#### **Immunology and Immunodeficiency for the Hematologist/Oncologist**

**Sung-Yun Pai, MD**

1. The lymphocyte profile of infants differs from that of adults in what way?

A. The lymphocyte count of infants starts low and increases with age.

B. T-cell numbers in adults are lower than in infants.

C. B-cell numbers are highest at birth and decrease with age.

D. Infants have a lower absolute neutrophil count than adults.

**Explanation**

The answer is B. Infants have a higher absolute lymphocyte count, averaging around 6,000/µL, compared with 2,000/µL in adults, primarily because of their higher CD3 T-cell count and higher CD19 B cell count. Thus, answer A is incorrect. B-cell numbers increase in toddlers and young children and then go back down in adults and therefore, are not highest at birth, so answer C is incorrect. Both the absolute lymphocyte count and the absolute neutrophil count are higher in infants; therefore, answer D is incorrect.

2. You receive a phone call from the mother of a former patient who was diagnosed with non-Hodgkin lymphoma at 4 years old and underwent an unsuccessful bone marrow transplant after the lymphoma recurred. The mother is concerned about her 11-year-old son, who has just been evaluated for recurrent sinusitis and impetigo and found to have low IgG and IgA levels. The mother reminds you that her brother died of fulminant hepatitis following infectious mononucleosis while in college.

What is the most likely disorder in her 11-year-old son?

A. Common variable immunodeficiency

B. X-linked hyper-IgM syndrome

C. X-linked lymphoproliferative syndrome

D. Autoimmune lymphoproliferative syndrome

E. IgA deficiency

**Explanation**

The answer is C. The family history of multiple male relatives on the maternal side that were affected is highly suspicious for an X-linked disease, making answers A, D, and E unlikely. The 11-year-old’s low IgG and IgA could be consistent with common variable immunodeficiency or X-linked hyper-IgM syndrome; however, neither of these syndromes is characterized by overwhelming illness after primary infectious mononucleosis. X-linked lymphoproliferative syndrome due to mutations in the *SH2D1A* gene, leading to lack of expression of the SAP protein, is associated with fatality after Epstein-Barr virus, lymphoma, and hypogammaglobulinemia or dysgammaglobulinemia.

3. You are asked to evaluate a 6-month-old infant in the ICU who has been diagnosed with *Pneumocystis* pneumonia. The CBC and lymphocyte profile shows the following:

WBC: 13,000/µL

Differential: 85% neutrophils, 2% lymphocytes, 10% monocytes, 2% eosinophils, 1% basophils

You request lymphocyte subsets, but the absolute lymphocyte count is so low that the lab does not run the test, and the personnel there report that T, B, and NK numbers are essentially zero.

What is the most likely diagnosis?

A. Severe combined immunodeficiency (SCID) due to mutation in the *IL2RG* gene

B. SCID due to adenosine deaminase (*ADA*) mutation

C. SCID due to *RAG1* mutation

D. Wiskott-Aldrich syndrome

E. HIV infection

**Explanation**

The answer is B. Presentation with *Pneumocystis* pneumonia is highly suggestive of T-cell immunodeficiency, and the profile indeed shows an absence of T and B cells. Thus, this patient does not have Wiskott-Aldrich syndrome, which is characterized by low platelets, eczema, and T/B cell dysfunction despite normal numbers. Likewise, HIV infection would not cause an absolute absence of CD8 T cells or CD19 B cells. Adenosine deaminase mutation affects the ability of all lymphocytes to detoxify the products of purine breakdown; therefore, those patients typically lack all lymphocytes, including NK cells. In contrast, a defect in antigen receptor (T-cell receptor, B-cell receptor) rearrangement due to lack of RAG1 (C) would leave intact NK cells, which do not have rearranged receptors. The X-linked form of SCID due to mutations in *IL2RG* (A) (also called common gamma chain) leads to a profile with absent T cells and present but nonfunctional B cells.

4. Which of these viral infections is most likely to occur within the first 30 days after transplant?

A. Herpes simplex stomatitis

B. Epstein-Barr virus (EBV)-associated lymphoproliferative disease

C. Shingles

D. Cytomegalovirus (CMV) colitis

E. Rotavirus

**Explanation**

The answer is A. Although all DNA viruses (herpes simplex virus [HSV], EBV, varicella zoster virus, CMV) are highly dependent on CD8+ virus–specific T cells for control, and although patients are very lymphopenic during the first 30 days after transplant, the most likely of these to reactivate early is HSV. This reactivation may be related to the role of myeloid cells (neutrophils, macrophages, monocytes) in phagocytosis of infected epithelial cells and production of cytokines to activate other arms of the immune system. In the era of uniform acyclovir prophylaxis, reactivation is usually prevented very effectively. Rotavirus may occur at any time and is not more prominent at this early time point after transplant.

5. A 5-year-old boy who is day +67 after mismatched unrelated donor transplant for treatment of severe aplastic anemia develops cough, hypoxia, and fever. He has a central line and had a history of *Pseudomonas* bacteremia during his original transplant admission. His parents say they have struggled with his medications, but he takes them most of the time. He is on cyclosporine, fluconazole, atovaquone, and magnesium replacement.

Which of the following organisms is *least* likely to be the cause of his symptoms?

A. Cytomegalovirus

B. Pneumocystis

C. Pseudomonas

D. Adenovirus

E. Aspergillus

**Explanation**

The answer is C. By this time after transplant, the primary immune defect is no longer neutropenia but instead severe T-cell lymphopenia, compounded by the use of calcineurin inhibitors such as cyclosporine and tacrolimus that suppress CD4 T-cell function. This is therefore a very common time for viral reactivation with cytomegalovirus or adenovirus to occur, and these could manifest as pneumonia. Pneumocystis could occur despite prophylaxis, and by being on atovaquone the child is not on optimal prophylaxis (ie, sulfamethoxazole/trimethoprim).

6. A 10-month-old boy presents with rectal bleeding and is found to have colitis. You are called to evaluate him because of a platelet count of 8,000/µL. On further questioning you learn that he had a maternal uncle who died of intracerebral hemorrhage as a toddler. The child has had several ear infections and two episodes of pneumonia. His physical examination is notable for mild eczema, mildly tender lower abdomen, and no hepatosplenomegaly.

Which of the following are you most likely to find on further testing and review?

A. Peripheral blasts

B. Abnormal platelet aggregation studies

C. Small platelet size

D. Absolute lymphopenia and absence of CD3 cells

E. Absence of IgG

**Explanation**

The answer is C. This patient has Wiskott-Aldrich syndrome, which, in addition to presenting with thrombocytopenia, eczema, and immunodeficiency, can present with autoimmune manifestations such as colitis. The presentation is not suggestive of leukemia; thus, answer A is incorrect. Small platelets are highly characteristic. Although the platelets are thought to not quite function normally, the defect is subtle and not well characterized; therefore, answer B is incorrect. Answer D would be more characteristic of severe combined immunodeficiency, which should not cause low platelets. Any profound T- or B-cell defect can lead to absence of IgG, but patients with Wiskott-Aldrich syndrome generally have preservation of T- and B-cell numbers; therefore, answer E is incorrect.

7. Which of the following is true regarding B-cell development and function?

A. CD19 is expressed throughout B-cell development, including pro- and pre-B cells.

B. Immunoglobulin class switching occurs in the bone marrow.

C. The majority of circulating immunoglobulin is IgM.

D. The immunoglobulin light chain locus (either IgL or IgK) rearranges before the heavy chain locus (IgH).

**Explanation**

The answer is A. CD19 is expressed on pro-B cells, pre-B cells, and all circulating B cells. B cells emerging from the bone marrow express IgM and then undergo class switching to IgG and IgA in the secondary lymphoid organs (spleen and lymph nodes) after antigen encounter; therefore, answer B is incorrect. The majority of circulating immunoglobulin is IgG; therefore, answer C is incorrect. During development, the heavy chain locus rearranges first, then the light chain locus rearranges, so answer D is incorrect.

8. A 15-year-old boy with T-cell acute lymphoblastic leukemia develops fever to 102 ºF 10 days after starting induction therapy. His ANC is 50. Blood cultures from all lumens of his central line are sent, and empiric antibiotics are started. Three days later, he remains febrile with ANC 80, negative cultures, and no localizing findings on physical examination.

What should your management include?

A. Addition of acyclovir due to history of cold sores

B. Addition of empiric fungal coverage

C. Continue current therapy and observation

D. Discontinue antibiotics for suspicion of drug fever

**Explanation**

The answer is B. A patient with persistent fever despite empiric antibacterial coverage is at high risk of fungal infection. Although herpes simplex reactivation may complicate high-dose chemotherapy, it is not common enough to warrant empiric addition; therefore, answer A is incorrect. Because the neutrophil count is not recovering, continuing current therapy or discontinuing antibiotics would put the patient at risk of neutropenic bacterial or fungal infection; therefore, answers C and D are incorrect.

9. Which of the following immunoglobulin subtypes is transferred from mother to child in significant amounts across the placenta?

A. IgM

B. IgA

C. IgG

D. IgE

E. IgD

**Explanation**

The answer is C. IgM and IgA, being pentameric and dimeric, respectively, are too large to cross the placenta. IgD and IgE are both very low in concentration, and the function of IgD, if any, is not known.

10. A 5-day-old boy has been called by the state lab to be evaluated because of absent T-cell receptor excision circles (TRECs). Lymphocyte subsets show the following:

WBC: 13,730

Hemoglobin: 15.7 g/dL

Hematocrit: 45.1

Platelets: 317,000

Absolute neutrophils: 9,970

Absolute lymphocytes: 2,300

CD3: 3%

CD4: 2%

CD8: 1%

CD19: 92%

CD16/56: 2%

What is the next appropriate step in diagnosis and management?

A. Reassure the family that the WBC, ANC, and ALC are normal.

B. Order an HIV antibody test.

C. Explain to the family that the baby has no B cells and needs to start on immunoglobulin replacement immediately.

D. Begin prophylactic penicillin.

E. Tell the family that the baby likely has severe combined immunodeficiency (SCID) and order additional testing.

**Explanation**

The correct answer is E. TRECs are now analyzed in newborn dried blood spots in more than 90% of births in the United States as a screen for T-cell lymphopenia and suspicion for SCID. This profile is characteristic of a patient with SCID, T−, B+ and NK−, likely X-linked SCID in a boy. The absolute T-cell count is very low: 3% of 2,300 = 69 cells/µL. Although normal for an adult, an absolute lymphocyte count of 2,000 is very low for a newborn. Thus, answer A is incorrect. Although the low CD4 count raises the possibility of HIV, the severity of lymphopenia is unusual for HIV infection at this age. Also, HIV antibody testing of a newborn will reflect maternal antibody, not neonatal infection, so answer B is incorrect. CD19 marks B cells, and the baby has plenty of B cells, so answer C is incorrect. Also, at this age the baby has maternally derived IgG, so he is not likely to have low IgG. Prophylactic penicillin would protect against bacterial infection due to the inability to make antibodies, but, more importantly, the T-cell defect here would predispose to opportunistic infections; thus, answer D is not the appropriate next step.

11. A 2-month-old boy is said to have X-linked severe combined immunodeficiency (SCID) after being screened at birth due to a positive family history. He is febrile and hypoxic, with interstitial pneumonitis on his chest X ray. The ICU doctor has consulted you and provided the following laboratory studies:

WBC: 12,500

Differential: 45% neutrophils, 50% lymphocytes, 5% monocytes, 2% eosinophils

Blood cultures: no growth for 48 hours

Rapid respiratory syncytial virus, influenza, parainfluenza testing from nasopharynx: negative

Cytomegalovirus (CMV) IgG: positive

CMV IgM: negative

Epstein-Barr virus (EBV) capsid IgG: positive

EBV IgM: negative

CMV and EBV PCRs from blood: negative

What is your interpretation of these findings?

A. The patient has been exposed to CMV, as evidenced by positive serology.

B. Although CMV pneumonitis is possible, it is ruled out by the negative PCR test in the blood.

C. The CBC with 50% lymphocytes is inconsistent with a diagnosis of SCID.

D. Bronchoscopy or biopsy is needed to make a diagnosis.

**Explanation**

The correct answer is D. The circulating IgG in any patient younger than 6 months old reflects the exposures of the mother; therefore, answer A is incorrect. CMV can cause a number of organ infections, including pneumonitis, and these can occur in the absence of viremia; therefore, answer B is incorrect. X-linked SCID is a form of SCID that preserves B-cell development (ie, this is a T− B+ form of SCID). The absolute lymphocyte count may be normal, and thus the CBC is still consistent with X-linked SCID, making answer C incorrect.

12. A 13-year-old girl with acute lymphoblastic leukemia who is day +7 after an unrelated donor transplant has a high fever, tachycardia, and hypotension. She is cytomegalovirus (CMV) seropositive, and the donor is CMV seronegative. On examination, she has just finished receiving a red blood cell transfusion, has mucositis, is tachypneic, has bounding pulses, and is uncomfortable. Total WBC is 0.05. She is on fluconazole and stopped taking sulfamethoxazole/trimethoprim on admission to the transplant floor.

Based on this clinical picture, what is the most likely cause of her fever?

A. *Pneumocystis jirovecii*

B. CMV

C. Gram-negative rods

D. Respiratory syncytial virus (RSV)

E. Transfusion reaction

**Explanation**

The correct answer is C. This patient is at high risk of bacteremia and sepsis due to mucositis and absolute neutropenia. It is uncommon to develop *Pneumocystis* pneumonia during the pancytopenic phase of transplant, so answer A is unlikely. Although the patient is at risk for CMV reactivation, due to being CMV seropositive with a seronegative donor, reactivation is unlikely to cause high fever and sepsis physiology, so answer B is unlikely. The profound systemic symptoms are inconsistent with RSV or transfusion reaction.

13. You have diagnosed an infant with severe combined immunodeficiency (SCID) due to mutation in *IL2RG*. HLA typing of his family reveals his 5-year-old sister to be a full HLA match. How should the child be treated?

A. Supportive care alone with IVIg and sulfamethoxazole/trimethoprim prophylaxis

B. Infusion of T-cell–depleted bone marrow from sibling donor

C. Referral for gene therapy

D. Infusion of unmanipulated bone marrow from sibling donor

E. Search for an unrelated donor, because the disease is familial

**Explanation**

The answer is D. SCID is caused by the absence of functioning autologous T cells; therefore, these patients are generally incapable of rejecting grafts from fully matched related donors. Transplants for SCID are special because sibling bone marrow transplants can be performed without prior conditioning and without the need for graft-versus-host disease prophylaxis. Thus, the treatment of choice is infusion of unmanipulated bone marrow. Answer A is incorrect because SCID always should be treated with a transplant as definitive therapy. Answers C and E are incorrect because a matched sibling donor is always the first choice for treatment of SCID and is associated with the best survival. In addition, defects in *IL2RG* cause the X-linked form of SCID; therefore, the sister would not be affected. Answer B is incorrect because matched T cells from a sibling contained in the bone marrow are tolerated by the patient with SCID and provide immediate immunity in the first few months after transplant.

14. A 4-year-old boy comes for evaluation due to refractory autoimmune hemolytic anemia despite treatment with steroids. According to his family, he has been in and out of the doctor’s office because of swollen glands for about a year. On examination you detect massive splenomegaly in addition to cervical adenopathy. Laboratory testing shows Coombs positive anemia and a platelet count of 32,000, with mean platelet volume of 11 fL. Lymphocyte subsets show normal numbers of T cells, B cells, and NK cells. IgG is elevated for age.

Which of the following findings are consistent with the most likely diagnosis?

A. Eczema, maternal uncle with lymphoma

B. Family history of chronic lymphadenopathy, elevated TCR αβ+ CD4− CD8− T cells

C. Low IgA, poor response to vaccines

D. Maternal T-cell engraftment, poor proliferation of lymphocytes to mitogens

**Explanation**

The correct answer is B, consistent with a diagnosis of autoimmune lymphoproliferative syndrome. Answer A is consistent with Wiskott-Aldrich syndrome, and although patients with Wiskott-Aldrich syndrome are at risk for autoimmunity including immune cytopenias, massive splenomegaly would be unusual, and typically the platelet volume is very low. Answer C is consistent with common variable immunodeficiency (CVID); although some patients with CVID have autoimmune cytopenias, adenopathy, or splenomegaly, the primary feature of CVID is humoral immune defect, with low IgG and low IgA or IgM. This child is hypergammaglobulinemic. Similarly, answer D is characteristic of a patient with severe combined immunodeficiency (SCID), who by definition would be hypogammaglobulinemic due to lack of T-cell help. It would be highly unusual for a child with SCID to present at 4 years of age.

15. Nine months after a matched unrelated donor bone marrow transplant, your patient, a 5-year-old girl, has developed a vesicular rash on the trunk, arms, and legs, with fever to 103 ºF. On further questioning, the mother reports that the patient was exposed to chicken pox 14 days ago. The child was fully immunized when diagnosed with high-risk leukemia at age 3.

What should your response be?

A. Give varicella-zoster immunoglobulin or intravenous immunoglobulin alone.

B. Treat with acyclovir intravenously, 500 mg/m2/dose every 8 hours.

C. Treat with ganciclovir intravenously, 5 mg/kg/dose every 12 hours.

D. Reassure mother that this is not likely to be chicken pox because she was vaccinated.

E. Treat with oral acyclovir 20 mg/kg/dose twice a day for 5 days.

**Explanation**

The correct answer is B. This child has either primary varicella or disseminated zoster reactivation, more likely the former. Because the patient has undergone a transplant, having been vaccinated in the past is no longer protective; therefore, answer D is incorrect. Treatment with antivirals is indicated for this immunocompromised patient; therefore, answer A is incorrect. The typical agent for treatment is acyclovir; therefore, answer C is incorrect. For immunocompromised patients with disseminated disease, IV treatment is warranted; therefore, answer E is incorrect. In addition, the half-life of oral acyclovir is short, so the dosing of twice a day in answer E is inadequate.