

# BL

## Blood and Lymph

### Course Goals

#### Goals

1. Recognize and describe the different blood cell types, their structure and function, their production and turnover, and associated disease states.
2. Define anemia; list the major causes and describe their pathophysiology, epidemiology, genetics, typical clinical and laboratory findings, and a rational approach to treatment. Discuss the impact of a chronic disease such as sickle cell anemia on a patient and family.
3. Describe the process of hemostasis, including regulation by anticoagulant and fibrinolytic pathways; describe pathologic states involving inadequate hemostasis or thrombosis, describe typical clinical and laboratory findings with hemostatic disorders and a rational approach to treatment, including use of anticoagulation and thrombolytic therapies.
4. List and describe available blood products for transfusion, how they are collected, tested, and stored, how blood typing and crossmatching occurs, and indications for transfusion; explain how ABO and Rh mismatch between mother and fetus can lead to hemolytic disease of the newborn.
5. Describe major features of the innate and adaptive immune systems; describe the anatomy and physiology of the immune system, and recognize major histologic features of the thymus and peripheral lymphoid organs.
6. Describe normal B and T cell function, the structure and function of the 5 classes of antibodies, genetic mechanisms leading to antibody and T cell receptor formation, and the role of MHC in T cell function and transplantation.
7. List and describe the major types of immunopathology (types 1-4), including their pathophysiology and some of the laboratory and clinical findings.
8. List and describe the major rheumatologic disorders, including their laboratory, radiologic, and clinical features, epidemiology, genetics, pathophysiology, and an approach to treatment; describe major classes of pharmacologic immunomodulators, their mechanism of action, and use in the treatment of rheumatic or autoimmune disease and in the setting of transplantation.
9. List and describe the major neoplastic diseases involving the hematopoietic system, recognize their histologic, cytogenic, molecular features and epidemiology, and describe their typical prognosis and clinical course. Discuss the impact of diagnosis of a hematologic malignancy on a patient and family and potential late effects of therapy.
10. Describe major defects of the innate and adaptive immune system leading to immunodeficiency, including characteristic clinical findings and types of infections, pathophysiology, and some of the known molecular defects.
11. Describe how vaccines work and discuss some of the barriers to vaccine use in Colorado; explain the role of immune system in tumor surveillance and a rationale and approach to development of tumor vaccines and other modulation of the immune system to treat cancer.

# Spring 2019

## Blood and Lymph

### Session Learning Objectives

#### BL - Acute Leukemias

1. Contrast acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) in regards to demographics of affected patients, and prognosis.
2. Explain the concept of a "leukemic stem cell".
3. List risk factors for acute leukemia, while recalling that the majority of acute leukemias occur in the apparent absence of risk factors.
4. List common signs and symptoms exhibited by patients with acute leukemia at initial presentation, and explain the reasons for these findings.
5. List methods for immunophenotyping in acute leukemias (covered in notes for previous Introduction lecture), and list a few basic markers (bolded in notes) that would help to assign blasts to a precursor-B, precursor-T, or myeloid lineage.
6. Contrast B-ALL and T-ALL in regards to patient age and sex, manner of manifestation, and prognosis.
7. List three commonly observed cytogenetic abnormalities in B-ALL, and recall the usual patient age group and prognosis associated with these abnormalities.
8. List five factors affecting prognosis in ALL.
9. List two types of findings that would allow for a diagnosis of AML.
10. Recognize an Auer rod, and relate its clinical significance.
11. Recall the associated prognosis for the five recurrent cytogenetic abnormalities for AML listed in the notes, and recall their typical patient populations (if one is listed).
12. Explain two reasons why it is important to recognize at initial diagnosis that a case of AML is the AML with t(15;17)(aka acute promyelocytic leukemia (APL)) subtype of AML.
13. Contrast the 2 main categories of therapy-related AML, and compare their prognosis.
14. List 3 molecular markers currently used to predict prognosis in patients with AML with normal karyotype (lacking recurrent cytogenetic abnormalities), and know which of these "trumps" the other two as a driving prognostic factor.

## **BL - Anatomy and Physiology of the Immune System**

1. Define: leukocytes, mononuclear cells, polymorphonuclear cells, granulocytes, mast cells, plasma and serum.
2. Sketch schematically a neutrophil; eosinophil; basophil; small lymphocyte; lymphoblast; plasma cell; monocyte. Include the characteristic features which are used to distinguish each cell type.
3. List the normal adult white cell count and differential percentages. From these, calculate absolute counts for the different cell types (as cells of that type/uL).
4. Name the major central and peripheral lymphoid organs.
5. Describe the recirculation of lymphocytes from blood to lymph and back; include in your discussion the specialized features of lymph node blood vessel endothelium that permit recirculation.
6. Define antigen, and compare it to immunogen. Define antigenic determinant and epitope.
7. Discuss lymphocyte activation by antigen with respect to: receptor binding, proliferation, differentiation. Draw a graph showing relative time on one axis and relative lymphocyte numbers on the other, in response to antigen administration.

## **BL - Anemia Cases Part I & II (Required)**

1. List important aspects of the patient history to ask when evaluating a patient with anemia.
2. List important aspects of the physical exam when evaluating a patient with anemia.
3. Interpret the CBC, peripheral smear, and reticulocyte count in a patient with anemia.

## **BL - Anemia Cases Part III: Clicker Session**

1. List important aspects of the patient history to ask when evaluating a patient with anemia.
2. List important aspects of the physical exam when evaluating a patient with anemia.
3. Interpret the CBC, peripheral smear, and reticulocyte count in a patient with anemia.

## **BL - Anemia Due to Decreased RBC Production**

1. Describe some of the major causes for underproduction anemia and typical clinical and laboratory findings.
2. Describe the pathophysiology of the anemia of chronic disease.
3. Describe the rationale and indications for the use of erythropoietin in the management of underproduction anemia.
4. Explain the biochemical basis for B12 and folate deficiency leading to a macrocytic anemia.
5. Identify the dietary sources of vitamin B12 and folate and describe their associated sites and mechanisms of absorption, means of transport, and duration and location of storage.
6. Describe the findings in the peripheral blood and bone marrow in a patient with B12 or folate deficiency.
7. Describe the differences between vitamin B12 deficiency and folate deficiency with respect to their most common causes, time to development, presence of neurologic abnormalities, and laboratory studies used to make a diagnosis.
8. Describe the appropriate therapies for B12 deficiency and folate deficiency.

## **BL - Anemia Due to Hemolysis**

1. Define hemolysis and describe the two main mechanisms of increased destruction of RBCs: intravascular and extravascular hemolysis.
2. Describe the biochemical pathways of breakdown of hemoglobin and the relevant clinical lab tests for hemolysis.
3. Describe the major constituents of the RBC membrane and cytoskeleton, identify the major defects in hereditary spherocytosis, and relate these to the clinical and laboratory findings of the disorder.
4. Interpret an osmotic fragility test for diagnosis of hereditary spherocytosis.
5. Explain when splenectomy is indicated for treatment of hereditary spherocytosis.
6. Describe the major energy and antioxidant pathways in the RBC and explain how G6PD deficiency and pyruvate kinase deficiency affect these pathways, leading to hemolysis and describe the inheritance patterns and discuss the clinical and laboratory findings in patients with these syndromes.
7. List some of the major foods, drugs, or other chemicals which can induce hemolytic anemia in patients with G6PD deficiency.
8. Describe the pathophysiology and site of RBC destruction of immune-mediated hemolysis.
9. Describe the direct antiglobulin test (DAT or direct Coombs) and the indirect antiglobulin test (IAT or indirect Coombs).
10. Distinguish warm antibody-induced autoimmune hemolytic anemia (AIHA) from cold antibody-induced autoimmune hemolytic anemia (AIHA).
11. List and describe some of the indications, risks and benefits of splenectomy. Explain when prophylactic antibiotics are indicated post-splenectomy and the role of vaccination.

## **BL - Anemia: Overview of the Approach to a Patient**

1. Define anemia and discuss the laboratory tests used to determine its existence in an individual, keeping in mind the influence of age and gender.
2. Define reticulocyte count, absolute reticulocyte count, and reticulocyte index and discuss how these measurements are used in assessing the rate of RBC production.
3. Recognize critical findings in the history and physical examination important in determining the cause of anemia.
4. Draw a general classification scheme of anemias based on mean corpuscular volume (MCV) and reticulocyte count.
5. Describe iron metabolism and the iron cycle, and describe where iron is distributed in the body. Describe the route by which iron from the diet becomes incorporated into hemoglobin (including absorption, transport, delivery, storage, and loss of iron in humans). List factors that increase or decrease iron absorption.
6. Describe the hematologic changes associated with the development of iron deficiency and the timeline by which they occur and recognize some of the major causes for iron deficiency.
7. Describe the symptoms, signs, and laboratory findings associated with iron deficiency anemia.
8. Describe the effects of over accumulation of iron in the body and describe two treatments for iron overload.

## BL - Antibody Function and Complement

1. Define: epitope, antibody valence, affinity, precipitation, agglutination.
2. Distinguish the five classes of immunoglobulins in terms of: passage across the placenta, ability to activate complement, involvement in allergic diseases, "first line of defense", and most resistant to enzymatic digestion.
3. Describe a quantitative precipitin test where amount of antigen/tube is varied while antibody/tube is constant. Draw a graph which compares, on the ordinate, amount of precipitate obtained, with amount of antigen added/tube. Identify the zones of antigen and antibody excess, and equivalence.
4. Sketch the immune complexes obtained in antigen or antibody excess, and at equivalence, using Y as antibody and + as antigen.
5. Discuss why a line of precipitate may form in agar gel when antigen and antibody diffuse towards each other.
6. Compare and contrast precipitation and agglutination in terms of the nature of the antigens involved, and sensitivity of the tests.
7. Discuss how complement plays roles in both innate and adaptive immunity.
8. List the components of complement in the order in which they become activated in the classical pathway. Name those that are also activated in the alternative pathway.
9. Describe how the lectin pathway of complement activation is triggered, and whether it is part of innate or adaptive immunity.
10. Discuss the different ways in which complement is activated by IgG and IgM.
11. Identify the complement components which are: opsonizing; lytic; anaphylatoxic; and chemotactic.
12. Discuss how complement is important in immunity to bacteria even if the bacteria are resistant to lysis by C9. Identify the family of bacteria for which lysis is necessary for their clearance.

## BL - Antibody Genes

1. Define: toxoid, DNA recombination, primary RNA transcript, RNA splicing, somatic mutation, and antibody affinity maturation.
2. Define cross-reactivity. Give an example of a non-self antigen which cross-reacts with a self antigen. Explain, in terms of lymphocyte activation, how a self antigen might not itself elicit antibody, but might react with antibody elicited by a cross-reacting antigen.
3. Discuss the Clonal Selection Theory in terms of: the number of different receptor specificities it postulates per cell; the role antigen plays in the initial expression of receptors; the role of antigen in clonal selection; an experiment which provides strong evidence for the theory; how it differs from an instructional theory; and whether it is Darwinian or Lamarckian.
4. Describe the way some antibody diversity is in the germ line, and the rest is generated by somatic mutation.
5. Define allotypic exclusion and state the number of chromosomes in a cell which bear H or L genes, including the number that actually contribute to a single B cell's antibody product.
6. Explain why we commonly write V(D)J instead of VDJ.
7. Draw a diagram of the heavy and light chain gene regions of human DNA, including the V, (D,) J, and C subregions, and an illustration of how a heavy or light chain gene is assembled out of these subregions during the differentiation of a B cell.
8. Describe the processes that produce N-region diversity.
9. Describe the somatic recombination model ("class switching"), which explains how antibodies of the same specificity (that is, with the same CDRs and idiotype) can be found in two or more different classes.

## **BL - Antibody Structure**

1. Define: H chain, L chain, kappa and lambda chains, hinge region, Fab, F(ab<sub>2</sub>), Fc, complementarity-determining regions (hypervariable regions), variable (V) and constant (C) domains, VL and CL, and VH and CH.
2. Diagram an electrophoretic separation of human, label the anode and cathode, and identify the albumin, alpha 1, alpha 2, beta and gamma peaks.
3. Name the 5 antibody classes, and their characteristic heavy chains.
4. Draw a diagram of the structure of typical molecules of each class, and label the heavy and light chains; Fc and Fab parts; J chains if any; antibody combining sites; main interchain disulfide bonds; and secretory component.
5. Arrange IgG, IgM and IgA in terms of molecular size, and give their approximate normal concentrations in serum.
6. Describe the structure of antibody combining sites.
7. Explain why complementarity-determining regions are also called hypervariable regions.
8. Give an example of a class, a subclass, an allotype, an idiotype.

## **BL - Chronic "Frustrated Immune Response"**

1. Describe the factors that regulate the differentiation of Th0 cells in the Peyer's Patches to Th1, Th2, or Th17 versus into Treg cells.
2. Discuss the relative influence of environment and genetics on the risk for inflammatory bowel disease.
3. Discuss the pathogenesis of Celiac disease, and the relative role played by antibody and T cells. Discuss the importance of HLA alleles in this condition.
4. Discuss immunological aspects of celiac disease that are non-autoimmune and autoimmune, and describe the mechanism whereby tTG2 is made.
5. Discuss the mechanism of chronic beryllium disease.
6. Outline the Hygiene or Old Friends Hypothesis, and the observations that support it.
7. Discuss the idea that it may be possible to switch Th1/Th2/Th17 responses to Treg instead.

## **BL - Course Introduction and Overview of Hematology**

1. Define: hematopoiesis, erythropoiesis, anemia, hemolysis, hemostasis, and thrombosis.
2. Describe the basic shape and composition of an erythrocyte.
3. List the five types of white blood cells in the blood.
4. Compare and contrast leukemia vs. lymphoma, acute leukemia vs. chronic leukemia and lymphoid leukemia vs. myeloid leukemia.
5. Explain what platelets are, where they come from, and their basic function.

## **BL - Deficiency of Adaptive Immunity (Immune Deficiencies)**

1. Draw an outline diagram of T and B lymphocyte development. On the diagram, indicate locations of abnormalities of development in:  
Severe Combined Immunodeficiency (SCID)  
X-Linked Agammaglobulinemia (XLA)  
Hyper IgM Syndrome  
Common Variable Immunodeficiency (CVID)  
DiGeorge Syndrome
2. Characterize the infections you would expect in a pure B cell deficiency and in a pure T cell deficiency.
3. Describe the clinical features which, although not immunological, are part of DiGeorge syndrome.
4. Discuss the incidence of selective IgA deficiency and associated features seen in those that are symptomatic.
5. Describe the immunological problem of the Nude mouse, and name the human immunodeficiency condition it resembles.
6. Name the most common enzyme deficiency seen in cases of SCID. Discuss possible approaches to replacing this enzyme.
7. Given a child with recurrent infections, describe in principle tests which could be done to determine if there is a T, B or combined immunodeficiency, or a PMN, macrophage or complement problem.
8. Describe the contents and routes of administration of immunoglobulin products and indicate the conditions in which it can be useful as replacement therapy.

## **BL - Hematologic Malignancy Clinical Cases (Required)**

1. List important aspects of the patient history to ask when evaluating a patient with a suspected hematologic malignancy.
2. List important aspects of the physical exam when evaluating a patient with a suspected hematologic malignancy.
3. List some of the important laboratory studies to obtain when evaluating a patient with a suspected hematologic malignancy.

## **BL - Hematopathology Cases**

1. Discuss hematopathology cases with accompanying histologic photos and answer related questions.

## **BL - Hematopoiesis, Hematopoietic Precursors, and Bone Marrow**

1. Define locations of hematopoiesis throughout human development.
2. Discriminate between mature peripheral blood cells based on morphologic characteristics.
3. List the main subtypes of hematopoietic cells (HPC).
4. Recall the names of HPC precursors encountered throughout lineage development.
5. List the major hematopoietic growth factors (HGFs).
6. Be able to match HGFs to their respective lineage.
7. Predict disease states based on bone marrow cellularity.

## **BL - Hemoglobin: Structure and Function**

1. Describe the overall structure of hemoglobin, indicating the site of oxygen binding. Explain the concepts of allostery and positive cooperativity as they relate to hemoglobin function and explain what is meant by taut (T) and relaxed (R) configurations.
2. Draw a typical oxygen dissociation curve. Explain why it is sigmoidal in shape. Define the p50. Explain the effects of pH, [CO<sub>2</sub>], temperature, and [2,3-BPG].
3. Compare oxygen dissociation curves for myoglobin and hemoglobin and explain the reason for the differences.
4. List and describe the typical hemoglobin variants seen during fetal development and in adulthood and explain how amounts of these different hemoglobins change during development.
5. Describe how structural differences in hemoglobin affect oxygen affinity and explain the physiologic effects of altered oxygen affinity.
6. Describe what methemoglobinemia is, what causes it, how to diagnose it, and how to treat it.
7. Explain the pathophysiology of carbon monoxide poisoning and its treatment.
8. Explain in basic terms how a pulse oximeter works. Describe situations where a pulse oximeter reading may inaccurately reflect a patient's true oxygenation status.

## **BL - Hemostasis Defects**

1. List the major congenital or acquired disease states causing bleeding and/or clotting.
2. Explain what the PT/INR, APTT, TT, bleeding time, and PFA are and what they are testing. Provide a differential diagnosis of an abnormal PT/INR, APTT, TT, bleeding time, and PFA. Describe some of the other tests used to evaluate patients with thrombotic or bleeding disorders.
3. Describe the clinical features and molecular basis for hemophilia A and B, factor VII deficiency, and von Willebrand disease.
4. Describe the role of liver disease in coagulopathy.
5. Describe disseminated intravascular coagulation (DIC) with its associated conditions. Explain diagnostic testing for DIC and associated conditions.
6. Explain what a lupus anticoagulant is, how it affects coagulation, and ways to test for it.
7. Explain how a 1:1 mixing study can distinguish a clotting factor deficiency from an inhibitor of coagulation.

## **BL - Hemostasis Introduction Part II**

1. Describe how antithrombin functions as a regulator of coagulation and explain how heparin affects its function.
2. Explain how protein C is activated and how the protein C - protein S system regulates coagulation.
3. Explain what factor V Leiden is.
4. Describe how tissue factor pathway inhibitor (TFPI) functions in regulating coagulation.
5. Explain the role of plasmin in fibrinolysis. Explain how plasminogen is activated to plasmin.
6. Describe how plasminogen activation inhibitor 1 (PAI-1), alpha2-antiplasmin, and thrombin-activatable fibrinolysis inhibitor (TAFI) regulate fibrinolysis.
7. List some of the mechanisms the endothelial cell lining uses to prevent clot formation in the resting state.
8. Explain the terms primary hemostasis and secondary hemostasis.



## **BL - Hemostasis/Thrombosis Cases (Required)**

1. List important aspects of the patient history to ask when evaluating a patient with excessive bleeding or suspected thromboembolism.
2. List important aspects of the physical exam when evaluating a patient with excessive bleeding or suspected thromboembolism.
3. Explain what the following laboratory tests are measuring and how they can be used to evaluate a patient with a bleeding disorder: CBC/peripheral smear, PT/INR, aPTT, TT, bleeding time, and PFA.

## **BL - Hemostasis: Platelets Disorders and Approach to the Bleeding Patient**

1. Discuss events occurring during hemostasis, comparing primary and secondary hemostasis.
2. Diagram the structure of a mature platelet and show the location of: dense granules, alpha granules, glycoprotein Ib, glycoprotein IIb/IIIa, and phospholipids.
3. List three functions of platelets.
4. Construct a simple diagram that depicts the process of platelet adhesion. Include in the drawing subendothelial collagen, von Willebrand factor, and glycoprotein Ib. Explain why platelet adhesion to blood vessels does not occur under normal circumstances.
5. Construct a simple diagram that shows the process of platelet aggregation, including the release reaction (ADP), thromboxane synthesis, ADP and thromboxane receptors, glycoprotein IIb/IIIa, and fibrinogen.
6. List and describe three mechanisms that could lead to thrombocytopenia.
7. Identify three methods of treating ITP and the mechanism by which they increase the platelet count.
8. Describe the molecular defect, typical clinical course, and general approach to treatment for a patient with Von Willebrand Disease.
9. List important questions to ask when obtaining a bleeding history in a patient with excessive bleeding.
10. List important laboratory studies to obtain when evaluating a patient with excessive bleeding.

## **BL - Histology of the Thymus and Peripheral Lymphoid Organs Part I**

1. Describe the basic structure and general movement of lymph and lymphocytes through a lymph node. What differentiates activated nodules (or secondary follicles) from non-activated (or primary follicles)?
2. Outline the vasculature of lymph nodes. Describe the function of the high endothelial venule.
3. Describe the blood flow through the thymus. Differentiate among the blood flow and vascular structures through a lymph node, thymic lymphoid tissue, and that of the spleen.
4. Identify the nuclei and cell bodies of reticuloendothelial cells in the thymus, Hassall's corpuscles, and describe how they are relevant to lymphocyte selection.
5. Identify the cellular components of white pulp and red pulp and describe their functions.
6. Identify regions of mucosal-associated lymphoid tissue and describe the major antibody type produced by lymphocytes in mucosae.
7. Describe why networks of reticular fibers are important in the lymph node and spleen.

## **BL - Histology of the Thymus and Peripheral Lymphoid Organs Part II**

1. Describe the functions and distribution of the lymph system.
2. Describe the types of lymphoid cells. Understand the functions and interactions between these cells.
3. Explain the functions of all major lymph organs (spleen, thymus, lymph nodes, MALT).
4. Delineate the differences between primary and secondary lymph organs.
5. Describe the structure of all major lymph organs and explain the function of the main lymph organ cell types and/or parts.
6. Describe the blood flow through the different encapsulated lymphoid organs, and the general flow of lymph through the lymph node.

## **BL - Hodgkin Lymphoma and Plasma Cell Neoplasms**

1. List and describe the major subtypes of classical Hodgkin lymphoma (CHL).
2. Describe and recognize the Reed-Sternberg (RS) cell in classical Hodgkin lymphoma (CHL).
3. Understand the difference between CHL and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL).
4. Be able to explain the major differences among plasma cell neoplasms (MGUS, smoldering myeloma, multiple myeloma).
5. Identify the commonly involved locations of multiple myeloma and plasmacytoma.
6. Be able to describe the morphologic features of neoplastic plasma cells and characteristic peripheral blood findings.
7. Describe typical radiographic and clinical laboratory findings in a patient presenting with multiple myeloma.
8. Recognize typical clinical and serologic features of Waldenström macroglobulinemia and lymphoplasmacytic lymphoma.

## **BL - Immunodeficiency/Autoimmunity Part I (Required)**

1. Use immunological and hematological data to narrow a set of diagnostic possibilities to propose a testable hypothesis.
2. Discuss positive and negative selection in the thymus.
3. Discuss the role of the AIRE gene and negative selection.
4. Name three differences between central and peripheral tolerance.
5. List 2 ways that a cytokine may be dysfunctional.
6. Explain potential consequences of genetic mutations and review the Genetic Code.
7. Explain how APS-1 is both an immunodeficiency and an autoimmune disease.

## **BL - Immunodeficiency/Autoimmunity Part II (Required)**

1. Discuss the different methodologies used to test for HIV infection and the advantages and disadvantages of each method.
2. Discuss the types of microorganisms to which patients with T cell immunodeficiency are most susceptible.
3. Discuss the risks of live vaccines in the immunodeficiency population.
4. Compare and contrast the different types of severe combined immunodeficiency (SCID).
5. Explain what the SCID newborn screen assay measures.
6. Discuss the treatment options for SCID.
7. Use immunological and hematological data to narrow a set of diagnostic possibilities to propose a testable hypothesis.
8. Discuss positive and negative selection in the thymus.
9. Discuss the role of the AIRE gene and negative selection.
10. Name three differences between central and peripheral tolerance.
11. List 2 ways that a cytokine may be dysfunctional.
12. Explain potential consequences of genetic mutations and review the Genetic Code.
13. Explain how APS-1 is both an immunodeficiency and an autoimmune disease.

## **BL - Immunodiagnostics and Review**

1. Describe the procedure used in serum protein electrophoresis, and the underlying principles.
2. Discuss the serum protein electrophoretic pattern which would be expected if a patient:
  - A. was normal
  - B. had selective IgA deficiency
  - C. had multiple myeloma
  - D. had severe pyogenic (pus-producing) infections
  - E. was hypogammaglobulinemic
3. Discuss single radial immunodiffusion, with regard to the types of antigens that can be quantified with it, and the way that quantization is done.
4. Describe tests that are used for determining if a patient has antibody to a soluble or particulate antigen.
5. Distinguish between direct and indirect immunofluorescence techniques.
6. Discuss the advantages of passive agglutination (e.g., with antigen-coated latex particles) over precipitation, and outline the technique.
7. Describe in principle the ELISA test. Diagram the reactions involved when the ELISA is used to measure antibody, and to measure antigen.
8. Describe a test which can be used to evaluate T cell immunocompetence in a clinic or on the ward.
9. Describe tests to evaluate T cell numbers and function in the lab.
10. Describe flow cytometry as used for measuring numbers of B cells, and T cell subsets.

## BL - Immunogenetics and Transplantation

1. Define the human Major Histocompatibility Complex. Distinguish between HLA-A and HLA-B antigens on the one hand, and the HLA-D group on the other, in terms of: which associate with foreign antigens for recognition by helper T cells; which, in association with foreign antigens, are the targets for killer T cells.
2. Distinguish Class I and Class II histocompatibility antigens.
3. Define alloantigen and haplotype.
4. Given the HLA-A, HLA-B and HLA-DR phenotypes of 2 parents and their child, work out the 4 haplotypes involved.
5. Identify the best probable donors of tissues or bone marrow to an individual, and discuss the reasons for your choice.
6. Describe the one-way mixed leukocyte reaction (MLR) and discuss its use.
7. Distinguish between "HLA-D" and HLA-DR, -DP, -DQ.
8. Explain the interaction of T cells recognizing antigen plus HLA-D and T cells recognizing antigen plus HLA-A or B in the generation of killer T cells. Include the roles of cytokines in your discussion.
9. Describe the cellular and molecular events which go on during graft rejection, both of the usual type and hyperacute rejection. Include: cytotoxic T cells, Th1 cells, and macrophages.
10. Discuss how T cells selected to recognize "self + X" also recognize foreign MHC (allorecognition).
11. Define and describe hyperacute graft rejection.
12. Give an example of a disease whose incidence is tightly linked to a particular HLA allele. Speculate on the mechanism which might explain the linkage.

## BL - Immunohematology ABO/Rh

1. For persons of the A, B, AB and O blood groups, give the following data: most and least common groups; red cell antigens; specificities of the ABO antibodies in their plasma; safe donors to that type; safe recipients of blood from that type; possible genotypes.
2. Name the antibody class of most ABO isohemagglutinins.
3. Explain the ABO antigen situation in a person of Bombay blood type, and the consequences of a transfusion of non-Bombay blood into such a patient.
4. Define the crossmatch, and explain why it is important. Explain how red cells are destroyed following a mismatched transfusion, and why this may be devastating to the recipient.
5. Compare and contrast the techniques of the direct and indirect antiglobulin tests and the questions they are designed to answer.
6. Define heterophile antibody, and identify a common disease in which one type is increased enough to be useful diagnostically.
7. In Hemolytic Disease of the Newborn, explain:
  - a. The consequences of severe hemolysis in the newborn.
  - b. The way in which the mother becomes sensitized.
  - c. The class of antibody to Rh(D) the mother makes.
  - d. The consequences of sensitization to subsequent fetuses.
  - e. The role of Rh-immune globulin.
8. Explain the situation in which ABO hemolytic disease of the newborn can occur.

## **BL - Immunology of AIDS**

1. Explain the difference between “HIV-seropositive” and “AIDS”.
2. Name the virus that causes AIDS, and its classification.
3. Discuss the origin of the AIDS virus and the origins of the current epidemic.
4. Identify the approximate number of cases in the U.S. and in the world, and discuss the rate of change in incidence.
5. Discuss the pathogenesis of AIDS, including target cell types, mode of entry of the virus into a cell, mode of exit, latency versus productive infection.
6. Discuss the role of Tfh in the persistence of HIV latency and active infection.
7. Discuss the types of infections seen in AIDS patients, and provide an immunological basis for this spectrum.
8. Discuss possible reasons for which the total number of CD4 cells in AIDS patients decline.
9. Discuss reasons for the apparent ineffectiveness of antibody in HIV infection.
10. Define and discuss “long-term survivors” and “elite controllers” in HIV infection.
11. Describe the laboratory diagnosis of AIDS.
12. Discuss the prospects and problems of AIDS vaccine development.

## **BL - Immunomodulators**

1. Define monoclonal antibodies, and describe in principle how they are made.
2. Discuss the use of monoclonal antibodies as anti-inflammatory agents.
3. Compare and contrast murine, chimeric, humanized, and human monoclonal antibodies. Discuss which might have disadvantages when used in human patients, and the reason for that.
4. Define NK cells and ADCC. Discuss the effect of Class I MHC expression levels on susceptibility of target cells to CTL and NK cells, respectively. Describe the mechanism for ADCC.
5. Describe how a monoclonal antibody against a T cell surface molecule could enhance the activity of a CTL.
6. Discuss the use of modified (drugs, isotopes) monoclonal antibodies in tumor diagnosis or therapy.
7. Discuss strategies for use of monoclonal antibodies to modify immune responses.
8. Discuss how the use of BRMs, which target known pathways of the immune system, can lead to serious and often predictable side effects.
9. Describe a generic BiTE (bi-specific T cell engager) and speculate on possible use of BiTEs with CD3 and any other binding ability.

## **BL - Immunopathology Type 1, Allergies**

1. Discuss the roles of IgG, IgE, M2 macrophages, and eosinophils in helminth immunity.
2. Define atopic, immediate hypersensitivity, allergy, allergen, anaphylaxis, asthma, hives, and wheal-and-flare reaction.
3. State the approximate incidence of atopic diseases in the general population, and in individuals with allergic parents.
4. Describe the mechanism of IgE-mediated hypersensitivity in terms of: IgE attachment to basophils or mast cells; reaction to allergens; mediator release; effects of mediators on target tissues and cells.
5. Discuss the features that the various atopic diseases have in common which justify lumping them together.
6. Discuss the reasons for using glucocorticoids in asthma treatment.
7. Discuss intradermal skin tests with reference to procedure, safety and specificity.
8. Discuss specific immunotherapy of allergic disease, considering duration of effect, risk of anaphylaxis, and percent of patients obtaining significant relief.
9. Describe the immediate allergic reaction and the late-phase reaction in terms of the time course of the reaction and mediators involved.

## **BL - Immunopathology Type 3, Immune Complex Disease (Recorded Content Only; No Lecture)**

1. Arthus reaction and serum sickness are local and general manifestations of immune complex disease; describe the mechanism of tissue damage. Discuss why this could reasonably be called 'innocent bystander injury.'
2. State the critical size at which immune complexes get stuck in basement membranes.
3. Describe 'one-shot' serum sickness. Make a chart showing antigen, antibody and immune complex levels in relation to relative time and to symptoms.
4. Discuss the types of tissues in which damage is most likely to occur from deposition of immune complexes.
5. Discuss the immunological mechanism of a typical Type III disease involving exogenous antigen.
6. Discuss how urticaria (hives) could result from interaction of antigen with either IgE or IgG antibody.
7. Name 3 different kinds of human immune complex disease or problem and indicate a type of antigen involved in each condition.
8. Discuss the meaning of finding a fluffy white precipitate in a patient's serum after a day in the refrigerator, including the name used for such precipitates, the most likely composition, and the interpretation of the phenomenon.
9. Define rheumatoid factor and discuss its components.
10. Discuss the pathogenesis of post-streptococcal glomerulonephritis. Describe the diagnosis of this condition by fluorescent antibody technique, and name the pattern of resulting fluorescence.
11. Discuss the pathogenesis of hypersensitivity pneumonitis, for example Farmer's Lung.

## **BL - Introduction to Hematologic Malignancies**

1. List the main manners in which hematologic malignancies may manifest, and explain how these may overlap.
2. Contrast basic concepts of high versus low grade lymphomas, and of acute versus chronic leukemias.
3. Recall the biological reason that many lymphomas contain balanced translocations involving the immunoglobulin and T cell receptor genes.
4. Relate the importance of specific recurrent translocations in certain hematologic malignancies in regard to the clinical care of patients.
5. List three viruses known to have oncogenic roles in some cases of lymphoma.
6. Contrast the incidences of leukemia and lymphoma in adult populations versus childhood populations.
7. Recall the currently recommended classification system for hematologic malignancies, and list parameters this system may use to aid in the classification of these malignancies.
8. List the basic functional categories for hematologic malignancies, as outlined in the notes, and contrast the basic expected findings in the blood and marrow for these categories.

## **BL - Introduction to Hemostasis Part I**

1. Explain what is meant by the term hemostasis, and list the different components involved in the hemostatic process.
2. Identify which coagulation factors are serine proteases and which are cofactors.
3. List and explain the role of the different components of the intrinsic tenase, extrinsic tenase, and prothrombinase complexes.
4. Explain the role of vitamin K in coagulation, and list the factors that are vitamin K dependent.
5. Describe how fibrinogen is converted to fibrin by thrombin, leading to formation of an insoluble fibrin network, and how factor XIII functions in stabilizing the forming clot.
6. List the two main functions of von Willebrand factor in coagulation.
7. List the components of the extrinsic and intrinsic coagulation pathways and relate these pathways to the PT and APTT coagulation screening tests.
8. Explain the current concept of the process of coagulation, describing what occurs during the initiation, amplification, and propagation phases.
9. Explain why thrombin is considered the central enzyme in blood coagulation.

## **BL - Introduction to Lymphomas and Non-Hodgkin Lymphoma (NHL)**

1. Describe the basic anatomy of a normal lymph node and the common abnormal lymph node patterns seen in lymphomas.
2. Define lymphadenopathy and list the common disease categories associated with lymphadenopathy.
3. Explain the basic principles for the WHO Classification of lymphomas.
4. List and describe the common types of lymphoma in adults and children.
5. Define indolent, aggressive and highly aggressive as these terms relate to lymphoma. Be familiar with some common types of indolent and aggressive lymphomas.
6. Define common Non-Hodgkin Lymphomas (NHLs) based on the cytology, pattern of growth, immunophenotype and genetic alteration.
7. Explain the importance of rearrangements involving the BCL2, BCL1(CCND1), IGH and MYC genes in the pathogenesis of NHL.
8. Describe the main differences between mycosis fungoides and Sézary syndrome.

## **BL - Introduction to Rheumatology and Miscellaneous Disorders I**

1. Explain what rheumatology is and the types disorders rheumatologists specialize in managing.
2. Identify the major sub-groups of rheumatic diseases.
3. Describe how rheumatologists evaluate patients.
4. Discuss the clinical manifestations of Fibromyalgia and that appropriate treatments address increased central pain processing.
5. Recognize that Raynaud's is treated with vasodilating agents and that it may or may not be associated with other diseases.
6. Recognize the clinical differences between gonococcal and non-gonococcal septic arthritis.
7. Describe how polymyalgia rheumatica is diagnosed and treated.
8. Be able to explain the major manifestations of SJA.

## **BL - Meet Cancer Survivors (Required Session; Will not be Recorded)**

1. Show professionalism in meeting and talking to cancer survivors.
2. Describe some of the late effects of cancer treatment, related both to chemotherapy and radiation therapy. Discuss risk of secondary malignancy following cancer treatment and list factors that increase that risk.
3. Describe some of the psychosocial difficulties that cancer survivors face, such as obtaining medical insurance coverage.
4. Estimate the percentage of the population who are cancer survivors.
5. Identify spiritual and religious issues dealing with cancer.

## **BL - Meet Sickle Cell Patients (Required Session; Will not be Recorded)**

1. Show professionalism when meeting and talking with patients with sickle cell disease.
2. Show increased awareness of the impact of a chronic illness on patients and their families.
3. Describe some of the barriers to health care access and treatment for patients with sickle cell disease.
4. Identify spiritual and religious issues in dealing with sickle cell disease.



## BL - Myelodysplastic Syndrome & Myeloproliferative Neoplasms

1. List the two main features that characterize myelodysplastic syndrome (MDS).
2. Describe the typical clinical presentation of patient with MDS.
3. List 3 different types of tests that could be performed to make a diagnosis of MDS.
4. List 4 possible causes of secondary myelodysplasia that might mimic MDS.
5. Contrast low grade MDS and high grade MDS with regards to diagnostic criteria and prognosis.
6. Compare and contrast MDS and myeloproliferative neoplasms (MPNs) in regards to usual number and appearance/functionality of cells in the blood and marrow.
7. List two reasons for the frequent occurrence of splenomegaly and hepatomegaly in patients with MPNs.
8. List 3 possible negative end points for MPNs.
9. Compare and contrast the 4 MPNs covered in the notes with regard to blood cell counts, marrow findings, and usual cytogenetic and molecular abnormalities.
10. Explain why there is a need for a second and third generation of protein tyrosine kinase inhibitors (PTKIs).
11. Recall the most common method of death attributable to disease in polycythemia vera (PV) patients, and list be aware of anatomic sites where thrombosis should always make one consider the possibility of PV.
12. Recall the (somewhat archaic) most common treatment for PV.
13. List findings that might be seen in the peripheral blood smear in a patient with leukoerythroblastosis, and know what the presence of leukoerythroblastosis in the blood implies about the state of the bone marrow.

## BL - Neutrophil Disorders

1. Calculate an absolute neutrophil count (ANC). Define mild, moderate, and severe neutropenia. Explain how age and race/ethnicity can impact neutrophil count.
2. Describe the clinical consequences of neutropenia.
3. Describe the clinical presentation and (when known) the underlying defect for the following neutropenic disorders:
  - a. Severe congenital neutropenia (Kostmann syndrome)
  - b. Cyclic neutropenia
  - c. Shwachman-Diamond syndrome
  - d. Autoimmune neutropenia
  - e. Chronic benign neutropenia of childhood
4. Describe approaches to treatment for neutropenic disorders. Explain the pros and cons of treatment with G-CSF.
5. Review the normal functions of neutrophils, including rolling, adherence, diapedesis, chemotaxis, ingestion, and degranulation/microbicidal activity.
6. Describe the clinical presentation, defect in neutrophil function, and (when known) the underlying genetic defect for the following neutrophil function disorders:
  - a. Leukocyte adhesion deficiency (LAD)
  - b. Hyperimmunoglobulin E syndrome (Job syndrome)
  - c. Chediak-Higashi syndrome
  - d. Myeloperoxidase deficiency
  - e. Chronic granulomatous disease
7. Describe approaches to treatment for neutrophil function disorders.

## BL - Ontogeny of the Immune System

1. Define: stem cell, B cell, T cell, pre-B cell, pre-T cell, self-tolerance, and titer.
2. Draw an outline diagram which shows bone marrow, thymus and lymph node. Indicate the development and movement of cells of the B and T lines, starting with the hematopoietic stem cell and ending with mature T and B cells.
3. Define the Bursa of Fabricius, and discuss where its functions take place in mammals.
4. Describe the sequence of appearance of cytoplasmic and surface immunoglobulins in developing B cells. Using these data, derive a model that could explain self-tolerance at the B cell level ("clonal deletion").
5. Draw a graph showing the antibody response to a typical antigen in a primary and in a secondary response. Show both IgM and IgG antibody levels.
6. Draw a graph which shows relative IgG and IgM levels in a normal infant from conception to one year of age. Distinguish maternal from infant's antibodies.
7. Given a newborn's antibody titer, interpret its significance if the antibody is IgG, or IgM. If IgG, calculate what the titer will be at 4 months of age, and state the assumptions that you made when you did the calculations.
8. Discuss the decrease in diversity seen in the immune repertoire of older people.
9. Discuss the relative values of immunizing the young and the old in an epidemic of a novel respiratory virus.

## BL - Overview: From Innate to Adaptive Immunity

1. Define: Pattern-recognition receptor, pathogen-associated molecular pattern, Toll-like receptor, damage-associated molecular pattern, and recognize their abbreviations.
2. Name some common foreign patterns recognized by TLR.
3. Identify the transcription factor that is most commonly activated in inflammation.
4. Define cytokine and chemokine.
5. Describe the function of the innate immune response.
6. Name the cell that forms the bridge between innate and adaptive immunity.
7. Discuss in principle the role T cells play in immunity.
8. Describe some of the functions of antibodies.
9. Give examples of immunopathology.
10. Distinguish between "humoral" (antibody-mediated) and cell-mediated immunity in terms of: the types of lymphocytes involved, and the nature of the molecules they release when activated.

## **BL - Pharmacology of Anticoagulation Therapy**

1. Describe the mechanism of action and pharmacokinetics of heparins and fondaparinux, and differences in management of patients on these therapies.
2. Describe the complications associated with heparin therapy, including excessive bleeding and heparin-induced thrombocytopenia with associated thrombosis.
3. Describe the alternative anticoagulant therapies used for patients with heparin-induced thrombocytopenia.
4. Describe the mechanism of action, pharmacokinetic and uses of oral anticoagulants (warfarin and direct oral anticoagulants).
5. Describe the adverse effects and potential complications associated with use of oral anticoagulants.
6. Describe the relationship between mechanisms of action and speed of onset of action of injectable anticoagulants and oral anticoagulants.
7. Describe the mechanisms of action and uses of fibrinolytic agents.

## **BL - Resistance, Immunity & Vaccines**

1. Compare the roles of cell-mediated and humoral immunity in virus infections with regards to: preventing the infection; controlling spread of viruses in the body; which is responsible for recovery from disease; how each can cause immunopathology.
2. Define "local immunity" and give an example.
3. Identify those organisms against which cell-mediated immunity is most effective.
4. Identify those organisms against which humoral immunity is most effective.
5. Give an example of a human and an animal antitoxin; a toxoid; a killed virus vaccine; and a live virus vaccine. Identify the one which produces the longest-lasting immunity. Discuss possible hazards of each type of preparation.
6. State the appropriate times for immunization of children against diphtheria, pertussis (whooping cough), tetanus, polio, and measles/mumps/rubella. Discuss why some live viral vaccines tend to be ineffective in the very young.
7. Discuss the use of IgG and IgM antibody titers in the diagnosis of intrauterine and neonatal infections.
8. Discuss the composition of a typical conjugate vaccine, and describe its mode of action.
9. Identify the oral and parenteral (injected) polio vaccines by the names of their developers. Discuss their relative advantages and disadvantages, and note which is currently used in the USA.
10. Define 'herd immunity.'
11. Identify an adjuvant, a specific vaccine it is used in, and the type of immunity it best induces.

## **BL - Rheumatology: Autoimmunity and Systemic Lupus Erythematosus (Required)**

1. Describe the clinical, laboratory, and X-ray features of SLE, including the organs involved and auto-antibodies.
2. Explain the difference between organ specific autoimmunity and systemic autoimmunity.
3. Describe the epidemiology and genetics of SLE including the predisposing factors and environmental factors that can modulate disease.
4. Explain the pathophysiology of SLE and the various theories used to explain autoimmunity.
5. Describe the treatment of SLE as it relates to the pathophysiology.

### **BL - Rheumatology: Crystal Arthroplasties (Required)**

1. Describe the pathophysiology in humans of purine metabolism and hyperuricemia including increased production or decreased renal excretion of uric acid, X-linked enzyme abnormalities in the purine degradation pathway, and the mechanism of renal tubular reabsorption of uric acid.
2. Describe the general clinical and synovial fluid analysis features of gout and calcium pyrophosphate deposition disease (CPDD), including crystal morphology and birefringence.
3. Contrast the differences in the pathophysiology of gout and CPDD.
4. Explain why attacks of crystal-related arthritis can be self-limited.
5. Describe the treatments for acute crystal-related arthritis and chronic symptomatic hyperuricemia.

### **BL - Rheumatology: Rheumatoid Arthritis (Required)**

1. Describe the general clinical, laboratory, and x-ray features of rheumatoid arthritis (RA), including joint distribution, synovial fluid analysis, auto-antibodies, and extra-articular manifestations.
2. Describe the genetic factors that may determine the severity of RA.
3. Explain the pathogenesis of RA in the synovial tissue and synovial fluid, including cell types, cytokines, and proteolytic enzymes.
4. Explain contribution of rheumatoid factors to disease pathophysiology and their clinical relevance.
5. Describe the treatment of RA as it relates to pathophysiology.
6. Contrast OA and RA on a clinical basis and discuss their differences in pathophysiology.

### **BL - Rheumatology: Axial and Peripheral Spondyloarthritis (Required)**

1. Describe the clinical, laboratory, and x-ray features of SpA, including any extraarticular manifestations.
2. Describe the epidemiology and genetics of the SpA.
3. Explain the theories of the pathogenesis of the SpA.
4. Describe the treatment of the SpA as it relates to the pathogenesis.

### **BL - Rheumatology: Inflammatory Myopathies & Dermatomyositis (Required)**

1. Review the classification scheme for inflammatory myopathies.
2. Describe the clinical and laboratory features of inflammatory myopathies including EMG, MRI, and biopsy findings.
3. Discuss the clinical and laboratory features of the anti-synthetase syndrome including anti-synthetase antibodies.
4. Recognize the significance of myositis-specific auto-antibodies.
5. Contrast the cellular differences in the pathology of polymyositis and dermatomyositis.
6. List the evidence suggesting viral infections as a cause or triggering factor in polymyositis or dermatomyositis.
7. Discuss the treatment of inflammatory myopathies as it relates to pathophysiology.

### **BL - Rheumatology: Osteoarthritis (Required)**

1. Describe the symptoms and signs, synovial fluid analysis, and x-ray features of OA.
2. Discuss the risk factors for developing OA.
3. Explain the various theories on the pathogenesis of OA including emerging information about the immunologic aspects of OA.
4. Discuss the treatment of OA as it relates to pathophysiology.

### **BL - Rheumatology: Vasculitis (Required)**

1. Name the different types of vasculitis per the Chapel Hill Consensus Conference classification.
2. Describe the clinical features and the laboratory abnormalities suggestive of vasculitis.
3. Describe the different immunopathogenic mechanisms that mediate vasculitis.
4. Distinguish the different types of anti-neutrophil cytoplasmic antibodies (ANCA) and describe their role in the pathogenesis of vasculitis.
5. Describe the treatment of vasculitis as it relates to the extent of organ involvement.

### **BL - Rheumatology: Wrap-up and Miscellaneous Disorders II**

1. Recognize that Sjogren Syndrome (SjS) is an autoimmune disease that causes dry mucous membranes by lymphocytic infiltration of exocrine glands.
2. Describe the two-hit hypothesis of Antiphospholipid Syndrome (APS) and that it is treated with anticoagulation.
3. Recognize that neuromuscular junction (NMJ) diseases have unique manifestations that differentiate them from myositis.
4. Describe clinical manifestations of mixed connective tissue disease (MCTD).
5. Recognize the clinical and laboratory differences between limited and diffuse systemic sclerosis.
6. Review how to work through a rheumatologic differential diagnosis and the key points about the disorders we covered in this course.

## BL - Sickle Cell Disease

1. Explain the molecular bases for sickle cell disease and how specific mutation leads to the phenotype. Describe the mode of inheritance.
2. Describe the geographic distribution of sickle cell disease and a situation where people heterozygous for sickle cell disease may have a survival advantage.
3. Describe the findings on the CBC and peripheral blood smear in patients with sickle cell disease.
4. Describe what "sickle trait" is and the consequences of having sickle cell trait.
5. Describe major variants of sickle cell disease, including sickle beta-thalassemia and SC disease.
6. Describe the precipitating factors and pathophysiologic process by which hemoglobin S causes sickling, as well as the signs and symptoms, both acute and chronic, of the consequences of sickling.
7. Explain the relationship between aplastic crisis and parvovirus B19.
8. Describe some of the therapies to treat patients with sickle cell disease and the rationale for therapies such as folic acid, penicillin, exchange transfusion, hydroxyurea, and bone marrow transplantation.
9. Explain iron chelation therapy, its indications, and its drawbacks.
10. Explain how newborn screens can be used to diagnose sickle cell disease.

## BL - T Cells: Part I & II

1. List the six main types of T cells, and define their functions. Discuss the positive and negative interactions between Th1, Th2, and Treg cells.
2. Describe the surface markers that can be used to distinguish between T and B cells in humans; and between helper and cytotoxic T cells.
3. Define cytokine, lymphokine, and chemokine.
4. Discuss the main lymphokines made by Th1, Th2, Th17 and Treg cells, and their biological functions.
5. Describe how Tfh cells help B cells get activated by antigen and switch immunoglobulin class.
6. Define mitogen. Suggest uses for T or B cell mitogens in the clinical laboratory.
7. Distinguish between the effects of a mitogen and an antigen, when added to normal blood lymphocytes.
8. Compare and contrast the antigen receptors of T and B cells.
9. Discuss the structures recognized by T cell receptors (see also Immunogenetics). Distinguish between antigen recognition by helper and cytotoxic T cells. Explain the special role of dendritic cells in this process.
10. Describe the role of T cells in ridding the body of a viral infection.
11. Describe the characteristics of T-independent antigens.
12. Outline an experiment that shows that an antibody response is "T-dependent".
13. Describe repertoire selection in the thymus, in terms of positive, negative and non-selection.

## **BL - Thalassemia**

1. Review the normal structure of hemoglobin and indicate the globin chains that typically make it up. Describe how the composition of globin chains in hemoglobin changes during fetal development and after birth.
2. Describe what thalassemia is and explain in a general way the molecular basis for it. Describe the basic genetic differences between alpha-thalassemia and beta-thalassemia.
3. Explain the meaning of the terms thalassemia major, thalassemia intermedia, and thalassemia minor.
4. Describe the genetic, hematologic, and clinical differences between alpha-thalassemia trait, hemoglobin H disease, and hydrops fetalis.
5. Describe clinical manifestations and findings on the CBC and peripheral blood smear in patients with thalassemia.
6. Describe the geographic distribution of thalassemia. Describe a situation where people heterozygous for thalassemia may have a survival advantage.
7. Explain why Southeast Asians with alpha-thalassemia are more likely than Africans with alpha-thalassemia to have a child with hydrops fetalis.
8. Describe approaches to treatment for thalassemia.
9. Explain how newborn screens can be used to diagnose thalassemia.

## **BL - The Complete Blood Count**

1. Define the components of peripheral blood that are measured when a CBC is requested.
2. Define the values that are typically calculated when a CBC is requested.
3. Calculate the MCV, MCH, and MCHC using the RBC count, HGB and HCT.
4. Describe various methods that laboratories may use to obtain the values reported when a CBC is performed.
5. Describe how the reference intervals are obtained and their limitations.
6. Recognize normal and abnormal CBC results.
7. Explain when a differential is performed and what additional information it provides.
8. Explain how a differential is performed.
9. Recognize normal blood components found on a peripheral smear.
10. Given the white blood cell differential and the total white blood cell count, calculate the absolute count of a particular white blood cell type.
11. Explain how a differential is performed.

## BL - Thrombosis

1. Identify the components of Virchow's triad and their pathophysiologic contribution to thrombosis.
2. Describe at least three major clinical symptoms that occur when a patient suffers from an acute iliofemoral thrombosis of the leg, and indicate the pathophysiologic reason for each one (for example, dilated superficial veins of the calf due to obstruction of venous return in the occluded deep veins).
3. Compare and contrast the cause and mechanism of a thrombus occurring in the arterial circulation (such as acute coronary artery thrombosis) from one that develops in a deep vein of the leg. Include the instigating factor(s) and composition of the clot.
4. List three clinical clues suggesting an inherited hypercoagulable disorder.
5. Briefly describe at the molecular level the pathophysiologic reason that patients with deficiencies of antithrombin, protein C, protein S, factor V Leiden or the prothrombin gene mutation are likely to have thrombosis. Explain what tests are used to identify these patients.
6. List and describe at least three acquired disorders that are associated with recurrent venous or arterial thromboembolism.
7. Describe the clinical features and criteria for diagnosis of antiphospholipid antibody syndrome.
8. Explain the key factor in determining how long someone should be anticoagulated for a venous thrombosis.

## BL - Tumor Immunology

1. State the concept of the immunosurveillance hypothesis. Discuss how data from immune suppressed and immunodeficient patients support this hypothesis.
2. Describe the concept of immunoediting.
3. Describe the origin and relative immunogenicity of the following kinds of tumor antigens: viral, mutant/neoantigens, oncofetal, and differentiation.
4. Define carcinoembryonic antigen (CEA) and discuss its usefulness in screening for, diagnosis, and follow-up of colon cancer.
5. Define what is meant by checkpoint inhibitory therapy for tumors, and describe their mechanisms of action.
6. Define chimeric antigen receptor T cell (CAR-T) therapy, and explain why it is called "chimeric" and why we have had better success with leukemias and lymphomas than solid tumors with this therapy.
7. Describe a mechanism by which BCG treatment causes tumor regression.



## BL - Type II Immunopathology

1. Describe the molecular and cellular details of the immunologic mechanisms by which tissue damage occurs in a Type II ("cytotoxic antibody") reaction.
2. Give an example of a Type II mechanism disease of muscle, kidney, heart, red cells, platelets, lung, and thyroid.
3. Describe the mechanism of rheumatic heart disease, and discuss reasons its incidence has declined in the West but not in developing countries.
4. Compare and contrast the immunopathologic mechanisms of Graves and Hashimoto thyroiditis.
5. Distinguish between the "lumpy-bumpy" and "linear" immunofluorescent patterns in terms of the most probable immunopathologies they represent.
6. Given patient's serum, fluorescent antibody to human immunoglobulins, and slices of normal kidney, describe how you could tell if the patient's glomerulonephritis was due to Goodpasture's Disease.
7. Describe how antibody-mediated tissue damage could result from the innocent bystander phenomenon, cross-reaction of a foreign antigen with self, coupling self antigen with a foreign antigenic "carrier," exposure of a sequestered antigen, and inadequacy of regulatory T cells.
8. Discuss how the Aire gene is involved in preventing autoimmune disease.

## BL - Type IV Immunopathology

1. Define Type IV immunopathology.
2. Describe the cellular and molecular events following intradermal injection of tuberculin antigen into a person who has cell-mediated immunity to it. Justify calling the process 'delayed hypersensitivity'. Characterize the cells that would be seen in a 48-hour biopsy of the site with regard to whether T cells or macrophages predominate.
3. Explain why a person usually has no observed symptoms when first exposed to a "contact sensitizer" like poison ivy.
4. Discuss how a chemical or small peptide might not need to be processed through an antigen-presenting cell to be presented by that cell to T cells.
5. Describe the problem that HLA-B\*5701 people may have with the HIV drug abacavir.
6. Discuss in principle how T cell immunity could be measured in the laboratory.
7. Explain why TB skin tests can be administered repeatedly to the same subject.
8. Differentiate between a first-set and second-set graft rejection.
9. Define hyperacute rejection and indicate the mechanism.
10. Discuss how autoimmunity can result from environmental exposure to tissues that cross-react with human organs.
11. Discuss the three requirements for graft-versus-host disease to occur.
12. Define the graft-versus-leukemia phenomenon.