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

**Sung-Yun Pai, MD**

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

A. NK-cell numbers are lowest at birth and increase with age.

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

C. T-cell numbers in infants are higher than in adults.

D. Infants have low lymphocyte counts that increase with age.

**Explanation**

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

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

**Recipient**

CMV IgG: negative

CMV IgM: negative

HSV I/II antibody: negative

Varicella IgG: positive (vaccinated)

Hepatitis B surface antigen: negative

Hepatitis B surface antibody: positive (vaccinated)

Hepatitis B core antibody: negative

Hepatitis C antibody: negative

**Donor**

CMV IgG: negative

CMV IgM: negative

HSV I/II antibody: positive

Varicella IgG: positive

Hepatitis B surface antigen: negative

Hepatitis B core antibody: negative

Hepatitis C antibody: negative

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

A. Acyclovir IV for herpes simplex virus (HSV) suppression

B. Weekly screening by polymerase chain reaction (PCR) for cytomegalovirus (CMV) in blood

C. Antifungal prophylaxis

D. Valganciclovir PO for CMV suppression

E. Foscarnet IV for CMV suppression

**Explanation**

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

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

Which of the following is the most likely diagnosis?

A. Congenital infection

B. Neonatal alloimmune thrombocytopenia

C. Wiskott-Aldrich syndrome

D. May-Hegglin anomaly

**Explanation**

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

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 6 days after starting induction therapy. His absolute neutrophil count (ANC) is 50. Blood cultures from all lumens of his central line are sent. He is tachycardic but clinically stable, with no localizing findings on physical examination.

Which of the following is appropriate management?

A. Anti-Pseudomonal beta-lactam

B. Await results of blood culture because there are no localizing findings

C. Antipseudomonal beta-lactam and second agent with activity against gram negative rods

D. Vancomycin and ceftriaxone

**Explanation**

The correct answer is A. Multiple studies in patients undergoing induction for acute leukemia or stem cell transplant support monotherapy for empiric therapy of fever and neutropenia. In a patient anticipated to have prolonged neutropenia, empiric coverage is indicated, and therefore option B is incorrect. Furthermore, the lack of localizing findings on exam is irrelevant. Without clinical instability, there is no need for a second agent, though one may be considered if there is suspicion of resistant infection or concerns based on local epidemiology, so option C is incorrect. The organisms targeted by empiric fever and neutropenia therapy include gram negative rods, in particular *Pseudomonas*, which is not covered by ceftriaxone, so option D is 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 developed high fever the afternoon of day +3 after unrelated donor transplant with neutropenia. Blood cultures were sent, and she was started on a broad-spectrum carbapenem in addition to fluconazole she has been on since admission. She remained febrile over the next several days with negative blood cultures. She is cytomegalovirus (CMV) seropositive, and the donor is CMV seronegative. When you examine her the morning of day +8, she is tachycardic but nontoxic, has no new symptoms or findings on examination other than mucositis, and total WBC is 0.05.

What is the next appropriate management step?

A. Begin treatment for CMV reactivation with foscarnet.

B. Add a second agent active against gram-negative rods.

C. Start empiric antifungal treatment with liposomal amphotericin.

D. Add vancomycin.

E. Stop antibiotics because blood cultures are negative.

**Explanation**

The correct answer is option C. A patient with persistent fever and neutropenia despite appropriate bacterial coverage should be treated for possible invasive fungal disease empirically, and liposomal amphotericin is appropriate to cover most yeast and mold. Although the patient is at risk for cytomegalovirus (CMV) reactivation, beginning treatment in the absence of evidence of reactivation is not appropriate, therefore option A is incorrect. With negative blood cultures, stable appearance clinically, and no localizing signs, there is no rationale to add a second agent for gram-negative rods nor vancomycin, therefore options B and D are incorrect. At day +8, the patient is anticipated to stay neutropenic for at least another week, and antibiotics should not be stopped until the patient is afebrile, with strong evidence of marrow recovery, so option E is incorrect.

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.