatic

Know the differentiating clinical characteristics of mild, moderate, and severe hemophilia A and B

Recognize the clinical features of retroperitoneal hemorrhage in a patient with hemophilia

Understand the relationship between age and the sites and frequency of bleeding episodes in a hemophiliac patient

Know the risk factors for inhibitor development

Recognize that inhibitors may be transient

Know the clinical indications for the use of human recombinant activated Factor VII concentrate

Understand the molecular basis for hemophilia

### **(b). Laboratory diagnosis**

Understand the various tests to prenatally diagnose Factor VIII and IX deficiency

Understand the various tests to diagnose the carrier state for Factor VIII or Factor IX deficiency

Know the limitations of the partial thromboplastin time in diagnosing plasma concentrations of Factor VIII or Factor IX

Understand the Bethesda assay using human Factor VIII

Know the differentiating laboratory characteristics of mild, moderate, and severe hemophilia A and B

### **(c). Management**

Understand the optimum replacement therapy in relation to severity and location of bleeding in a patient with hemophilia

Know the indications for and potential complications of DDAVP in patients with hemophilia

Know the advantages and disadvantages of specific therapies for Factor VIII deficiency

Know the probable causes of therapeutic failure in Factor VIII deficiency

Know the therapeutic approaches to a hemophiliac patient with inhibitor

Know the management of dental extractions in hemophiliac patients

Know the therapeutic approaches to a hemophiliac patient with hematuria

Know the advantages and disadvantages of specific therapies for Factor IX deficiency

Know the proper management and appropriate pre- and postoperative treatment for a patient with Factor VIII or IX deficiency

Understand the indications for prophylaxis in Factor VIII and IX deficiencies

Understand the management approaches to chronic arthropathy in a patient with hemophilia

Know the diagnostic and therapeutic approaches for a patient with hemophilia

Understand the management principles of hemophilia in a neonate or young infant

## **(2). Von Willebrand disease**

Recognize the clinical features of von Willebrand disease

Know the relationship of decreased von Willebrand antigen with von Willebrand disease

Correlate the response to DDAVP with various types of von Willebrand disease

Know the therapeutic options for the treatment of severe von Willebrand disease

Know how to diagnose and treat subtypes of von Willebrand disease

Know the inheritance patterns of von Willebrand disease

Know the effect of blood type and other factors on von Willebrand antigen concentration

## **(3). Other inherited coagulation disorders**

Recognize the bleeding patterns in less common coagulation defects (eg, Factors II, V, VII, X, XI)

Know the appropriate therapy for Factor XIII deficiency

Recognize the clinical features of afibrinogenemias and dysfibrinogenemias

Know how to investigate the cause of a prolonged thrombin time

Know the appropriate therapy for afibrinogenemia and dysfibrinogenemia

Understand that clinical bleeding does not occur with prekallikrein deficiency, high-molecular-weight kininogen deficiency, or Factor XII deficiency

Know the inheritance pattern for Factor XIII deficiency

## **d. Hypercoagulable thrombotic states**

### **(1). General**

Know the important antithrombotic properties of vascular endothelium

Know that removal of activated coagulation factors by the liver is important in preventing thrombosis

Know that estrogen-containing contraceptives are associated with an increased risk of venous thromboembolism, stroke, and acute myocardial infarction

### **(2). Diagnosis**

Know how to evaluate a hypercoagulable state

For each of the known hereditary thrombotic states, know how to diagnose the defect in infants and older children

Understand the clinical manifestations of antithrombin III and proteins C and S deficiencies (homozygous versus heterozygous)

Know how to evaluate a child with established deep venous thrombosis of unknown cause (laboratory tests, imaging)

Know how the normal concentrations of hemostatic factors in neonates complicates the diagnosis of hypercoagulable states

Know the predisposing causes to deep venous thrombosis in infants, children, and adolescents

Know the acquired conditions that have been associated with venous and arterial thromboembolism

Know the clinical signs and symptoms of venous thrombosis in children

Know the clinical signs and symptoms of pulmonary embolism in children

Know the laboratory measures important in evaluating a child with venous thrombosis and pulmonary embolism

Know the clinical presentation, laboratory features, and epidemiology of activated protein C resistance (Factor V Leiden)

Know the problems inherent in diagnosing hypercoagulable states in patients receiving coumadin therapy

Know the clinical presentation and laboratory diagnosis of patients with prothrombin mutations

### **(3). Treatment**



**(a). General considerations**

Know the treatment of a hypercoagulable state in a newborn infant

Know the action of anticoagulant drugs used in thrombotic states or in patients with thrombophilia

Know the indications for and treatment of acquired hypercoagulable states

**(b). Warfarin**

Recognize the embryopathic potential of warfarin therapy

Know the mechanism of action of warfarin and other vitamin K antagonists used as anticoagulants for therapeutic purposes

Recognize the association of skin necrosis with warfarin therapy in patients with heterozygous protein C or protein S deficiency

Know the indications for use of vitamin K antagonists

Know the importance of the International Normalized Ratio (INR) and its use in monitoring vitamin K antagonists

Recognize that many dietary items and drugs can interact with vitamin K antagonists

**(c). Heparin**

Recognize the clinical and laboratory correlates of iatrogenic bleeding secondary to heparin administration

Know how to screen blood samples for the presence of heparin

Understand the structure and mechanisms of action of heparin and heparin-like substances

Know the causes of heparin resistance

Recognize the effect of heparin on coagulation assays in specimens from plasma, including those drawn from central catheters

Know the syndrome and treatment of heparin-induced thrombocytopenia, including its association with thrombosis

Know how to monitor heparin and low-molecular-weight heparin therapy

Know the relative advantages and disadvantages of standard heparin vs. low-molecular-weight heparin

**(d). Direct anti-thrombin drugs**

Know the benefits, pharmacokinetics, and monitoring of direct anti-thrombin drugs

Know the various means to reverse vitamin K antagonists

**(e). Fibrinolytic drugs**

Know the indications for and risks of using fibrinolytic therapy

Know how to monitor fibrinolytic therapy

**IV. Pediatric Transfusion Medicine**

**A. Collection and storage characteristics**

**1. Erythrocytes (liquid storage)**

Know the biochemical changes that occur during erythrocyte storage

Know that washed erythrocytes can be stored for up to 24 hours before expiration

Know that erythrocytes can be stored for up to 28 days after irradiation

Know the normal storage time of erythrocytes

**2. Platelets**

Recognize the normal storage conditions for platelets (ie, constant agitation, room temperature, maximum length of storage)

Know that single-donor platelets obtained by apheresis have the equivalent of multiple random donor platelet units

**3. Leukocytes**

Know the techniques for collecting granulocytes and the shelf-life of granulocytes

**4. Plasma**

Understand the process of collection and separation of plasma

Know the different coagulation and anticoagulation proteins present in fresh frozen plasma

**5. Plasma-derived products**

Understand the process of manufacturing Factor VIII concentrate, prothrombin complex concentrate, and activated prothrombin complex concentrate, and coagulation Factor IX, cryoprecipitate, and other factor concentrates

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

Know the viruses that are not effectively attenuated or removed by the various methods of treatment of plasma-derived products

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**

Know why women should be screened early in gestation for minor group antibodies

Be able to interpret the results of direct and indirect antiglobulin tests

Know the common alloantibodies that develop in children with sickle cell disease receiving transfusions

### **2. Platelets**

Know when platelets should be Rh(D) and ABO-compatible

Understand platelet crossmatching, its indications and limitations

## **C. Indications for transfusion**

### **1. Whole blood**

### **2. Packed erythrocytes**

Recognize that washing erythrocytes causes loss of red cells

Know the clinical indications for leukocyte reduction (e.g., decreased risk of HLA sensitization, CMV transmission, and febrile transfusion reactions)

Know the indications for packed erythrocytes

### **3. Cryopreserved erythrocytes**

Know the value of frozen erythrocytes for patients with rare compatibility problems

### **4. Leukocytes**

Know the indications for use of granulocyte concentrates

Know the limitations and risks of using granulocyte concentrates

## **5. Platelets**

Recognize indications for use of HLA-matched platelets and crossmatched platelets

Know the risk for alloimmunization in patients needing repeated platelet transfusions

Know the in vivo recovery and survival of transfused platelets in situations of decreased production and increased destruction

Know the tests and observations required to diagnose alloimmunization

Recognize the indications for platelet transfusion

## **6. Irradiated blood and blood components**

Recognize the immunocompromised conditions in which the use of irradiated blood products is indicated

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

Know that blood products from all blood relatives must be irradiated to prevent graft-versus-host disease, even in immunocompetent recipients

Understand the reasons for irradiation of transfused blood products

Know that leukoreduction does not effectively prevent graft-versus-host disease

## **7. Plasma**

Know the appropriate use of fresh frozen plasma

## **8. Cryoprecipitate**

Know the indications for the transfusion of cryoprecipitate

## **9. Coagulation factor concentrates**

Know the risks of using prothrombin complex concentrate and activated prothrombin concentrates

Know that parvovirus is resistant to solvent detergent and heating methods of inactivation

Know the clinical indications for the use of activated prothrombin complex concentrate

## **10. Immunoglobulin intravenously**

Know the hematologic indications for intravenous administration of immune

globulin

Know the side effects of intravenous administration of immune globulin

## **11. Therapeutic pheresis**

Recognize the hematologic indications for therapeutic plasma exchange

Know the indications for leukapheresis

Know the indications for erythrocyte exchange transfusions

## **12. Autologous erythrocytes**

Recognize the usefulness of autologous erythrocytes in older children scheduled for orthopedic surgery, scoliosis repair, marrow-donor harvest, or other conditions

Recognize the usefulness of autologous erythrocytes for individuals with rare blood groups or compatibility problems

## **13. Directed donors**

Recognize that testing requirements often make it impossible to have directed blood donors in emergent situations

Recognize that relatives should not be used as blood component donors for potential HSCT recipients

Recognize that first-time donors exhibit higher rates of infectious disease markers such as HIV, hepatitis B, and hepatitis C than repeat volunteer donors

## **D. Selection of appropriate blood type**

Know the proper approach to elective transfusion in a patient with a known erythrocyte alloantibody

Know the appropriate use of erythrocyte products in patients with autoimmune hemolysis

## **E. Computation of dose, rate of delivery, modifying conditions**

Know the in vivo recovery and survival of infused Factor VIII, Factor IX, fibrinogen, and prothrombin

Select and calculate the value of the appropriate erythrocyte product for treating anemia

Calculate the dose of platelet concentrate for transfusion of patients with thrombocytopenia

## **F. Complications of blood and blood product transfusions**

## 1. Transfusion-transmitted disease

Know the risk of transmission of HIV-1, hepatitis B, and hepatitis C, in transfusion of single-donor blood components

Recognize the clinical and laboratory manifestations of transfusion-acquired CMV infection

Know that frozen or filtered (leukocyte reduced) erythrocytes will reduce transmission of cytomegalovirus to recipients

Recognize the significance of chronic liver disease following hepatitis C transmission by transfusion

Recognize parvovirus infection in HIV-positive recipients

Know how to identify bacterial contamination of blood products

Know the most frequent pathogens that exist in refrigerated units of packed erythrocytes

## 2. Transfusion reactions - acute and delayed

### a. Etiology

Recognize the major factors leading to incompatible blood transfusion

Recognize that febrile reactions in chronically transfused patients may be due to antileukocyte, anti-platelet, or anti-HLA antibodies

Know that anaphylactic reaction to blood transfusion is associated with IgA deficiency in the recipient

Recognize that a fever may be the first sign of a bacterially contaminated transfusion or an acute hemolytic transfusion reaction

Know the cause of allergic transfusion reactions

### b. Pathogenesis

Recognize that anamnestic antibody production causes delayed hemolytic transfusion reactions and that a compatible crossmatch does not prevent delayed hemolytic transfusion reaction

Know the incidence of alloimmunization to random donor platelets and the effect of leukoreduction

Understand the pathogenesis and clinical symptoms of transfusion-related acute lung injury

### c. Recognition

Recognize an acute hemolytic transfusion reaction

Recognize the clinical presentation of a delayed transfusion reaction due to minor blood group incompatibility

Recognize the complications of massive blood transfusion

**d. Management**

Know the proper therapeutic approach to a patient refractory to platelet transfusions

Know the proper erythrocyte types for patient with delayed hemolytic transfusion reaction

Know what to do if an Rh-positive blood product is administered to an Rh-negative female patient of child-bearing age or younger

Know what to do if an Rh-positive blood product is administered to an Rh-negative male patient

Know the management of acute hemolytic transfusion reaction

Know what precautions should be taken when transfusing patients with IgA deficiency

**e. Prevention**

Know various strategies to prevent alloimmunization to platelets

**V. Pediatric Oncology**

**A. General**

**1. Epidemiology of cancer**

**a. Age-related incidence**

Know the age distribution of childhood tumors

**b. Race-related incidence**

Recognize the differences in childhood cancer based on race and/or ethnic origin

**c. Predisposing factors**

**(1). Genetic factors**

Know the constitutional chromosomal abnormalities associated with specific malignancies

Know the tumors associated with genetic disorders

Know the tumors associated with Beckwith-Wiedemann syndrome

Know which tumors are associated with genomic imprinting

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

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

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

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

**(2). Chemical-related**

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

Know the relationship between chemical carcinogens and cancer

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

**(3). Environmental**

Know the association between hepatitis viruses and hepatocellular carcinoma

Know which tumors are associated with specific viruses

Know which tumors are more common after exposure to ionizing radiation

**(4). Immunologic**

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

**2. Tumor molecular and cellular biology**

Understand DNA ploidy and its prognostic significance

Understand the use and interpretation of Southern blot

Understand lyonization and clonality

Understand the role of transcription factors and growth

Understand apoptosis

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



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

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

Know the difference between the "two-hit" and sporadic mechanisms of carcinogenesis

### **3. Oncogenesis and cell growth regulation**

Know the mechanisms of proto-oncogene activation

Understand the concept of gene amplification

Know the role of protein kinases in cell growth and transformation

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

Understand the use of clonogenic assays

Identify the phases and regulation of the cell cycle

Understand principles used to measure cell cycle kinetics

Know the mechanism of action of tumor suppressor genes and how activation or deletion can contribute to malignant transformation

Know the relationship between defects in DNA repair and oncogenesis

Understand clinically important proto-oncogene amplification in tumors of children

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**

Know the effects of hypoxia on tumor and normal tissue sensitivity to radiation

Know the advantages of and indications for using brachytherapy

Know the effects of radiation on cells in different phases

Know which variables influence the response to therapeutic radiation

Know the principles underlying the use of fractionated radiation therapy

Know the tumor characteristics that make it amenable to treatment with stereotactic radiosurgery (such as "gamma knife")

Know the difference between conformal and conventional radiotherapy

Know which chemotherapy agents act as radiation sensitizers

**b. Complications of radiotherapy**

**(1). Organ-specific toxicity**

Know the early and late effects of varying doses of radiation on normal gonads

Know the early and late effects of varying doses of radiation on the normal thyroid

Know the early and late effects of varying doses and types of radiation on the normal brain, including the impact of age at treatment

Know the early and late effects of varying doses of radiation on the normal heart

Know the clinical, laboratory, and radiologic findings of radiation pneumonitis

Know the early and late effects of varying doses of radiation on normal kidneys

Know the early and late effects of varying doses of radiation on normal skin

Know the early and late effects of varying doses of radiation on the normal liver

Know the long-term effects of varying doses of radiation on normal bones at various ages

Know the early and late effects of varying doses on radiation on normal lungs

Know the early and late effects of varying doses of radiation on the normal gastrointestinal tract

Recognize the marrow toxicity of radiation therapy

Know the effects of varying doses of radiation on normal lungs

**(a). Secondary tumors**

Know the risks of second malignant neoplasms according to radiation dosage, specific tumors, and combined therapy

Know the frequency of tumor types seen as second malignancies

**5. Chemotherapy**

**a. Principles of chemotherapy**

Know the sequence of peripheral blood cell recovery following chemotherapy

Know the sites of action, metabolism, and toxicities of chemotherapeutic agents

Recognize the effect of hepatic dysfunction on chemotherapeutic drug toxicity and efficacy

Recognize the effect of renal dysfunction on chemotherapeutic drug toxicity

Understand the principles of tumor cell kill kinetics by chemotherapeutic agent

Know the phases of the cell cycle in which specific chemotherapeutic agents exert their effects

Know that specific chemotherapeutic agents, as well as pubertal status, increase the risk of infertility

Know the age-related physiologic differences that affect drug distribution

Understand terms used to define pharmacokinetics (eg, clearance, half-life, AUC, volume of distribution, bioavailability and biotransformation)

Know the classification of chemotherapeutic agents by mechanism of cytotoxicity

Know the drugs capable of causing tissue damage when extravasated and mechanisms of prevention

**b. Principles of combination chemotherapy**

Know the rationale for combination chemotherapy

Know the rationale for adjuvant combination chemotherapy

Know the rationale for primary or neoadjuvant chemotherapy

**c. Principles of drug resistance**

Know the role of the *mdr* gene and p-glycoprotein in the development of drug resistance

Know mechanisms by which cells develop resistance to anticancer drugs

Know strategies to overcome drug resistance

**d. Groups of chemotherapy drugs**

**(1). Alkylating drugs**

Know which chemotherapy drugs are alkylating drugs

Know the potential short- and long-term toxicities of the chemotherapy

alkylating drugs

**(2). Anti-metabolites**

Know which chemotherapy agents used in children with cancer are anti-metabolites

Know the mechanism of action of the cancer drugs that are anti-metabolites

Know that second malignant neoplasms have not been shown to be associated with anti-metabolite therapy

**(3). Naturally derived drugs**

Know the mechanisms of action of the chemotherapy agents that are antibiotics

**(4). Topoisomerase inhibitors**

Know which chemotherapy drugs are topoisomerase inhibitors

Know the potential short- and long-term toxicities of chemotherapy topoisomerase inhibitors

Know the mechanisms of action of chemotherapy topoisomerase inhibitors

**(5). Mitotic inhibitors**

Know the potential short- and long-term toxicities of chemotherapy mitotic inhibitors

Know the mechanisms of action of chemotherapy mitotic inhibitors

Know which chemotherapy drugs are mitotic inhibitors

**e. Specific agents**

**(1). 6-Mercaptopurine**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of 6-mercaptopurine

Know the effect of allopurinol on bioavailability of 6-mercaptopurine

Understand the pharmacogenetics of 6-mercaptopurine

**(b). Complications and their management**

Recognize the pattern of hepatic toxicity associated with mercaptopurine

Know the potential toxicities associated with the use of 6-mercaptopurine

**(2). 6-Thioguanine**

**(a). Clinical pharmacology and pharmacokinetics**

Know how thioguanine differs from mercaptopurine in metabolism and bioavailability

**(b). Complications and their management**

Know how thioguanine differs from mercaptopurine in toxicity

**(3). Methotrexate (conventional and high-dose)**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of methotrexate

Know the kinetics and therapeutic principles of high-dose methotrexate with leucovorin rescue

Know that oral methotrexate absorption is highly variable

Know that renal dysfunction delays methotrexate clearance

Know what drugs interfere with methotrexate clearance

Know that methotrexate has little tendency to develop cross-resistance with other drugs

Know the potential differences in methotrexate exposure by dosage, route, and schedule of administration

**(b). Complications and their management**

Recognize the clinical features of acute methotrexate toxicity

Know the effects of repeated doses of parenteral methotrexate on the brain

**(4). Cytarabine**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of cytarabine

Know the metabolism of cytarabine and impact of organ dysfunction and role of cytidine deaminase

Know the potential differences in cytarabine exposure by dosage, route, and schedule of administration

**(b). Complications and their management**

Know the toxicities of cytarabine and the impact of organ dysfunction

Know the neurologic toxicity that can occur with high dose cytarabine

**(c). Clinical use**

Know how cytarabine is used in the treatment of childhood malignancy

Know how cytarabine is used in CNS preventive therapy and in CNS relapse in acute leukemia

Know that intrathecal cytarabine and intravenous high dose cytarabine given in close proximity can cause transverse myelitis

**(5). Corticosteroids**

**(a). Clinical pharmacology and pharmacokinetics**

Know the mechanism(s) of action of glucocorticoids and the role of glucocorticoid receptors

Understand the pharmacology of different glucocorticoids

Know that systemic dexamethasone achieves higher CNS levels, as compared to prednisone

**(b). Complications and their management**

Know the acute and delayed toxic effects of corticosteroids and the differences between prednisone and dexamethasone

Know how to manage hyperglycemia associated with corticosteroid administration

Recognize the acute toxicity of corticosteroid therapy, such as mood changes and Cushingoid changes

Know that osteoporosis is a complication of corticosteroid therapy and that schedule of administration influences the likelihood of development of this complication

Know that corticosteroids increase the likelihood of systemic bacterial and fungal infections

Know the difference between potential toxicities of prednisone and dexamethasone

**(c). Clinical use**

Know the role that systemic corticosteroids play in the treatment of ALL, non-Hodgkin lymphoma, Hodgkin disease, and histiocytoses

Know how corticosteroids can be used in managing some of the complications of cancer (ie, nausea and vomiting, increased intra-cranial pressure, hypercalcemia, and allergic reactions)

**(6). Hydroxyurea**

Understand the mechanism of action, complications, and clinical use of hydroxyurea

**(7). Anthracyclines**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of the anthracyclines

Know the metabolism of anthracyclines and the impact of organ dysfunction

Understand the pharmacologic differences of the anthracyclines

**(b). Complications and their management**

Know the toxicities (acute and long-term) of the anthracyclines and the impact of organ dysfunction

Know the risk factors, presentation, evaluation, and management of acute and late anthracycline cardiotoxicity

Know that anthracyclines potentiate radiation toxicity

Understand the relationship between anthracyclines and second tumors, and be able to distinguish anthracycline-induced AML from other treatment-induced leukemias

Know the potential role of dexrazoxane in preventing cardiotoxicity of anthracyclines

**(c). Clinical use**

Know the principal clinical uses for each of the anthracyclines

**(8). Dactinomycin**

**(a). Clinical pharmacology and pharmacokinetics**

Know the mechanism of action of dactinomycin

Know the metabolism of dactinomycin and the impact of organ dysfunction

**(b). Complications and their management**

Know the toxicities of dactinomycin

Know that dactinomycin is a radiation sensitizer

Know that infants are at higher risk of dactinomycin toxicity and the appropriate prevention strategies

**(c). Clinical uses**

Know the primary ways in which dactinomycin is used in the treatment of childhood malignancies

**(9). Bleomycin**

**(a). Clinical pharmacology and pharmacokinetics**

Know the metabolism of bleomycin and the impact of organ dysfunction

Know the mechanism of action of bleomycin

**(b). Complications and their management**

Recognize the pulmonary complications of bleomycin and the role of total dose

Know the toxicities of bleomycin and that pulmonary toxicity is related to cumulative dose

**(c). Clinical uses**

Know how bleomycin is used in the treatment of childhood malignancies

**(10). Vincristine**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of vincristine

Know the metabolism of vincristine and the impact of organ dysfunction

**(b). Complications and their management**

Know the toxicities of vincristine

**(c). Clinical use**

Understand the use of vincristine in the treatment of various childhood malignancies

**(11). Vinblastine**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of vinblastine



Know the metabolism of vinblastine

**(b). Complications and their management**

Know that the dose-limiting toxicity of vinblastine is different from that of vincristine

Know the toxicities of vinblastine

**(c). Clinical use**

Understand the clinical use of vinblastine in treating childhood malignancies

**(12). Cyclophosphamide**

**(a). Clinical pharmacology and pharmacokinetics**

Know the metabolism of cyclophosphamide and the impact of organ dysfunction

Know the mechanism of action of cyclophosphamide

Know that cyclophosphamide is both myelosuppressive and immunosuppressive

Know the potential differences in cyclophosphamide exposure by dosage, route, and schedule of administration

**(b). Complications and their management**

Know the acute and long-term complications of cyclophosphamide therapy

Know the methods (and their rationale) used to reduce the risk of hemorrhagic cystitis associated with the use of cyclophosphamide

Know the toxicities of cyclophosphamide

**(c). Clinical use**

Understand the clinical use of cyclophosphamide in treating childhood malignancies

**(13). Ifosfamide**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of ifosfamide

Know the metabolism of ifosfamide

Know the pharmacologic differences between cyclophosphamide and ifosfamide

**(b). Complications and their management**

Know how to diagnose and manage renal tubular dysfunction resulting from ifosfamide therapy

Recognize the acute and late toxicities of ifosfamide therapy

Know the diagnosis, causes, and treatment of acute neurotoxicity of ifosfamide therapy

**(c). Clinical use**

Understand the clinical uses of ifosfamide in treating childhood malignancies

**(14). Mechlorethamine**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of mechlorethamine

Understand the history of mechlorethamine in treating childhood malignancies

**(b). Complications and their management**

Know the acute and late toxicities of mechlorethamine therapy

Know the precautions needed for administration of mechlorethamine via peripheral vein

**(c). Clinical use**

Understand the clinical use of mechlorethamine in treating childhood malignancies

**(15). Carmustine**

**(a). Clinical pharmacology and pharmacokinetics**

Know the metabolism of carmustine

Know the mechanism of action of carmustine

**(b). Complications and their management**

Know the acute and delayed toxicities of carmustine, including the time course for myelosuppression

Know that prolonged thrombocytopenia can occur with carmustine

**(c). Clinical use**

Understand the clinical uses of carmustine in the management of childhood malignancies

**(16). Lomustine**

**(a). Clinical pharmacology and pharmacokinetics**

Know the metabolism of lomustine

Know the mechanism of action of lomustine

**(b). Complications and their management**

Know the acute and late toxicities of lomustine

Know the relationship between progressive renal atrophy and cumulative doses of lomustine

**(17). Asparaginase (E. coli, Erwinia, PEG-E coli)**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of asparaginase

Know that asparaginase can be used to modify the toxic effects of methotrexate and cytarabine

Know the different preparations of asparaginase and their pharmacokinetics

Know how PEG asparaginase is made from E. coli asparaginase

**(b). Complications and their management**

Know the hemostatic complications of asparaginase therapy

Know that asparaginase causes allergic reactions

Know the toxicities of asparaginase

Recognize acute pancreatitis as a complication of asparaginase therapy

Know the treatment options for a patient who is allergic to E. coli, Erwinia, or PEG asparaginase

Recognize hyperglycemia due to decreased insulin production as a complication of asparaginase therapy

Recognize hypoalbuminemia as a complication of asparaginase therapy

**(c). Clinical use**

Know the uses for asparaginase in the treatment of childhood malignancies

**(18). Cisplatin**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of cisplatin

Know the metabolism of cisplatin

**(b). Complications and their management**

Understand the measures to minimize the risk of renal toxicity from cisplatin

Know the toxicities associated with cisplatin therapy

Know the type of hearing loss that occurs with cisplatin and the relationship to cumulative dose

Know that hypomagnesemia is common after cisplatin therapy

**(c). Clinical use**

Understand the uses of cisplatin in the treatment of childhood malignancies

**(19). Carboplatin**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of carboplatin

Understand the metabolism of carboplatin

**(b). Complications and their management**

Know the toxicities associated with carboplatin

Differentiate carboplatin toxicity from cisplatin toxicity

Know that carboplatin can cause delayed nadirs in platelet counts and absolute granulocyte counts

**(20). Busulfan**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of busulfan

Understand the metabolism of busulfan, including the role of age

**(b). Complications and their management**

Know the toxicities associated with busulfan therapy

**(21). Epipodophyllotoxins (VP-16, VM-26)**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of the epipodophyllotoxins

Know the metabolism of the epipodophyllotoxins

**(b). Complications and their management**

Understand the relationship between epipodophyllotoxins and secondary AML and distinguish it from secondary AML associated with alkylators

Know the acute and late toxicities of epipodophyllotoxins

**(c). Clinical use**

Know the clinical use of epipodophyllotoxins in the treatment of childhood malignancies

**(22). Camptothecans (eg, topotecan, irinotecan)**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of camptothecans

Know the metabolism of the camptothecans

**(b). Complications and their management**

Know the toxicities associated with the camptothecans

Know how to manage the diarrhea that can be associated with irinotecan

**(c). Clinical use**

Know the uses of topotecan and irinotecan in the treatment of pediatric malignancies

**(23). Temozolomide**

**(a). Clinical pharmacology and pharmacokinetics**

Understand the mechanism of action of temozolomide

Know the metabolism of temozolomide

**(b). Complications and their management**

Know the toxicities associated with temozolomide

Know that myelosuppression is the dose-limiting toxicity of temozolomide, but is not cumulative

**(c). Clinical use**

Know how temazolomide is used in the treatment of childhood malignancies

**(24). Procarbazine**

**(a). Clinical pharmacology and pharmacokinetics**

Know the mechanism of action of procarbazine

Know the toxicities associated with procarbazine

Know the clinical use of procarbazine in the treatment of childhood malignancies

**(25). Clofarabine**

Know the clinical indications for treatment with clofarabine

**(26). Nelarabine**

Know the clinical indications for treatment with nelarabine

**6. Biologic response modifiers and immunotherapy**

Recognize the common side effects of interferon therapy

Know the mechanism of action, indications, and common side effects of 13-cis-retinoic acid

Know the mechanism of action, indications, and common side effects of all trans-retinoic acid

Know the mechanism of action, indications, and common side effects of tyrosine kinase inhibitors such as imatinib

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**

Know the rationale for use, indications, mechanism of action, and toxicity of filgrastim (G-CSF) and sargramostim (GM-CSF) in children receiving chemotherapy

Know the rationale for use, indications, mechanism of action, and toxicity of erythropoietin in children receiving chemotherapy

Know the different preparations of filgrastim (G-CSF) and their

pharmacokinetics

**b. Antiemetics**

Know the mechanism of action and side effect profile of various classes of antiemetics (not including serotonin S3 receptor antagonists and NK1 inhibitors)

Know the rationale for use, indications, mechanism of action, and toxicity of the serotonin S3 receptor antagonists

Know the rationale for use, indications, mechanism of action, and toxicity of NK1 inhibitors

**c. Miscellaneous**

Know the rationale for use, indications, mechanism of action, and potential side effects of rasburicase

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**

Recognize normal marrow osteoclasts or osteoblasts and differentiate from tumor cells

Know that bone marrow aspiration alone is not adequate to rule out involvement of marrow in lymphomas and solid tumors

Know the definitions for M1, M2, and M3 marrow in the acute leukemias

**2. Diagnostic x-ray studies/scans**

Know the indications for MRI compared to CT

Know the uses for gallium scans in assessing pediatric malignancies

Know the indications for PET scanning in assessing pediatric malignancies

**3. Examination of the cerebrospinal fluid**

Know the risks associated with lumbar puncture for examination of cerebrospinal fluid

Know the definitions of CNS 1, CNS 2, CNS 3 in the acute leukemias

**4. Biochemical markers**

Know the biochemical abnormalities that characterize different neoplasms

**5. Immunologic studies**

Understand the use of tumor-specific antigens for diagnostic and prognostic purposes

## **C. Leukemia, general**

### **1. Incidence and epidemiology**

Know the incidence of acute lymphoblastic leukemia and acute myelogenous leukemia, and the peak age at which each of these occur

Know the concordance rate of acute lymphoblastic leukemia and AML in identical twins

Know the incidence of chronic myelogenous leukemia in children

### **2. Leukemogenesis**

Know which constitutional and genetic conditions predispose to the development of leukemia

Know that Down syndrome is associated with an increased incidence of both acute lymphoblastic and acute myeloid leukemia

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

### **3. Cell biology**

#### **a. Cytogenetics and oncogenes**

Know the non-random chromosomal abnormalities and correlated molecular genetic abnormalities associated with specific phenotypes of acute lymphoblastic leukemia and acute myeloid leukemia

#### **b. Leukemic cell proliferation in vitro**

#### **c. Biologic characterization**

Identify the cell morphology of different types of leukemia

Know the immunophenotypic differences between acute lymphoid and acute myeloid leukemia

Know how to identify lymphoid/myeloid mixed lineage acute lymphoblastic leukemia and biphenotypic leukemia (by immunophenotyping)

## **D. Acute lymphoblastic leukemia (ALL)**

### **1. Clinical and laboratory features**

Know the clinical and laboratory features of B-lineage (non-T, non-B) acute



lymphoblastic leukemia

Know the epidemiologic, clinical, and laboratory features that characterize B-cell (Burkitt) acute lymphoblastic leukemia

Know the epidemiologic, clinical and laboratory features that characterize T-cell lymphoblastic leukemia

Recognize the clinical complications related to the hematologic abnormalities in acute leukemia

Recognize hypereosinophilia as a rare presenting feature of acute lymphoblastic leukemia

**a. Pancytopenia**

Formulate a differential diagnosis for pancytopenia in childhood

**b. Bone pain**

Know that acute lymphoblastic leukemia can mimic juvenile rheumatoid arthritis at presentation

Recognize the changes on x-ray studies of the skeleton in association with acute lymphoblastic leukemia

Know the differential diagnosis of bone pain in a child

**c. Organomegaly**

Know the differential diagnosis of hepatosplenomegaly and pancytopenia

**d. Purpura**

Recognize how the clinical presentation of leukemia differs from idiopathic thrombocytopenic purpura

**e. Leukocytosis**

Recognize the complications associated with hyperleukocytosis

Know the differential diagnosis of an absolute lymphocytosis

**f. Extramedullary leukemia**

Know the criteria for the diagnosis of central nervous system leukemia

Know the clinical manifestations of central nervous system leukemia

Know the significance of an enlarged testis in acute lymphoblastic leukemia

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**

Recognize the morphology of acute lymphoblastic leukemia, including the unique morphology of L3 ALL

Know how to distinguish atypical lymphocytes from lymphoblasts

Know how to recognize granular acute lymphoblastic leukemia

### **b. Histochemistry and Biochemistry**

Know that CD10+ lymphoblasts and T-lymphoblasts both have terminal deoxynucleotidyl transferase activity

### **c. Immunologic classification**

Know how to interpret cell surface markers in the diagnosis and classification of ALL, including CD10+ HLA-DR expression

Know the prognostic significance of biologic markers in acute lymphoblastic leukemia

Know the relationship between the expression of surface or cytoplasmic immunoglobulin and specific subsets of leukemia

### **d. Gene rearrangements**

Know the gene rearrangement characteristics of acute lymphoblastic leukemia

Know the prognostic significance of the molecular translocations that occur in ALL

## **3. Prognostic factors**

Know the clinical and laboratory findings that influence prognosis in acute lymphoblastic leukemia

Know that the significance of prognostic factors varies among different treatment regimens

Know the National Cancer Institute consensus risk stratification of acute lymphoblastic leukemia

### **a. Initial leukocyte count**

Recognize initial leukocyte count as a risk factor in acute lymphoblastic leukemia

**b. Age**

Recognize age as a significant risk factor in acute lymphoblastic leukemia

Recognize age subgroups as a prognostic factor within infants < 12 months of age at diagnosis

**c. Response to therapy**

Know that rapidity of response to chemotherapy in acute lymphoblastic leukemia is predictive of outcome

Know the methods that can be used to measure rapidity of response in acute lymphoblastic leukemia, including day 8 and day 15 bone marrow examinations and peripheral blood assessments

Know the methods for quantitating minimal residual disease (MRD)

Know the rationale for using minimal residual disease in predicting outcome in acute lymphoblastic leukemia

**d. Central nervous system**

Know which acute lymphoblastic leukemia immunophenotypes are most likely to have CNS disease at diagnosis

**e. Cytogenetics**

Know the prognostic significance of cytogenetic and molecular diagnostic findings in acute lymphoblastic leukemia

Know the prognostic significance of hyperploidy (greater than approximately 52 chromosomes) in acute lymphoblastic leukemia

Know the prognostic significance of Ph chromosome in acute lymphoblastic leukemia

Know the prognostic significance of DNA index (DI) ploidy, and how it correlates with chromosome count

Know that a "normal" leukemic cell karyotype may reflect inadequate growth of tumor cells or an occult translocation

Know the prognostic significance of hypodiploidy in acute lymphoblastic leukemia

Know the cytogenetic/molecular abnormalities most likely to be seen in the leukemic cells of infants less than 12 months old with acute lymphoblastic leukemia

Know that TEL-AML 1 is the molecular counterpart of t(12;21)

Know that the occult t(12;21) is the most common non-random cytogenetic abnormality in B-lineage acute lymphoblastic leukemia

**f. Immunophenotype**

Know the prognoses of B-precursor, T-cell, and B-cell (Burkitt) acute lymphoblastic leukemia, respectively

Know the non-random chromosome abnormalities seen in B-precursor, B-cell, and T-cell acute lymphoblastic leukemia, respectively

**4. Therapy**

**a. Chemotherapy**

Identify drugs most valuable for remission induction of acute lymphoblastic leukemia

Recognize delayed intensification as a useful strategy for standard and high risk acute lymphoblastic leukemia

Recognize the importance of risk-adjusted therapy for acute lymphoblastic leukemia prognostic subgroups

Know the principles of treatment for different risk groups of acute lymphoblastic leukemia

**b. Irradiation**

Plan the radiation field for prophylactic irradiation of the cranium in acute lymphoblastic leukemia

Know the complications of intrathecal methotrexate and central nervous system irradiation in a patient with acute lymphoblastic leukemia

Know that irradiation can be avoided in many patients if any effective central and intrathecal chemotherapy are given

**c. Late effects of therapy**

Recognize the late complications of cranial radiation for acute lymphoblastic leukemia

Know that brain tumor is a late complication of cranial irradiation for acute lymphoblastic leukemia

Know the relationship between treatments for acute leukemia and late central nervous system complications

Know the effect of age on neuropsychologic function after cranial irradiation in acute lymphoblastic leukemia

## **5. Management and treatment of complications of ALL**

Know the complications of induction therapy for acute lymphoblastic leukemia

Plan the management of a patient with pancytopenia during induction therapy for acute lymphoblastic leukemia

Know the clinical and laboratory features of tumor lysis syndrome and its prophylaxis and management

### **a. Central nervous system (CNS)**

Know the management of central nervous system leukemia that develops after prophylaxis

Plan the management of central nervous system leukemia detected at the time of diagnosis of acute lymphoblastic leukemia

Plan the diagnostic evaluation and management of a patient with ALL who has a seizure

### **b. Testicular**

Plan the management of testicular relapse of acute lymphoblastic leukemia

### **c. Bone marrow relapse**

Know the importance of the duration of first remission as a prognostic factor after relapse

Know the role of various types of stem cell transplantation in the management of acute lymphoblastic leukemia relapse (see also section VII.B., #909)

## **E. Acute myeloid leukemia (AML)**

### **1. Clinical and laboratory features**

Know the clinical presentations and FAB classification of AML

#### **a. Purpura**

Recognize the association of disseminated intravascular coagulation with M3 acute myeloid leukemia

#### **b. Leukocytosis**

Recognize and manage the myeloproliferative syndrome in infants with Down syndrome and differentiate it from acute myeloid leukemia

Recognize the potential complications of hyperleukocytosis in acute myeloid leukemia

**c. Central nervous system**

Recognize that central nervous system leukemia can complicate acute myeloid leukemia

**d. Extramedullary disease**

Recognize that leukemia cutis can be the presenting feature of acute myeloid leukemia in infants

Recognize chloroma as a manifestation of acute myeloid leukemia

**2. Biologic characterization and classification**

**a. Morphology**

Be able to recognize acute myeloid leukemia subtypes M0 through M7

Know the relationship between myelodysplastic syndromes and acute myeloid leukemia

**b. Histochemistry, immunologic classification**

Recognize the clinical picture, morphologic characteristics, and blast cell surface marker characteristics of acute megakaryocytic leukemia

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**

Correlate clinical characteristics with chromosomal abnormalities in acute myeloid leukemia

Understand the significance of rearrangements of the ATRA receptor gene in M3 acute myeloid leukemia

Recognize specific clinical syndromes associated with t(8;21), inv (16), t(9;11), t(15;17), and monosomy 7 or 7q- in acute myeloid leukemia

Know the molecular abnormalities with which specific and recurring chromosomal abnormalities are associated in acute nonlymphoblastic leukemia

Know the characteristic chromosomal abnormalities and clinical characteristics in secondary acute myeloid leukemia resulting from topoisomerase II inhibitors and from alkylators, respectively

**3. Prognostic factors**

Know prognosis of various French-American-British sub-types of acute myeloid

leukemia

Know the prognostic significance of the non-random cytogenetic abnormalities in acute myeloid leukemia

Know the prognostic importance of Down syndrome in acute nonlymphoblastic leukemia

#### **4. Therapy**

Know that therapy is an important prognostic factor in acute myeloid leukemia

##### **a. Chemotherapy**

Plan the further chemotherapy of a patient with acute myeloid leukemia in remission and drug-induced neutropenia and thrombocytopenia

Know the role of all-trans-retinoic acid and chemotherapy in the treatment of M3 acute nonlymphoblastic leukemia

Know that high-dose cytarabine is effective in the treatment of acute myeloid leukemia

Know which drug combinations are most effective in the treatment of acute myeloid leukemia

Know the role of CNS prophylaxis in the treatment of acute myeloid leukemia

Know the evidence against the use of extended maintenance therapy for AML

##### **b. Supportive care**

Know the various components of prophylactic and acute supportive care for children with acute myeloid leukemia receiving treatment

##### **c. Hematopoietic stem cell transplantation (HSCT) (see also section VII)**

Know the indications for allogeneic HSCT in AML

#### **F. Myeloproliferative disorders**

##### **1. Clinical and laboratory features**

Know the clinical, laboratory, and prognostic features of adult chronic myeloid leukemia and juvenile myelomonocytic leukemia

Know the clinical and laboratory characteristics that differentiate Ph<sup>+</sup> chronic myeloid leukemia from Ph<sup>+</sup> acute lymphocytic leukemia

Recognize priapism as a presenting feature of chronic myeloid leukemia

Recognize the hematologic changes associated with a blast crisis in chronic

myeloid leukemia

Know that a blast crisis in chronic myeloid leukemia can involve other cell lines

Know the biologic properties of the malignant cells in juvenile myelomonocytic leukemia

Know the criteria for the diagnosis of juvenile myelomonocytic leukemia

## **2. Biologic characterization and classification**

Know the association of bcr-Ab1 oncogene with chronic myeloid leukemia

Know the molecular difference in Ph<sup>+</sup> chronic myeloid leukemia and Ph<sup>+</sup> acute lymphoblastic leukemia in children

## **3. Therapy**

### **a. Chemotherapy**

Know the principles of chemotherapy to treat chronic myeloid leukemia

Plan the treatment of a blast crisis in a patient with chronic myeloid leukemia

Know the principles of therapy for juvenile myelomonocytic leukemia and for monosomy 7 syndrome

Know the principles of using targeted therapy (such as imatinib) in patients with chronic myeloid leukemia

### **b. Immunotherapy**

Know the therapeutic effects and side effects of alpha interferon in treatment of chronic myeloid leukemia

### **c. HSCT (See also section VII)**

Know the indications for and timing of HSCT in a patient with chronic myeloid leukemia

Know the therapeutic options for a patient who has a recurrence of chronic myeloid leukemia after HSCT

## **G. Lymphomas**

### **1. Hodgkin disease**

#### **a. Epidemiology/predisposing factors/genetics**

Know the epidemiologic features of Hodgkin disease in children

Recognize that Hodgkin disease may occur in families



**b. Pathology**

Recognize the pathologic subtypes of Hodgkin disease

Know the biologic characteristics of the Reed-Sternberg cell

Know the incidence of each of the pathologic subtypes of Hodgkin disease in children

Recognize the morphologic and immunophenotypic characteristics of Reed-Sternberg cells and of Reed-Sternberg cell variants

**c. Clinical presentation**

Recognize the clinical presentation and pattern of spread of Hodgkin disease by anatomic site

Know the differential diagnosis of acute lymphadenopathy and chronic lymphadenopathy simulating malignant lymphoma

Recognize impaired cellular immunity in a patient with Hodgkin disease

Know the most common clinical presentation of Hodgkin disease in children

Know the laboratory abnormalities that may be seen in children with Hodgkin disease at the time of diagnosis

**d. Diagnosis and staging**

Utilize imaging modalities appropriately to determine the extent of primary disease and metastatic spread of Hodgkin disease

Know the criteria for Ann Arbor staging in patients with Hodgkin disease

**e. Treatment (See also VII.B.)**

Know the role of radiation therapy in the treatment of Hodgkin disease in children and adolescents

Know the role of chemotherapy in the treatment of Hodgkin disease in children and adolescents

Be able to monitor appropriately the response to treatment of Hodgkin disease

Plan the treatment of a relapse in a patient with Hodgkin disease

Know the principles of treatment for different stages of Hodgkin disease

**f. Prognosis**

Know the prognostic features of Hodgkin disease

Know the prognosis of Hodgkin disease according to such variables as stage and histology

**g. Complications/late effects**

Evaluate and manage a febrile patient with Hodgkin disease who has previously undergone splenectomy

Recognize the radiologic, clinical, and laboratory manifestations of recurrent Hodgkin disease

Know the complications and late effects of treatment for Hodgkin disease

Recognize the significance of persistent abnormalities revealed by computed tomography after therapy for Hodgkin disease

Know the increased risk for and kinds of second malignant neoplasms that are most likely after treatment for Hodgkin disease

**2. Non-Hodgkin lymphoma**

**a. Epidemiology/predisposing factors/genetics**

Know the association of Epstein-Barr virus and human immunodeficiency virus with non-Hodgkin lymphoma

Know the cytogenetic and molecular genetic abnormalities associated with non-Hodgkin lymphoma

Know the chromosomal alterations associated with Burkitt lymphoma

Know the gene rearrangement patterns which distinguish monoclonal and polyclonal lymphoproliferative processes

Understand the relationship of oncogenes to structural genes in chromosome 8:14 translocation

Recognize the clinical and epidemiologic characteristics that distinguish "endemic" from "sporadic" Burkitt lymphoma

Know that the inherited and acquired immunodeficiency states predispose to the development of non-Hodgkin lymphoma

**b. Histopathology and immunophenotype**

Recognize the pathologic subtypes of non-Hodgkin lymphoma in children and adolescents

Recognize the pathologic subtypes of non-Hodgkin lymphoma relative to primary site and pattern of spread

Know the characteristic immunophenotype of Burkitt and Burkitt-like

lymphomas

Know the relative importance of heavy and light chain immunoglobulin expression in the diagnosis of Burkitt or Burkitt-like lymphomas

Know the characteristic immunophenotype of T-cell lymphoblastic NHL

Know that immunopheno typically, Burkitt and Burkitt-like lymphomas are identical to B-cell ALL, and T-cell lymphoblastic lymphomas are identical to T-cell ALL

Know the variety of immunophenotypes which may be seen in large cell lymphomas in children

**c. Clinical presentation**

Recognize the clinical presentation of non-Hodgkin lymphoma by anatomic site, such as superior vena cava syndrome

Know the clinical presentation and laboratory findings of Burkitt lymphoma

Recognize when tumor lysis syndrome can be present in non-Hodgkin lymphoma

Recognize the large B-cell lymphomas that arise in the anterior mediastinum

**d. Diagnosis and staging**

Utilize appropriate imaging modalities to determine the extent of non-Hodgkin lymphoma

Utilize appropriate laboratory studies to determine the extent of non-Hodgkin lymphoma

Know that diagnosis of non-Hodgkin lymphoma can sometimes be made on pleural effusion or ascitic fluid

Recognize CNS involvement in a patient with non-Hodgkin lymphoma

Know how to use the degree of bone marrow involvement to distinguish stage IV non-Hodgkin lymphoma and acute leukemia of similar immunophenotype

Recognize that advanced stage T-cell lymphoblastic lymphoma and T-cell acute lymphoblastic leukemia represent different stages of the same disease

Recognize that advanced stage Burkitt lymphoma or Burkitt-like non-Hodgkin lymphoma and B-cell acute lymphoblastic leukemia represent different stages of the same disease

**e. Treatment (See also VII.B.)**

Know the role of surgery in the treatment of non-Hodgkin lymphoma

Know the role of radiation therapy in the treatment of non-Hodgkin lymphoma

Know the role of chemotherapy in the treatment of specific types of non-Hodgkin lymphoma

Know the emergency management of a large mediastinal mass in non-Hodgkin lymphoma

Know the emergency management of tumor lysis syndrome in non-Hodgkin lymphoma

Know the emergency management of spinal cord compression in non-Hodgkin lymphoma

Appropriately monitor the response to treatment of non-Hodgkin lymphoma

Plan the treatment for a patient with advanced stage Burkitt lymphoma or Burkitt-like non-Hodgkin lymphoma

Know the principles of treatment for different stages and histologies of non-Hodgkin lymphoma

Plan the treatment for a patient with limited non-Hodgkin lymphoma

**f. Prognosis**

Know the prognostic features of non-Hodgkin lymphoma

Know the prognosis of non-Hodgkin lymphoma according to such variables as stage, histology, and immunophenotype

**g. Complications/late effects**

Know the complications and late effects of the treatment of non-Hodgkin lymphoma

**H. Malignant solid tumors**

**1. Bone tumors**

**a. Osteosarcoma**

**(1). Epidemiology/predisposing factors/genetics**

Know the cytogenetic and molecular genetic abnormalities associated with osteosarcoma

Know the epidemiology of osteosarcoma

Know that osteosarcoma can occur as a late effect of radiation therapy

Know that patients with hereditary retinoblastoma are at increased risk for

osteosarcoma

**(2). Pathology**

Recognize the pathologic subtypes of osteosarcoma

Know that the histopathologic basis for making the diagnosis of osteosarcoma is finding osteoid-producing malignant cells

**(3). Clinical presentation**

Recognize the most common skeletal locations for primary osteosarcoma

Know the most common metastatic sites in osteosarcoma

**(4). Diagnosis and staging**

Utilize appropriate imaging modalities to determine the extent and metastatic spread of osteosarcoma

Identify the radiologic appearance of osteosarcoma of long bones

Know the differential diagnoses for a primary bone lesion suspected of being osteosarcoma

**(5). Treatment**

Know the role of surgery in the treatment of primary osteosarcoma and in the treatment of metastatic osteosarcoma

Know the role of chemotherapy in the treatment of osteosarcoma

Know the role of neoadjuvant and post-operative chemotherapy in the treatment of osteosarcoma

Know the available surgical options for treatment of osteosarcoma

Plan the treatment of parosteal and periosteal variants of osteosarcoma

Know the principles of treatment for different stages of osteosarcoma

Be able to monitor appropriately a patient's response to treatment of osteosarcoma

**(6). Prognosis**

Know the laboratory findings that have prognostic importance in osteosarcoma

Know the prognostic features and prognosis of osteosarcoma, including stage and histology

Know the prognosis of osteosarcoma according to stage and histology

Know how the location of the primary tumor in osteosarcoma influences the prognosis

Know that the histopathologic response (% necrosis) in osteosarcoma to preoperative chemotherapy is of prognostic significance

Know how tumor size at diagnosis of osteosarcoma influences prognosis

**(7). Complications/late effects**

Know the complications and late effects of osteosarcoma

Know the complications and late effects of surgery performed in the treatment of osteosarcoma

Know the complications and late effects of chemotherapy in the treatment of osteosarcoma

**b. Ewing sarcoma**

**(1). Epidemiology/predisposing factors/genetics**

Know the cytogenetic and molecular genetic abnormalities associated with Ewing sarcoma

Know the association of t(11:22) with both Ewing sarcoma and primitive neuroectodermal tumor

**(2). Pathology**

Formulate a differential diagnosis of small round cell tumors of bone based on pathologic characteristics

Recognize the pathologic similarities and differences between Ewing sarcoma and primitive neuroectodermal tumor

Understand the use of molecular assays in the diagnosis of Ewing sarcoma and primitive neuroectodermal tumor

**(3). Clinical presentation**

Recognize the clinical presentation of Ewing sarcoma by anatomic site and know the most common primary sites

Know the laboratory features of extraosseous Ewing sarcoma

**(4). Diagnosis and staging**

Utilize appropriate imaging modalities to determine the extent and metastatic spread of Ewing sarcoma

Recognize the radiologic findings of Ewing sarcoma

**(5). Treatment (see also section VII.B)**

Know the role of surgery in the treatment of Ewing sarcoma

Know the role of irradiation in the treatment of Ewing sarcoma

Know the role of chemotherapy and preoperative chemotherapy in the treatment of Ewing sarcoma

Be able to appropriately monitor the response to treatment of Ewing sarcoma

Know the principles of treatment for different stages of Ewing sarcoma

**(6). Prognosis**

Understand the prognostic variables in Ewing sarcoma

**(7). Complications/late effects**

Know the complications and late effects of treatment of Ewing sarcoma according to type of therapy

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**

Understand the inheritance pattern of unilateral and bilateral retinoblastoma

Know the cytogenetic and molecular genetic abnormalities associated with retinoblastoma

Understand the limitations and use of DNA-based diagnoses in genetic counseling of patients with retinoblastoma

**b. Pathology**

Recognize the importance of pathologic examination relative to the extent of primary tumor and pattern of spread in retinoblastoma

**c. Clinical presentation**

Recognize the clinical presentation of retinoblastoma, including the differences between unilateral and bilateral

Recognize the clinical manifestations of trilateral retinoblastoma

**d. Diagnosis and staging**

Know the differential diagnosis of retinoblastoma

Be able to appropriately utilize imaging modalities to determine the extent and metastatic spread of retinoblastoma

Stage retinoblastoma according to the intraocular extent of the tumor

Stage retinoblastoma according to the pathologic findings after enucleation

Know the most common metastatic sites of retinoblastoma

**e. Treatment**

Know the role of surgery in the treatment of retinoblastoma

Know the role of irradiation in the treatment of retinoblastoma

Know the role of chemotherapy in the treatment of retinoblastoma

Know the role of local surgical techniques, such as photocoagulation, in the treatment of retinoblastoma

Appropriately monitor the response to treatment of retinoblastoma

Plan the treatment according to disease stage of a patient with bilateral retinoblastoma

Know the management of unilateral retinoblastoma

Know the proper follow-up monitoring of an infant who has had enucleation for unilateral retinoblastoma

Know the proper screening and follow-up for children who are siblings of a patient with retinoblastoma

Know the principles of treatment for various stages of retinoblastoma

**f. Prognosis**

Know the prognostic features and the prognosis of retinoblastoma

**g. Complications/late effects**

Know the complications and late effects of retinoblastoma and its associated treatment

**3. Neuroblastic tumors**

**a. Epidemiology/predisposing factors/genetics**

Know the cytogenetic and molecular genetic abnormalities associated with



neuroblastoma

**b. Pathology**

Recognize the characteristic pathologic features of neuroblastomic tumors

Know the relationship of pathologic classification to prognosis and outcome in patients with neuroblastoma

**c. Clinical presentation**

Know the association of myoclonic encephalopathy with neuroblastoma

Recognize the clinical and laboratory findings of neuroblastoma

Know the association of intractable secretory diarrhea with neuroblastomic tumors

**d. Diagnosis and staging**

Know how to distinguish neuroblastoma in bone marrow from other abnormal cells

Utilize appropriate imaging modalities to determine the extent and metastatic spread of neuroblastoma

Utilize appropriate laboratory studies to determine the extent and metastatic spread of neuroblastoma

**e. Treatment (See also VII.B.)**

Know the principles of treatment for various stages of neuroblastoma

Know the role of surgery in the treatment of neuroblastoma

Know the role of irradiation in the treatment of neuroblastoma

Know the role of chemotherapy in the treatment of neuroblastoma

Know the role of biologic response modifiers in the treatment of neuroblastoma

Be able to appropriately monitor the response to treatment of neuroblastoma

**f. Prognosis**

Know the laboratory, pathologic, and molecular biologic variables of prognostic significance (eg, DNA index, MYCN amplification) in patients with neuroblastoma

Know the clinical variables (such as age and stage) of prognostic significance and their associated prognoses, in patients with neuroblastoma

**g. Complications/late effects**

Know the complications and late effects of neuroblastoma and its treatment

Know the neurologic complications and late effects of neuroblastoma presenting with myoclonic encephalopathy

**4. Peripheral neuroectodermal tumors**

**a. Clinical presentation**

Recognize the clinical presentation of peripheral neuroectodermal tumors by anatomic site

**b. Diagnosis and staging**

Recognize esthesioneuroblastoma

Utilize appropriate imaging modalities to determine the extent and metastatic spread of peripheral neuroectodermal tumors

Utilize appropriate laboratory studies to determine the extent and metastatic spread of peripheral neuroectodermal tumors

Know the chromosomal and molecular alterations characteristic of peripheral neuroectodermal tumor

**c. Treatment**

Know the role of surgery in the treatment of peripheral neuroectodermal tumors

Know the role of irradiation in the treatment of peripheral neuroectodermal tumors

Know the role of chemotherapy in the treatment of peripheral neuroectodermal tumors

Be able to appropriately monitor the response to treatment of peripheral neuroectodermal tumors

Know the principles of treatment for peripheral neuroectodermal tumors

**d. Prognosis**

Know the prognostic factors, and their associated prognoses, of primitive neuroectodermal tumors

**e. Complications/late effects**

Know the complications and late effects of primitive neuroectodermal tumors and their treatment

## 5. Brain tumors

### a. Epidemiology/predisposing factors/genetics

Know the cytogenetic and molecular genetic abnormalities associated with brain tumors

Recognize the association between brain tumors and heritable syndromes (eg, neurofibromatosis, tuberous sclerosis)

Know the association between pineoblastoma and retinoblastoma

### b. Pathology

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

Recognize the pathologic subtypes of brain tumors relative to primary tumor site and pattern of spread

Recognize the relationship between histologic grade of gliomas and prognosis

### c. Clinical presentation

Recognize the clinical presentation of brain tumors by anatomic site

Know the clinical and laboratory manifestations of different central nervous system tumors

Know the clinical and laboratory features of medulloblastoma

Know the clinical and laboratory features of cerebellar astrocytoma

Know the clinical and laboratory features of brain stem glioma

Know the clinical and laboratory features of pineal tumors

Know the clinical and laboratory features of ependymoma

Know the clinical and laboratory features of primitive neuroectodermal tumors

Know the clinical and laboratory features of optic pathway gliomas

Recognize the relationship between age and anatomic site in the clinical presentation of brain tumors

Know the clinical and laboratory features of hypothalamic tumors

Know the clinical and laboratory features of intramedullary spinal cord tumors

### d. Diagnosis and staging

Utilize appropriate imaging modalities to determine the extent and metastatic spread of brain tumors

Know which central nervous system tumors are associated with spinal cord metastases

Know the appropriate imaging, CSF, and other laboratory studies to use for staging CNS tumors

Know the patterns of metastasis and spread characteristic of CNS tumors

**e. Treatment (see also section VII.B)**

Know the role of surgery in the treatment of brain tumors

Recognize that surgery alone is curative for cerebellar astrocytoma

Know the role of irradiation in the treatment of brain tumors

Know the role of chemotherapy in the treatment of brain tumors

Monitor the response to treatment of brain tumors using clinical modalities

Monitor the response to treatment of brain tumors using imaging modalities

Monitor the response to treatment of brain tumors using biochemical markers

Know the principles of management for patients with medulloblastoma

Know the principles of management for patients with low grade astrocytoma

Know the principles of management for patients with brain stem glioma

Know the principles of management for patients with pineal tumors

Know the principles of management for patients with ependymoma

Know the principles of management for patients with primitive neuroectodermal tumors

Know the principles of management for patients with high grade gliomas (anaplastic astrocytoma and glioblastoma multiforme)

Know the principles of management of patients with central nervous system germ cell tumors

**f. Prognosis**

Know the prognostic features (eg, stage and histology), and their associated prognoses, of brain tumors

Know the natural history of medulloblastoma

Know the natural history of low grade astrocytoma

Know the natural history of brain stem glioma

Know the natural history of pineal cell tumors

Know the natural history of ependymoma

Know the natural history of central nervous system primitive neuroectodermal tumors

Identify the prognostic factors in patients with medulloblastoma

Identify the prognostic factors in patients with astrocytoma

Identify the prognostic factors in patients with brain stem glioma

Identify the prognostic factors in patients with pineal cell tumors

Identify the prognostic factors in patients with ependymoma

Identify the prognostic factors in patients with primitive neuroectodermal tumors

Know the natural history of high grade gliomas

Identify the prognostic factors in patients with central nervous system germ cell tumors

**g. Complications/late effects**

Know the complications and late effects of brain tumors

Know the late effects of brain tumors and their treatment in patients of various ages

Know the secondary malignancies associated with treatment of brain tumors

Know the potential neurologic sequelae of brain tumors and their treatment

Know the potential endocrine sequelae of brain tumors and their treatment

Know the potential intellectual sequelae of brain tumors and their treatment

Know the complications and late effects of surgery performed in the treatment of brain tumors

Know the complications and late effects of irradiation in the treatment of brain tumors

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**

Know the cytogenetic and molecular genetic abnormalities associated with hepatoblastoma and hepatocellular carcinoma

Know the association of familial polyposis coli with hepatoblastoma and hepatocellular carcinoma

Know which congenital conditions are associated with an increased risk of hepatoblastoma

Know the association of hepatocellular carcinoma with inborn errors of metabolism causing cirrhosis

### **b. Pathology**

Recognize the pathologic subtypes of hepatoblastoma and hepatocellular carcinoma relative to prognosis and pattern of spread

### **c. Clinical presentation**

Recognize the clinical presentation of hepatoblastoma and hepatocellular carcinoma

### **d. Diagnosis and staging**

Utilize appropriate imaging modalities to determine the extent and metastatic spread of hepatoblastoma and hepatocellular carcinoma

Utilize appropriate laboratory studies to determine the extent and metastatic spread of hepatoblastoma and hepatocellular carcinoma

### **e. Treatment**

Know the role of surgery in the treatment of hepatoblastoma and hepatocellular carcinoma

Know the role of irradiation in the treatment of hepatoblastoma and hepatocellular carcinoma

Know the role of chemotherapy in the treatment of hepatoblastoma and hepatocellular carcinoma

Know the role of liver transplantation in the treatment of hepatoblastoma and hepatocellular carcinoma

Appropriately monitor the response to treatment of hepatoblastoma and hepatocellular carcinoma

Know the principles of management of hepatoblastoma and hepatocellular carcinoma

**f. Prognosis**

Know the prognostic features, and their associated prognoses, of hepatoblastoma and hepatocellular carcinoma

**g. Complications/late effects**

Know the complications and late effects of hepatoblastoma and hepatocellular carcinoma and their therapy

**7. Renal tumors**

**a. Epidemiology/predisposing factors/genetics**

Know the cytogenetic and molecular genetic abnormalities associated with renal tumors

Know the somatic abnormalities associated with Wilms tumor

**b. Pathology**

Recognize the pathologic subtypes of renal tumors relative to primary tumor and pattern of spread

Know the relationship between histologic pattern of Wilms tumor and prognosis

Know the significance of the presence of nephroblastomatosis in a patient with Wilms tumor

Know the biologic characteristics and clinical management of mesoblastic nephroma

**c. Clinical presentation**

Recognize the clinical presentation of renal tumors

Know the congenital anomalies that are associated with an increased risk of Wilms tumor

**d. Diagnosis and staging**

Utilize appropriate imaging modalities to determine the extent metastatic spread of renal tumors

Utilize appropriate laboratory studies to determine the extent and metastatic spread of renal tumors

Know the procedures necessary to stage Wilms tumor (stages I-V)

**e. Treatment**

Know the complications of radiation therapy in patients with Wilms tumor

Know the role of surgery in the treatment of renal tumors

Plan the management of an infant with a mesoblastic nephroma

Know the role of irradiation in the treatment of renal tumors

Know the role of chemotherapy in the treatment of renal tumors

Be able to appropriately monitor the response to treatment of renal tumors

Understand the therapy of pulmonary metastases of Wilms tumor

Know the appropriate treatment of Wilms tumor in relation to stage and histologic subtype

Plan the management of a patient with recurrent Wilms tumor

Know the principles of management of renal tumors

**f. Prognosis**

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

**g. Complications/late effects**

Know the complications and late effects of renal tumors and their treatment

**8. Rhabdomyosarcoma**

**a. Epidemiology/predisposing factors/genetics**

Know the cytogenetic and molecular genetic abnormalities associated with rhabdomyosarcoma

**b. Pathology**

Recognize how rhabdomyosarcoma is differentiated from similar tumors by immunohistochemical tests

Recognize the pathologic subtypes of rhabdomyosarcoma relative to prognosis and patterns of presentation and spread

**c. Clinical presentation**

**(1). Head/neck (parameningeal vs nonparameningeal)**

Recognize the clinical presentation of rhabdomyosarcoma affecting the head and neck (parameningeal versus nonparameningeal)

**(2). Orbit and nasopharynx**



Recognize the clinical presentation of orbital rhabdomyosarcoma

Recognize the clinical presentation of nasopharyngeal rhabdomyosarcoma

**(3). Trunk**

Recognize the clinical presentation of rhabdomyosarcoma affecting the trunk

**(4). Genitourinary system**

**(a). Bladder**

Recognize the clinical presentation of rhabdomyosarcoma affecting the bladder

**(b). Prostate gland**

Recognize the clinical presentation of rhabdomyosarcoma affecting the prostate gland

**(c). Vagina**

Recognize the clinical presentation of vaginal rhabdomyosarcoma

**(5). Extremities**

Recognize the clinical presentation of rhabdomyosarcoma affecting the extremities

**d. Diagnosis and staging**

Be able to appropriately utilize imaging and laboratory modalities to determine the extent and metastatic spread of rhabdomyosarcoma

**e. Treatment**

Know the role of surgery in the treatment of rhabdomyosarcoma

Know the role of irradiation in the treatment of rhabdomyosarcoma

Know the role of chemotherapy in the treatment of rhabdomyosarcoma

Be able to monitor appropriately the response to treatment of rhabdomyosarcoma

Know the principles of management of rhabdomyosarcoma

**f. Prognosis**

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

Know the prognostic significance of tumor recurrence in rhabdomyosarcoma

**g. Complications/late effects**

Know the complications and late effects of rhabdomyosarcoma and its therapy

**9. Soft tissue sarcomas other than rhabdomyosarcoma**

**a. Epidemiology/predisposing factors/genetics**

Recognize the cytogenetic and molecular genetic abnormalities associated with soft tissue sarcomas other than rhabdomyosarcoma

**b. Pathology**

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

**c. Clinical presentation**

Recognize the clinical presentation of soft tissue sarcomas other than rhabdomyosarcoma by anatomic site

**d. Diagnosis and staging**

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

**e. Treatment**

Know the role of surgery in the treatment of soft tissue sarcomas other than rhabdomyosarcoma

Know the role of irradiation in the treatment of soft tissue sarcomas other than rhabdomyosarcoma

Know the role of chemotherapy in the treatment of soft tissue sarcomas other than rhabdomyosarcoma

Appropriately monitor the response to treatment of soft tissue sarcomas other than rhabdomyosarcoma

Know the principles of management of soft-tissue sarcomas other than rhabdomyosarcoma

**f. Prognosis**

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

**g. Complications/late effects**

Know the complications and late effects of soft-tissue sarcomas other than rhabdomyosarcoma and their treatment

**10. Gonadal/Germ cell tumors**

**a. Epidemiology/predisposing factors/genetics**

Know the cytogenetic and molecular genetic abnormalities associated with gonadal/germ cell tumors

Know the age distribution of patients with gonadal/germ cell tumors

**b. Pathology**

Recognize the pathologic subtypes of gonadal/germ cell tumors relative to prognosis and patterns of spread

**c. Clinical presentation**

Recognize the clinical presentation of gonadal/germ cell tumors by anatomic site

Know the biologic markers and clinical correlates of germ cell tumors

**d. Diagnosis and staging**

Utilize appropriate imaging modalities and laboratory studies to determine the extent and metastatic spread of gonadal/germ cell tumors

**e. Treatment**

Know the role of surgery in the treatment of gonadal/germ cell tumors

Know the role of radiation therapy in the treatment of gonadal/germ cell tumors

Know the role of chemotherapy in the treatment of gonadal/germ cell tumors

Be able to monitor appropriately the response to treatment of gonadal/germ cell tumors

Know the principles of management of gonadal/germ cell tumors

**f. Prognosis**

Know the prognostic features, and their associated prognoses, of gonadal/germ cell tumors

Know the clinical, radiologic, and prognostic features of sacrococcygeal germ cell tumors

**g. Complications/late effects**

Know the complications and late effects of gonadal/germ cell tumors and their treatment

## **I. Histiocytic disorders**

### **1. Epidemiology/predisposing factors/genetics**

Know the inheritance pattern of familial hemophagocytic lymphohistiocytosis

### **2. Pathology**

Know the pathologic classification of childhood histiocytosis

Recognize the histopathologic features of histiocytosis

### **3. Clinical presentation**

Recognize the clinical and laboratory features of Langerhans cell histiocytosis

Recognize the clinical and laboratory features of sinus histiocytosis with massive lymphadenopathy

Recognize the clinical and laboratory features of familial hemophagocytic lymphohistiocytosis

### **4. Diagnosis and staging**

Recognize hemophagocytosis in bone marrow

Know the appropriate laboratory and imaging studies to determine the extent of Langerhans cell histiocytosis

Know the appropriate laboratory and imaging studies to determine the extent of hemophagocytic lymphohistiocytosis

### **5. Treatment**

Plan appropriate management of Langerhans cell histiocytosis based on disease effects, location and extent

Plan appropriate management of hemophagocytic lymphohistiocytosis

### **6. Prognosis**

Know the prognostic features, and their associated prognoses, of Langerhans cell histiocytosis

Know the prognostic features, and their associated prognoses, of viral-associated hemophagocytic syndrome and familial erythrophagocytic lymphohistiocytosis

Know the prognostic features, and their associated prognoses, of sinus histiocytosis

## **7. Complications/late effects**

Know the complications of Langerhans cell histiocytosis and its treatment

## **J. Supportive care**

### **1. Nutrition**

Know the nutritional needs of patients of different ages undergoing antineoplastic therapy

Understand the principles and complications of total parenteral nutrition

Know the role of nasogastric feeding and gastrostomy in the care of patients

### **2. Dental care and oral hygiene**

Know the importance of dental hygiene in patients receiving antineoplastic treatment and/or HSCT

Know the importance of prophylactic dental treatment in patients receiving radiation therapy to the head and neck

Know how to treat buccal ulceration in a patient receiving antineoplastic therapy

### **3. Central venous access**

Know the indications for and the complications of central venous catheterization

Know the advantages and disadvantages of the different types of central venous access

Know the indications for removing a central venous access

### **4. Pain control**

Know which factors predispose children to narcotic addiction in the management of pain

Understand the principles of pain control, including pain assessment

Know the various analgesic and narcotic drugs and their routes of administration and side effects

Know the treatment for opioid overdose and the attendant risks of such treatment

Understand the management approach to procedural pain

### **5. Fatal illness and terminal care**

Know how to arrange for terminal home care for a child with cancer

Know how to counsel family members at times of diagnosis, relapse, and terminal illness

Know the effect of fatal illness and its treatment on the patient's family members, including siblings

Know the community resources available to assist the family of a child with cancer

Know the principles and approach to management for a child who is approaching death as a result of terminal illness

## **6. Antiemetics**

Know the principles of management for acute and delayed therapy- induced vomiting

Know how to prevent and treat side effects of a phenothiazine antiemetic

## **7. Schooling**

Know how to achieve appropriate and optimal school re-entry for patients receiving antineoplastic therapy

Know how to utilize community and school-based resources in maintaining educational continuity for the child receiving antineoplastic treatment

# **VI. Immunologic Abnormalities**

## **A. Infections in immunocompromised patients**

### **1. Prophylaxis**

#### **a. Bacterial**

##### **(1). Indications for antimicrobials**

Know the role of prophylactic antibiotics in preventing bacterial infection in an immunocompromised patient

Know the indications for and risks and benefits of trimethoprim with sulfamethoxazole for prophylaxis against bacterial infections in an immunocompromised patient

Know the indications for and benefits of antibiotic prophylaxis for patients with anatomic or functional asplenia

#### **b. Fungal**

Know the indications and alternative topical and systemic methods of achieving antifungal prophylaxis in an immunocompromised patient

**c. Viral**

**(1). Rubeola**

Know the management of rubeola exposure in a nonimmunized immunocompromised patient

Know the clinical manifestations of rubeola in immunocompromised patients

**(2). Cytomegalovirus (CMV) (see also IV.F.1, CSS 721)**

Know the association of CMV disease with reduced T-lymphocyte mediated immunity in the post-transplantation period

Understand the use of CMV-negative blood products in the prevention of CMV infection

Understand the issues surrounding leukocyte depletion by filtration of cellular blood products in prevention of CMV infection in an immunocompromised host

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

Know the clinical manifestations of CMV disease in immunocompromised patients

Know the laboratory assays that confirm the presence of acute CMV infection

Know the modalities for CMV treatment in an immunocompromised patient

**(3). Herpes zoster, varicella, and herpes simplex**

Know the management of varicella exposure in an immunocompromised patient

Understand that prophylaxis can prevent herpes simplex virus and varicella zoster virus reactivation in immunocompromised patients

Understand the risk factors for herpes simplex reactivation in the immunocompromised patient

**d. Pneumocystis jiroveci (carinii)**

Know the medications available for prophylaxis against *P. jiroveci* (carinii) in immunosuppressed patients

**2. Treatment of infection in immunocompromised patients**

**a. Bacterial**

Know the common and uncommon bacteria causing infections in the immunocompromised host

Know the appropriate antimicrobial therapy for treatment of suspected or proven bacterial infection in an immunocompromised patient

**(1). Indications for antimicrobials**

Know the evaluation and management of fever in a patient with neutropenia

**(2). Complications of antimicrobials**

Recognize the interaction of antibiotics and chemotherapeutic agents

**b. Fungal**

Know the common and uncommon fungi causing infections in the immunocompromised host

Know the appropriate antimicrobial therapy for treatment of suspected or proven fungal infection in an immunocompromised patient

Know the indications for empiric anti-fungal therapy in the febrile, neutropenic patient

**c. Viral**

Know the common and uncommon viruses causing infections in the immunocompromised host

Know the appropriate antimicrobial therapy for treatment of suspected or proven viral infection in an immunocompromised patient

Know the clinical manifestations of herpes simplex infection in immunocompromised patients

Know the risk, presentation, and management of varicella zoster virus dissemination in the immunocompromised host who has chickenpox

**d. Protozoal infections**

Know the common and uncommon protozoans causing infections in the immunocompromised host

Know the appropriate antimicrobial therapy for treatment of suspected or proven protozoan infection in an immunocompromised patient

Know the approach to diagnosis and modalities of treatment for *P. jiroveci* (carinii) infection

**e. Other**

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**

Know how to evaluate a child with recurrent infections for possible congenital immunodeficiency diseases

Know the patterns of inheritance of immunologic disorders

#### **b. Relationship between immunodeficiency and cancer**

Understand which immune deficiencies can lead to lymphoproliferative disease

Understand which immunodeficiency states are associated with increased incidence of cancer

Know the mechanisms by which immunodeficiency states can have increased risk for cancer

#### **c. Specific congenital immune deficiencies**

##### **(1). Wiskott-Aldrich syndrome**

Know the clinical manifestations, inheritance, and laboratory findings associated with Wiskott-Aldrich syndrome

Know that T-lymphocyte dysfunction is associated with Wiskott-Aldrich syndrome

Know the roles of splenectomy and HSCT in managing thrombocytopenia in Wiskott-Aldrich syndrome

##### **(2). Disorders of immunoglobulin production**

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)**

Recognize the hematological manifestations of various forms of SCID

Know that some patients with SCID may have panhypogammaglobulinemia and increased lymphocyte counts

Know the characteristics of maternal lymphocyte engraftment in SCID

Appreciate the risk of transfusion-associated graft-versus-host disease in SCID

**(4). X-linked lymphoproliferative disease**

Know the hematologic disorders associated with X-linked lymphoproliferative disease

Recognize the importance of a family history of lymphoproliferative disease, bone marrow failure, and immunodeficiency in male maternal relatives

Know the abnormal response of patients with X-linked lymphoproliferative disease to Epstein-Barr virus

**2. Acquired immunodeficiency syndrome (AIDS)**

Know the hematologic abnormalities associated with HIV infection and retroviral therapies

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)**

Know the lymph node pathology that occurs in ALPS and the tests used to screen for the diagnosis of ALPS

Know that autoimmune cytopenias and lymphoma are associated with ALPS

**VII. Hematopoietic Stem Cell Transplantation (HSCT)**

**A. Biologic Principles**

**1. Types of hematopoietic stem cell transplantation**

Know the definitions of allogeneic, syngeneic, and autologous hematopoietic stem cell transplantation

**2. Hematopoietic stem cells for transplantation**

Know from which tissues hematopoietic stem cells may be harvested

**3. HLA system**

Recognize the difference between class I and class II antigens

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

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)**

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

Recognize that allogeneic marrow graft rejection is mediated by residual host T-lymphocytes responding to histocompatibility differences in the donor cells

## B. Indications

Know the role of HSCT for acute lymphoblastic leukemia in different disease stages (see also section V.D.5.c)

Know the role of HSCT in the treatment of Hodgkin disease (see also section V.G.1.e)

Know the role of HSCT in the treatment of non-Hodgkin lymphoma (see also section V.G.2.e)

Know the possible role of HSCT in the treatment of Ewing sarcoma (see also section V.H.1.b.(5))

Know the possible role of HSCT in the treatment of neuroblastoma (see also section V.H.3.e)

Know the possible role of HSCT in the treatment of brain tumors (see also section V.H.5.e)

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)

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

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

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

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

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

Understand the rationale for HSCT in patients with genetic disorders

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

Recognize donor or recipient conditions that may preclude HSCT

## **C. Methods**

### **1. Donor selection**

Judge the suitability of a donor-recipient match, given the major and minor HLA class I and II typing

Understand the advantages and disadvantages of allogeneic HSCT as compared with autologous HSCT in various disorders

Know the potential indications for the use of peripheral blood stem cells

Recognize pertinent factors besides HLA typing that should be considered in selection of allogeneic HSCT donors

Understand the advantages and disadvantages of the various available hematopoietic stem cell sources with regard to degree of match, engraftment, and incidence of GVHD

Understand the components of an HSCT donor evaluation

Understand the relative advantages and disadvantages of stem cell source, comparing peripheral blood vs bone marrow vs cord blood

### **2. Preparative therapy**

Recognize the need to adjust preparative regimens for patients with DNA repair defects like Fanconi anemia or dyskeratosis congenita

Understand the rationale for preparative therapy in HSCT for different clinical indications and using different donor types

Understand that preparative therapy may not be necessary in some patients with SCID

Understand the role of submyeloablative therapy in HSCT

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**

Understand the methods of collecting and preserving peripheral blood stem cells

Understand the methods available to mobilize peripheral blood stem cells

#### **b. Umbilical cord stem cells**

Understand collection and storage methods of umbilical cord stem cells

**c. Stem cell dose**

Understand the importance of CD34 quantification on HSCT product preparation and selection

Recognize the appropriate stem cell dose for HSCT

Understand the relationship between cell dose and engraftment

**4. Marrow processing**

**a. T cell**

Understand the risks and benefits of lymphocyte depletion for graft-versus-host disease prophylaxis

Recognize the methods by which T-lymphocytes can be separated and/or removed from marrow or peripheral blood stem cells

**b. Tumor cell**

Know the methods for purging autologous marrow or peripheral blood of malignant cells (positive and negative selection)

**D. Outcomes**

**1. Graft versus host disease**

Recognize the clinical and laboratory manifestations of acute graft-versus-host disease

Recognize the clinical and laboratory manifestations of chronic graft-versus-host disease

Evaluate a patient who has undergone HSCT and differentiate graft-versus-host disease from other complications of HSCT

Know which drugs are useful for prevention and/or treatment of graft-versus-host disease after HSCT

Recognize risk factors for acute graft-versus-host disease following HSCT

Recognize risk factors for chronic graft-versus-host disease following HSCT

Recognize which histocompatibility antigens are most influential in the causation of graft-versus-host disease

**2. Graft rejection**

Know the factors associated with graft rejection

Know the options for management of graft rejection

### **3. Complications**

#### **a. Infections**

Recognize the spectrum, timing, and specific organisms involved in the infectious complications that may occur following HSCT

Know how post-transplant immune reconstitution influences the pattern and frequency of infection

Recognize risk factors for infection following HSCT

Recognize the factors that influence the rate of immune reconstitution following HSCT

Know the microorganisms that cause pneumonia following HSCT

Know the infectious complications and their management following autologous HSCT

Know the strategies available for the prevention of infection following HSCT

#### **b. Non-infectious complications**

##### **(1). Early onset**

Recognize the unique problems of patients with Fanconi anemia, and other DNA-repair defects, undergoing HSCT

Know what factors increase the risk of post HSCT EBV lymphoproliferative disease

Recognize the causes of interstitial pneumonitis following HSCT

Recognize the signs, symptoms, and diagnostic findings of hepatic veno-occlusive disease following HSCT

Recognize the risk of and factors associated with cardiac failure following HSCT

Recognize the risk of and factors associated with renal dysfunction following HSCT

Know the toxicities associated with hematopoietic stem cell infusion

Know the clinical presentation, laboratory findings, and treatment of thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome associated with HSCT

Recognize the risk of and factors associated with hepatic dysfunction following HSCT

Recognize the risk of and factors associated with neurologic dysfunction following HSCT

Recognize the risk of and factors associated with blood group incompatibility and hemolytic complications

**(2). Late sequelae**

Know the risk for the development of cataracts in patients who have undergone HSCT

Know the risk of infertility after HSCT

Know the risk for development of endocrinopathies in patients who have undergone HSCT

Know the relationship of the conditioning regimen and the complications of HSCT

Recognize the risk of second malignancies following HSCT

Recognize the risk of and factors associated with chronic lung disease following HSCT

**c. Other**

Understand how donor source and degree of match influence the frequency and type of complications after HSCT

Understand the principles and methods for immune modulation to manage relapse after HSCT

**4. Survival**

Recognize relapse potential following HSCT for leukemias

Recognize the factors influencing post-transplant survival

Know the anticipated outcome and disease-free survival for HSCT based on donor, source of hematopoietic stem cells, and primary diagnosis

Recognize how donor, stem cell source, recipient disease, and disease status influence mortality after HSCT

**VIII. Core Knowledge in Scholarly Activities**

**A. Principles of Use of Biostatistics in Research**

**1. Types of variables**

Distinguish types of variables (eg, continuous, categorical, ordinal, nominal)

Understand how the type of variable (eg, continuous, categorical, nominal)

affects the choice of statistical test

## **2. Distribution of Data**

Understand how distribution of data affects the choice of statistical test

Differentiate normal from skewed distribution of data

Understand the appropriate use of the mean, median, and mode

Understand the appropriate use of standard deviation

Understand the appropriate use of standard error

## **3. Hypothesis testing**

Distinguish the null hypothesis from an alternative hypothesis

Interpret the results of hypothesis testing

## **4. Statistical tests**

Understand the appropriate use of the chi-square test versus a t-test

Understand the appropriate use of analysis of variance (ANOVA)

Understand the appropriate use of parametric (eg, t-test, ANOVA) versus non-parametric (eg, Mann-Whitney U, Wilcoxon) statistical tests

Interpret the results of chi-square tests

Interpret the results of t-tests

Understand the appropriate use of a paired and non-paired t-test

Determine the appropriate use of a 1- versus 2-tailed test of significance

Interpret a p-value

Interpret a p-value when multiple comparisons have been made

Interpret a confidence interval

Identify a type I error

Identify a type II error

## **5. Measurement of association**

Differentiate relative risk reduction from absolute risk reduction

Calculate and interpret a relative risk



Calculate and interpret an odds ratio

Interpret a hazard ratio

Understand the uses and limitations of a correlation coefficient

## **6. Regression**

Identify when to apply regression analysis (eg, linear, logistic)

Interpret a regression analysis (eg, linear, logistic)

Identify when to apply survival analysis (eg, Kaplan-Meier)

Interpret a survival analysis (eg, Kaplan-Meier)

## **7. Diagnostic tests**

Recognize the importance of an independent "gold standard" in evaluating a diagnostic test

Calculate and interpret sensitivity and specificity

Calculate and interpret positive and negative predictive values

Understand how disease prevalence affects the positive and negative predictive value of a test

Calculate and interpret likelihood ratios

Interpret a receiver operator characteristic curve

Interpret and apply a clinical prediction rule

## **8. Systematic reviews and meta-analysis**

Understand the purpose of a systematic review

Understand the advantages of adding a meta-analysis to a systematic review

Interpret the results of a meta-analysis

Identify the limitations of a systematic review

Identify the limitations of a meta-analysis

## **B. Principles of Epidemiology and Clinical Research Design**

### **1. Study types**

Distinguish between Phase I, II, III, and IV clinical trials

Recognize a retrospective study

Understand the strengths and limitations of retrospective studies

Recognize a case series

Understand the strengths and limitations of case series

Recognize a cross-sectional study

Understand the strengths and limitations of cross-sectional studies

Recognize a case-control study

Understand the strengths and limitations of case-control studies

Recognize a longitudinal study

Understand the strengths and limitations of longitudinal studies

Recognize a cohort study

Understand the strengths and limitations of cohort studies

Recognize a randomized-controlled study

Understand the strengths and limitations of randomized-controlled studies

Recognize a before-after study

Understand the strengths and limitations of before-after studies

Recognize a crossover study

Understand the strengths and limitations of crossover studies

Recognize an open-label study

Understand the strengths and limitations of open-label studies

Recognize a post-hoc analysis

Understand the strengths and limitations of post-hoc analyses

Recognize a subgroup analysis

Understand the strengths and limitations of subgroup analyses

## **2. Bias and Confounding**

Understand how bias affects the validity of results

Understand how confounding affects the validity of results

Identify common strategies in study design to avoid or reduce bias

Identify common strategies in study design to avoid or reduce confounding

Understand how study results may differ between distinct sub-populations (effect modification)

### **3. Causation**

Understand the difference between association and causation

Identify factors that strengthen causal inference in observational studies (eg, temporal sequence, dose response, repetition in a different population, consistency with other studies, biologic plausibility)

### **4. Incidence and Prevalence**

Distinguish disease incidence from disease prevalence

### **5. Screening**

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)

### **6. Decision analysis**

Understand the strengths and limitations of decision analyses

Interpret a decision analysis

### **7. Cost-benefit, cost-effectiveness, and outcomes**

Differentiate cost-benefit from cost-effectiveness analysis

Understand how quality-adjusted life years are used in cost analyses

Understand the multiple perspectives (eg, of an individual, payor, society) that influence interpretation of cost-benefit and cost-effectiveness analyses

### **8. Sensitivity analysis**

Understand the strengths and limitations of sensitivity analysis

Interpret the results of sensitivity analysis

### **9. Measurement**

Understand the types of validity that relate to measurement (eg, face, construct, criterion, predictive, content)

Distinguish validity from reliability

Distinguish internal from external validity

Distinguish accuracy from precision

Understand and interpret measurements of interobserver reliability (eg, kappa)

Understand and interpret Cronbach's alpha

## **C. Applying Research to Clinical Practice**

### **1. Assessment of study design, performance & analysis (internal validity)**

Recognize when appropriate control groups have been selected for a case-control study

Recognize when appropriate control groups have been selected for a cohort study

Recognize the use and limitations of surrogate endpoints

Understand the use of intent-to-treat analysis

Understand how sample size affects the power of a study

Understand how sample size may limit the ability to detect adverse events

Understand how to calculate an adequate sample size for a controlled trial (ie, clinically meaningful difference, variability in measurement, choice of alpha and beta)

### **2. Assessment of generalizability (external validity)**

Identify factors that contribute to or jeopardize generalizability

Understand how non-representative samples can bias results

Assess how the data source (eg, diaries, billing data, discharge diagnostic code) may affect study results

### **3. Application of information for patient care**

Estimate the post-test probability of a disease, given the pretest probability of the disease and the likelihood ratio for the test

Calculate absolute risk reduction

Calculate and interpret the number-needed-to treat

Distinguish statistical significance from clinical importance

#### **4. Using the medical literature**

Given the need for specific clinical information, identify a clear, structured, searchable clinical question

Identify the study design most likely to yield valid information about the accuracy of a diagnostic test

Identify the study design most likely to yield valid information about the benefits and/or harms of an intervention

Identify the study design most likely to yield valid information about the prognosis of a condition

### **D. Principles of Teaching and Learning**

#### **1. Educational theory**

Understand the basic principles of adult learning theory (eg, adult learners are self-directed, goal-oriented, practical; need to feel respected, build on life experiences; learn best when learning is based on an existing framework)

Understand the attributes of an effective learning environment

Understand the importance of "reflective practice" in teaching and learning

Identify strategies that motivate learners

Recognize the impact of the "hidden curriculum" on learning

#### **2. Feedback and Evaluation**

Identify components of effective feedback

Distinguish between formative and summative feedback

Distinguish between evaluation and feedback

Understand the strengths and weaknesses of various methods to evaluate learners

#### **3. Teaching Methods**

Understand the strengths and weaknesses of various teaching methods (eg, lecture, small group discussion, bedside teaching, simulation)

Understand that individuals may learn more effectively with certain teaching methods (eg, reading, hearing, doing) than with others

#### **4. Educational Planning**

Understand the role of needs assessment in educational planning

Distinguish between goals and learning objectives

Identify components of well-formulated learning objectives

Recognize the strengths and weaknesses of various educational outcome measures (eg, participant satisfaction, acquisition of knowledge and skills, behavioral change, patient outcomes)

## **E. Ethics in Research**

### **1. Conflicts of Interest and Commitment**

Evaluate whether an investigator has a conflict of interest during the course of a study

Understand ways to manage a conflict of interest

Understand what constitutes a conflict of commitment

### **2. Professionalism and Misconduct in Research**

Identify forms of research misconduct (eg, plagiarism, fabrication, falsification)

Differentiate honest error and differences of opinion from research misconduct

Understand the criteria for authorship of clinical research publications

### **3. Principles of Research with Human Subjects**

Understand and apply the three main principles of research ethics articulated in the Belmont Report (ie, respect for persons, beneficence, and justice)

Understand the role of analysis of risks and benefits in the ethical conduct of research

Understand the federal regulatory definitions regarding which activities are considered research

Understand the federal regulatory definitions regarding when research includes the use of human subjects

Understand the federal regulatory definition of minimal risk

Understand the functions of an Institutional Review Board

Understand when an exemption from review by the Institutional Review Board is permissible

Understand the functions of a Data Safety Monitoring Board

Understand the importance of clinical equipoise in research with human subjects

Understand the impact of "therapeutic fallacy" on clinical research with human subjects

Understand the ethical considerations of study design (eg, placebo, harm of intervention, deception, flawed design)

Understand the privacy rules regarding recruitment and participation of subjects in a research study and reporting the results of that study

#### **4. Principles of Consent and Assent**

Understand what constitutes informed consent in research

Understand how undue influence can affect obtaining consent for research

Understand how coercion can affect obtaining consent for research

Understand when an exemption from review by the Institutional Review Board is permissible (eg, medical record review of de-identified data)

Understand the special ethical considerations related to research utilizing children because of their inability to give informed consent

Distinguish among consent, assent, and permission in research involving children

#### **5. Vulnerable Populations**

Recognize that the definition of "children" is related to the underlying clinical intervention in the jurisdiction in which the child is located rather than a fixed nationwide notion of age

Recognize the types of protections that might be accorded to vulnerable populations (eg, incarcerated individuals, pregnant women, fetuses, children, mentally disabled individuals, educationally or economically disadvantaged individuals)

Understand the concept of minimal risk as it applies to research involving children

Understand the circumstances under which research that involves children and that entails greater than minimal risk may be permissible

Last Revised October 2009