Chapter 5
Primary Immunodeficiency Diseases

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Introduction

The immune system has a fundamental role in protection from infection. One manner of protection is mediated by innate immunity through blocking the entry of microbes and mediating inflammation and subsequent direct microbial killing [1]. Another mode of defense is necessary for the elimination of those pathogens that resist innate immunity. For that reason, adaptive immunity ensured by T and B lymphocytes is important to maintain proper protection [2]. Several studies have shown high rate of infections in patients who have deleterious genetic mutations that affect immune system and lead to primary immunodeficiency diseases (PIDs). The International Union of Immunological Societies listed in their recent report more than 350 PIDs. PIDs are classified according to the primary defective component of

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the immune system. Defects of innate immunity include congenital defects of phagocyte number or function, Toll-like receptors (TLR) signaling pathway deficiency, and complement deficiencies. On the other hand, PIDs due to defect in adaptive immunity include severe combined immunodeficiencies (SCIDs), combined immunodeficiencies (CIDs) with or without syndromic features, antibody deficiencies, and immune dysregulation [3].

Patients with PID are most often present with recurrent infections that range from mild infection to severe sepsis with multi-organ failure. They can also present with other manifestations including allergy, autoimmunity, persistent inflammation, lymphoproliferation, and cancers [4]. Therapeutic options for PID patients range from starting antimicrobial agents and immunoglobulin replacement therapy to the advanced treatments like hematopoietic cell transplantation and gene therapy. This group of patients requires an urgent management to decrease disease-associated morbidity and mortality. However, a significant number of those patients need critical care management because of life-threatening complications.

The aim of this review is to highlight the defining features of PIDs as well as their classification and phenotypes with particular emphasis on the management of these serious disorders.

Normal Immune System

The immune system is a very complex system that has a crucial role in protecting our body from dangerous invaders. These invaders can elicit immune responses and include a wide range of infectious and noninfectious antigens. Therefore, the immune system must be able to defend against different types of microbial antigens. This protective measure explains the high frequency of the infectious complications in those patients with immune system defects. It is also important for this system to recognize the harmful noninfectious antigens such as foreign macromolecules, tumor cells, and transplanted organs or tissues. Our immune system has the capability to differentiate between self- and nonself antigens to avoid attacking the body's own tissue. Failure of this fundamental property, self-tolerance, results in immune dysregulation and autoimmunity. In this section, we will outline the normal functions of innate and adaptive immunity.

Innate Immunity

Innate or naïve immunity is the first line of defense that provides a nonspecific and immediate protection against a wide variety of organisms. It is a mature system that does not require previous exposure to the pathogen to work effectively. This immune response is important in preventing and controlling infections by promoting inflammation and antiviral defense as well as stimulating the adaptive immune system to respond to the invading antigens. It provides protection through multiple defensive

mechanisms including (1) physical and chemical barriers such as the skin, mucous membranes, low stomach pH, lysozymes, and others; (2) proteins that include complements, C-reactive protein, and cytokines; and (3) numerous cells such as granulocytes, macrophages, dendritic cells, natural killer cells, and other innate lymphoid cells. This part of the immune system uses molecules and receptors such as Toll-like receptors and NOD-like receptors to recognize invaders by identifying the common shared structures between classes of microbes (pathogen-associated molecular patterns) or some molecules released from damaged cells (damaged-associated molecular patterns) [5].

Adaptive Immunity

There are two types of adaptive or acquired immunity: cellular and humoral immunity. The main cellular components of humoral immunity are B lymphocytes, while the T lymphocytes are the main component of cellular immunity. Both lymphocytes, B and T, developed from bone marrow stem cells that give rise to the common lymphoid progenitors. B lymphocytes continue steps of differentiation in the bone marrow starting from the stage of pro-B cells to the mature B cells that subsequently move to the secondary lymphoid organs. These mature B cells proliferate on exposure to foreign antigens and differentiate into plasma cells that secrete antibodies. Those antibodies are vital for protection against extracellular organisms as they neutralize toxins, prevent the entry of pathogens, and activate the complement system to enhance microbial phagocytosis. On the other hand, T lymphocytes differentiate into mature T cells and get trained to recognize self- and nonself antigens in thymus. Subsequently, they move on from thymus to the blood and lymphoid organs as variable cell subsets including T-helper cells (CD4), T-cytotoxic cells (CD8), and T-regulatory cells. Cell-mediated immunity is important for protection against intracellular organisms like some bacteria, viruses, fungi, and parasites. The T-cell response starts with microbial phagocytosis by antigen-presenting cells like macrophages, which process and present the antigen on their cell surface. T-helper cells recognize the presented antigen and initiate activation and proliferation of multiple cells including phagocytes, B cells, cytotoxic T cells, and other cells to promote an effective destruction of the microbe. For subsequent exposures, cellular immunity is important in the development of memory T and B cells that is needed to mount future immune responses against previous antigens. Finally, both innate and adaptive immunity need to have good collaboration to provide effective defense against invaders [6].

Primary Immunodeficiency Diseases

Defects in innate or adaptive immunity can lead to serious disorders known as immunodeficiency disorders. These immune defects are classified into primary (congenital) and secondary (acquired) immunodeficiencies. PIDs are a

heterogeneous group of genetic disorders that lead to increased susceptibility to infections, tumors, and/or autoimmunity. Secondary immunodeficiency disorders are not inherited like PIDs but acquired during life as a consequence of other causes, such as severe malnutrition, immunosuppressive medications, or infections. In this section, we will focus on the classification and the clinical manifestations of PIDs [7].

Classification

PIDs are classified according to the clinical features and the primary component of the immune system that is affected. Innate immunity disorders include congenital phagocytic disorders, complement deficiencies, Toll-like receptor (TLR) pathway defects, and interleukin-12/interferon-gamma (IL-12/INF-γ) pathway defects. Adaptive immunity disorders include humoral immune defects like hypogammaglobulinemia and cellular immune defects such as DiGeorge syndrome. Most of the defects in cellular immunity lead to combined immunodeficiencies (CIDs) or even severe combined immunodeficiencies (SCIDs) which highlights the importance of cellular immunity in providing effective B-cell-mediated antibody production and class switching [3].

Clinical Manifestations

The clinical manifestations of PIDs are variable according to the component of the immune system that is primarily disrupted (Table 5.1).

Innate Immunodeficiencies

Phagocytes: Microbial phagocytosis by macrophages and neutrophils is one of the most important mechanisms of innate immunity. The phagocytic defects range from defects in phagocytic number like neutropenia to defects in migration or intracellular killing like leukocyte adhesion defects (LAD) and chronic granulomatous disease (CGD). Patients with phagocytic defects suffer from recurrent chest infections, lymphadenitis, deep-seated abscesses, and oral stomatitis. Those infections are usually due to bacterial (catalase positive bacteria), fungal (*Candida and Aspergillus*), and mycobacterial infections [8, 9].

Complements: The complement system is an essential part of innate immunity as it promotes inflammation (C3a, C5a), opsonization (C3b), and microbial killing (membrane attack complex). It consists of three pathways: classical, alternative, and lectin pathway. Early classical pathway defects (C1q, C1r, C1s, C4, C2, C3) lead to autoimmunity and increased risk of infections due to encapsulated organisms, while late classical pathway defects (C5–C9) as well as alternative pathway

Table 5.1 Classification and clinical presentations of primary immunodeficiency diseases

Classification	Examples	Clinical manifestations
Immunodeficiencies affecting cellular and humoral immunity	Severe combined immunodeficiencies	Respiratory and gastrointestinal infections. Oral thrush and disseminated BCGitis
	Combined immunodeficiencies	Respiratory and gastrointestinal infections and liver/biliary tract disease
Combined immunodeficiencies with associated or syndromic features	Wiskott-Aldrich syndrome	Thrombocytopenia with small platelets, recurrent bacterial and viral infections, bloody diarrhea, eczema, lymphoma, and autoimmune disease
	Ataxia-telangiectasia	Ataxia, telangiectasia, pulmonary infections, lymphoreticular and other malignancies, increased alpha fetoprotein, increased radiosensitivity, and chromosomal instability
Predominantly antibody deficiencies	Agammaglobulinemia	Severe bacterial infections with absent B cells
	Common variable immunodeficiency	Clinical phenotypes vary: most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias, and/or granulomatous disease
Diseases of immune dysregulation	IPEX (immune dysregulation, polyendocrinopathy, enteropathy X-linked)	Autoimmune enteropathy, early-onset diabetes, thyroiditis, hemolytic anemia, thrombocytopenia, eczema, elevated IgE, and IgA.
	Familial hemophagocytic lymphohistiocytosis (HLH)	Fever, hepatosplenomegaly HLH, and cytopenias
Congenital defects of phagocyte number or function	Leukocyte adhesion deficiency	Delayed cord separation, skin ulcers, periodontitis, leukocytosis
	Chronic granulomatous disease	Infections with deep-seated abscesses, autoinflammatory, and IBD phenotype
Defects in intrinsic and innate immunity	Mendelian susceptibility to mycobacterial disease (MSMD)	Susceptibility to mycobacteria and salmonella
	TLR signaling pathway deficiency with bacterial susceptibility	Pyogenic bacterial infections
Complement deficiencies	Deficiency in early complement pathway components (C1q, C1r, C2, C4)	Systemic lupus erythematosus, multiple autoimmune diseases and infections with encapsulated organisms
	Deficiency in late complement pathway components (C5, C6, C7, C8, C9)	Neisserial infections

defects (factor D, properdin) are associated with recurrent meningitis caused by *Neisseria* species [10].

Toll-Like receptors: TLRs, pattern recognition receptors, are important in recognizing different microbes and dying cells. Defects in TLRs lead to a wide range of infections. TLR3 pathway defects increase the risk for herpes simplex encephalitis, while defects in myeloid differentiation primary response 88 (MyD88) and interleukin-1 receptor-associated kinase 4 (IRAK4) are associated with increased susceptibility to pyogenic bacterial infections that cause meningitis or other invasive infections.

IL-12/INF-γ pathway: Patients with disseminated mycobacterial disease and recurrent infections with *Salmonella* species or herpesviruses should be screened for defects in IL-12/INF-γ pathway. Genetic defects in this pathway lead to Mendelian susceptibility to mycobacterial disease (MSMD). These defects include mutations in INF-γ receptor 1/2, IL-12 p40, IL-12 receptor B1, signal transducer and activator of transcription1 (*STAT1*), interferon-stimulated gene15 (*ISG15*), and interferon regulatory factor 8 (*IRF8).* In addition to IL-12/INF-γ pathway defects, the risk for disseminated mycobacterial diseases is increased in other disorders that involve NF-κB pathway like NF-κB essential modulator (NEMO) deficiency [11].

Humoral Immunodeficiencies

Humoral immune defects are the most common type of PIDs. Patients with antibody deficiency, due to defective B-cell development, maturation, and/or function, present with recurrent sinopulmonary infections and chronic suppurative otitis media. The most common isolated organisms are extracellular microbes like *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Defects in humoral immunity might lead to other clinical manifestations including skin abscesses, viral meningitis, intestinal giardiasis, lung lymphocytic infiltration, and autoimmunity [12].

Cellular Immunodeficiencies

SCIDs are the most serious form of cellular immunodeficiencies in which there is a profound defect in lymphocyte-dependent adaptive immunity. Patients with SCID usually start to acquire life-threatening infections early in life and typically die in infancy if untreated. These infections include pneumonia, meningitis, chronic diarrhea, and disseminated viral, bacterial, and mycobacterial diseases. The most common isolated organisms are the intracellular pathogens that include *Candida albicans*, *Pneumocystis jirovecii*, *Cryptosporidium*, *Mycobacterium* species, and herpesviruses. There is also an increased susceptibility to extracellular organisms in patients with SCID due to defective antibody response that might be attributed to intrinsic B-cell defect or lack of T-cell help. Physical examination reveals failure to thrive, oral thrush, skin rash, lack of palpable lymphoid tissue, and absence of thymic shadow in chest imaging. SCIDs are classified according to the peripheral lymphocytic profile to four general categories including $T^-/B^+/NK^+$, $T^-/B^+/NK^-$, $T^-/B^-/NK^+$, and $T^-/B^-/NK^-$ [13]. CIDs and leaky SCIDs like Omenn syndrome might present like the classical SCID, but they are usually less severe due to the presence of residual T-lymphocyte number and/or function [14].

Immune Dysregulation

Some forms of PID are associated with significant autoimmunity and lymphoproliferation due to defective immune tolerance. Central immune tolerance for cellular immunity is achieved in thymic tissue by clonal deletion or successful inactivation of the autoreactive T-cell clones that recognize self-antigens with high affinity [15]. Compelling evidence has shown high rates of autoimmunity in genetic disorders that affect thymic central tolerance like the observed profound immune dysregulatory manifestations in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome due to *AIRE* gene mutation [16]. Peripheral immune tolerance is important for the autoreactive T cells that escaped thymic tissue to the periphery. This kind of tolerance is usually obtained by the suppressive function of the T-regulatory cells [17]. Defects that affect T-regulatory cell number and/or function, like the immunodysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance syndrome (IPEX) and IPEX-like disorders, present with autoimmunity, lymphoproliferation with lymphocytic infiltration in multiple organs, and allergic disorders [18]. Immune homeostasis in the periphery is also achieved by apoptosis of these autoreactive lymphocytes. Autoimmune lymphoproliferative syndrome (ALPS) is an example of immune dysregulation due to defect in apoptosis [19].

Diagnosis

The diagnosis of PID is readily entertained when a patient presents with unexplained frequent or invasive infections. A detailed history including family history and physical examination are important to delineate the possible underlying defect of the immune system that leads to high microbial susceptibility and other immune complications. The laboratory evaluation is essential for the diagnosis of primary immunodeficiency and also for providing early effective treatment that leads to reduced patient morbidity and mortality (Table 5.2) [20].

Investigation of patients with putative phagocytic defect includes absolute neutrophilic count (ANC) and peripheral blood smear for congenital neutropenia, serial ANCs for cyclic neutropenia, oxidative burst test for CGD and CD18 expression for LAD1. Patients who have sinopulmonary infections and or autoimmunity should be screened for suspected complement deficiency by measuring C3 and C4 levels as well as testing the total hemolytic complement activity (CH50) and alternative pathway hemolytic activity (AP50). Regarding TLRs, it can be tested independently by measuring IL-1β, IL-6, TNF-α, and CXCL10 productions after the stimulation of peripheral blood mononuclear cells with TLR-specific ligands.

Evaluation of humoral immunodeficiency involves B lymphocyte enumeration by flow cytometry, measurement of serum immunoglobulins (IgA, IgM, IgG, and IgE), and specific antibody titers in response to protein and polysaccharide antigens. It is important to compare serum immunoglobulin levels with the age-adjusted normal values. If any specific antibody titer is below normal range, it is recommended

Table 5.2 Laboratory tests of immune function

Immune function	Screening tests
Humoral immunity	Serum immunoglobulin levels Serum-specific antibody titers Flow cytometry to enumerate B-cell subsets
Cellular immunity	T-cell receptor excision circles (TREC) newborn screening Flow cytometry to enumerate T-cell subsets and NK cells In vitro proliferative response to mitogens and antigens
Phagocytic cells	Blood cell count with differential Neutrophil staining, morphology on a peripheral blood smear Dihydrorhodamine (DHR) reduction or nitro blue tetrazolium Flow cytometry for adhesion molecules
Complement	CH50 assay (total hemolytic complement activity) AH50 assay (alternative pathway hemolytic activity) Level or function of individual complement components Lectin pathway function

to revaccinate the patient with killed vaccine and to assess the titer 4–6 weeks after vaccination.

The initial evaluation for patients with an underlying cellular immune defect is obtained by calculating the absolute lymphocyte count (ALC). It is important to exclude HIV infection in patients with low lymphocytic count before entertaining the diagnosis of PID due to cellular immune defect. Lymphocyte enumeration, naive/memory T-cell flow cytometry, and T-lymphocyte proliferations after both antigen and mitogen stimulation are helpful in confirming a diagnosis of SCID or CID.

Genetic testing is widely available nowadays. Knowing the genetic defect is important not only for confirming diagnosis but also essential for anticipating prognosis and family counseling [21].

Complications

Patients with PID are prone to multiple complications that need urgent diagnosis and appropriate management. Some of these complications are attributed to progression of the disease, while others are secondary to the offered therapy like Hematopoietic cell transplantation (HCT). In this section, we will discuss some of the complications related to the disease progression.

Infectious Complications

The knowledge of the type of immunodeficiency is crucial to guide us for the best empirical antimicrobial treatment as the early administration and appropriateness of antimicrobials are major prognostic factors in treating sepsis in PID patients [22]. The main infections for antibody and complement deficiencies are sinopulmonary infections due to extracellular encapsulated organisms. Infections due to

Table 5.3 Type of organisms associated with PIDs

Immune defect	Type of organisms
Antibody deficiencies	Enteroviruses
	Encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*). *Pseudomonas aeruginosa*, *Mycoplasma*
	Giardia lamblia
SCIDs/CIDs	CMV, EBV, RSV, and other viruses
	Encapsulated organisms and other organisms like *Listeria monocytogenes* and gram-negative organisms
	Atypical mycobacterium, including BCGitis
	Candida species, *Aspergillus* species, and other fungal infections
	Pneumocystis jirovecii, *Toxoplasma gondii*, *Cryptosporidium parvum*
Phagocytic defects	Catalase-positive organisms (*Staphylococcus aureus*, *Pseudomonas*, *Burkholderia*, and *Serratia*)
	Atypical mycobacterium
	Candida, *Aspergillus*, and *Nocardia*
Complement deficiencies	Encapsulated organisms (*Streptococcus pneumoniae* and *Neisseria*)

intracellular organisms like Gram-negative bacteria, fungal, and mycobacterium are more prominent in cellular and phagocytic immune defects. Chest infection attributed to *Pneumocystis jirovecii* is classically described in patients with severe CD4 lymphopenia like those patients with SCID. Viral infections and other opportunistic infections are likely to occur early in SCID patients but usually later in CID. The main observed viruses in humeral immunodeficiency are enteroviruses while in cellular immunodeficiency they are herpesviruses (CMV, HSV, VZV, HHV6) and respiratory viruses such as influenza, RSV, and adenovirus (Table 5.3).

Noninfectious Complications

Pulmonary complications: Pulmonary complications are very common in patients with PID. Most of these complications are attributed to the infection of either upper airway leading to sinusitis and otitis media or lower airway and lung parenchyma causing bronchiolitis, bronchitis, pneumonia, and lung abscesses. Noninfectious pulmonary complications also have been reported among patients with PID. Chronic bronchiectasis is a major pulmonary complication in humoral and combined immunodeficiencies. Chest high-resolution computed tomography (HRCT) should be considered for all immunodeficient patients with chronic chest symptoms to monitor their disease progression. High-dose immunoglobulin replacement therapy, aggressive antibiotic treatment, and physiotherapy are the most important preventive measures. Interstitial lung disease (ILD) is another noninfectious complication especially in those with humoral immunodeficiency. ILD includes lymphocytic interstitial pneumonia, follicular bronchiolitis, granulomatous lung disease, and organizing pneumonia. Granulomatous-lymphocytic interstitial lung disease (GLILD) is the most common form of ILD that is associated with poor clinical

outcomes, and using immunosuppressive therapies like rituximab and azathioprine can lead to clinical improvement. Patients with PID may also present with hilar and/or mediastinal adenopathies either due to infections, lymphoproliferative disorders, or malignancy. Organizing pneumonia (OP), known as bronchiolitis obliterans, is a relatively rare complication in PID patients. It is recommended to do inspiratory and expiratory HRCT to show the characteristic air trapping, alveolar opacities, and ground-glass consolidation. Lung biopsy might be considered to confirm the diagnosis. There are other rare complications that should be considered in PID patients including pulmonary alveolar proteinosis in patients with SCID due to adenosine deaminase deficiency and pulmonary dysgenesis in patients with DiGeorge syndrome [23–25].

Hemophagocytic lymphohistiocytosis (HLH) in PIDs: HLH is a life-threatening syndrome that should be considered in any critically ill child who has history of persistent fever, hepatosplenomegaly, and pancytopenia. It is caused by hyperstimulated but inefficient immune system that results in hyperinflammatory response and cytokine storm [26]. Diagnosis is based on fulfillment of HLH-2004 diagnostic criteria [27]. HLH is a known complication of some PIDs such as SCID, CID, and CGD. Most cases of HLH in PID are associated with infections. Viral infections due to EBV, CMV, and adenovirus are frequently observed with HLH in SCID and CID patients, while bacterial, fungal, and Leishmanial infections are more associated with HLH in CGD patients [28]. Although an etoposide-based regimen (HLH-94) is the standard treatment protocol in patients with familial HLH and XLP, there is no consistent approach to treat HLH in patients with PID [29]. Steroids and IVIG are important components of therapy; however, the use of etoposide might be harmful in some patients [28]. The addition of rituximab should be considered in EBV-induced HLH [30]. The definitive therapy for PID patients who presents with HLH is HCT.

Autoimmunity: Autoimmunity is a significant manifestation of PID that presents with antibody-mediated inflammation and lymphoproliferation [31]. The most common autoimmune disorders in PID patients are immune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA). IVIG, steroids, rituximab, sirolimus, abatacept, and ultimately HCT are examples of treatment strategies to manage autoimmunity in PID [32].

Inflammation and autoimmunity in Omenn syndrome (OS): Oligoclonal autoreactive T cells in Omenn syndrome can trigger a severe inflammatory reaction that affects multiple organs causing generalized skin erythroderma, hepatosplenomegaly, lymphadenopathy, and other autoimmune manifestations. OS is associated with hypereosinophilia, high IgE, and high memory cells in the absence of maternal engraftment [14]. It is important to diagnose OS promptly to start immunosuppressive therapies such as steroids and cyclosporine to suppress the autoreactive T-cell clones and to ameliorate the autoimmune manifestations prior to HCT [33].

Graft-versus-host disease (GVHD) secondary to transplacental maternal engraftment (TME): The immune system in normal newborns eliminates maternal T cells that pass through the placenta. However, typical SCID patients might not be able to reject transplacental maternal T cells leading to persistent TME [34]. TME in SCID patients might be uneventful; however, some patients will have features of GVHD,

mostly in the skin and liver, that could be severe and resemble OS [35]. In addition, TME increases the risk of GVHD and possibility of graft rejection posttransplant in SCID patients [34, 36]. It is imperative that all SCID patients receive irradiated blood products to prevent transfusion-associated GVHD that could be fatal and it occurs secondary to engraftment and proliferation of transfused T cells [37].

Management

General Medical Management

PID patient needs urgent medical treatment to eliminate disease-associated complications [7]. Treatment of the innate immunity disorders depends on the type of defect. Phagocytic defects are primarily managed by supportive therapy that includes antibiotic such as cotrimoxazole and antifungal such as itraconazole prophylaxis. INF-γ-replacement therapy was reported to be beneficial in patients with CGD. Subcutaneous recombinant granulocyte colony-stimulating factor has been used successfully to increase ANC in severe congenital neutropenia.

Immunoglobulin G (Ig) replacement therapy is the mainstay of therapy in antibody deficiency. It comes in different preparations that can be given through intravenous access (IVIG) or subcutaneously (SCIG). The usual dose of IVIG is 400–600 mg/kg/month, while the usual dose of SCIG is 100 mg/kg/week. Providing higher doses of Ig has been reported to be effective in treating some complications of hypogammaglobinemia like bronchiectasis, viral meningoencephalitis, and autoimmunity. Prophylactic antibiotic such as amoxicillin might be beneficial in those patients who are continuing to have persistent sinopulmonary infections despite optimal Ig replacement therapy.

Patients with SCID or CID require aggressive management with Ig replacement therapy and prophylactic antibiotic (cotrimoxazole) to decrease infection-related morbidity and mortality. Antifungal and antiviral prophylactic therapies are usually recommended for high-risk patients. Infections should be treated aggressively with parenteral broad-spectrum antibiotics that will be narrowed subsequently based on the results of cultures. Positive pressure isolation and meticulous skin and mucosal hygienic care are necessary to avoid infections. Good nutritional support is recommended for those patients with diarrhea and failure to thrive. Blood products must be irradiated and lymphocyte depleted to prevent fatal (GVHD). Patients should avoid all live virus vaccines as they could develop disease from attenuated viruses and may even die after exposure to these vaccines. Babies with SCID should avoid breastfeeding from CMV-seropositive mothers. Enzyme replacement therapy with polyethylene glycol-modified bovine adenosine deaminase (PEG-ADA) is recommended for the management of SCID patients due to adenosine deaminase deficiency before HCT [21]. Immunosuppressive medications might be used to control autoimmunity in PID patients and also to control the persistent inflammation that associated with maternal engraftment or autoreactive leaky SCID like Omenn syndrome [38].

Critical Care Management

Patients with PID are at high risk for morbidity and mortality due to their underlying compromised immune systems. The most common reason for admission to pediatric intensive care unit (PICU) is infectious pulmonary complications that require assessed ventilation. Avoiding intubation and mechanical ventilation if possible is a major goal in the management of respiratory failure in PID patients as the mortality risk is higher in those patients requiring ventilation support [39]. Severe infections that need broad-spectrum antibiotics and inotropic support are important indications for critical care management. Sepsis and pneumonia were reported to be the most common causes of death in PID patients. For that reason, infections in this group of patients need urgent intervention to avoid major complications [40]. Empirical broad-spectrum antimicrobial treatment should be initiated as soon as possible in any event of fever or more severe symptoms. It is very important to monitor central line devices and to consider antibiotic locks if needed. Persistent positive blood culture may require central line removal.

Other complications that necessitate PICU management include bleeding, acute kidney injury (AKI), cardiac, and liver dysfunction. Early diagnosis and appropriate interventions that include inotropic support and renal replacement therapy might be life-saving in critically ill PID patients.

There are several risk factors that predict poor outcome in PID patients including requirement of mechanical ventilation, the use of inotropes and renal replacement therapy, presence of organ failures, higher pediatric logistic organ dysfunction (PELOD) score, and prolonged length of PICU stay [39]. Previous studies showed that the overall mortality rate of PID patients was 1.99% [41]. The highest rate was seen in younger children less than 5 years of age due to the early in life presentation of SCID and other severe forms of PID. Mortality rate varied considerably between patients affected by different PID categories. The death rate was highest among patients with combined T- and B-cell immunodeficiency, familial HLH, and neutrophil dysfunction [40].

Hematopoietic Cell Transplantation

Allogeneic (HCT) is the treatment of choice in many immunodeficiency disorders including SCIDs, CIDs and phagocytic disorders [42]. The purpose of transplantation in PIDs is to replace the defective immune cells, i.e., restoring the immune system with a functional lymphocytes or neutrophils. However, if the defect is in trafficking at the thymus level, HCT may not solve the problem such as DiGeorge syndrome. HCTs include transplantation from matched or mismatched related and unrelated donors, cord blood transplantation, and haploidentical transplantation.

Since SCID is fatal, HCT should be initiated as soon as possible. Using stem cells from an (HLA)-matched sibling, it provides good immune recovery and excellent long-term outcome. Encouraging results have been reported among patients with SCID who underwent HCT at the age of 3.5 months or younger regardless of donor type [43]. However, the outcome of HCT is less satisfactory in older patients except for those who have no active infections at the time of transplantation. Patients

with some types of SCID can receive stem cells without conditioning therapy – this will correct T cells, but B cells may take longer time to recover. Many experts consider giving conditioning or immunosuppressive therapy in Omenn syndrome with autoreactive T cells or SCID with maternal engraftment. The rate of complications is higher in patients with radiation-sensitive SCID and Omenn syndrome who do not have HLA-matched sibling donors [44].

Recently, many patients with combined immunodeficiencies have been identified and offered HCT with conditioning therapy as a potentially curative treatment option. The intensity of the regimen depends on the underlying genetic defect, patient factors such as the presence of active infection, and the source of stem cells. HCT from a matched sibling donor provides curative treatment for patients with Wiskott-Aldrich syndrome [45]. Results from matched unrelated donors are also good, but mixed chimerism and autoimmune cytopenia are common posttransplantations.

Although, patients with immune dysregulation and autoimmunity benefit from immunosuppressive therapies, alternative strategies can be considered depending on the severity of the underlying defect. In particular, HCT is highly recommended for patients with IPEX and IPEX-like disorders [46].

Cellular therapy is the treatment of choice for phagocytic defects like CGD and LAD who have HLA-matched family donors. Overall survival in patients with CGD is currently around 93% after using reduced intensity regimen with no obvious difference between transplants from related and unrelated donors [47].

HCT should be considered without delay in patients with X-linked lymphoproliferative disease (XLP) and Chediak-Higashi syndrome (CHS). Immunosuppressive treatment is required to treat the accelerated phase in XLP. HCT can cure the hematological and immunological manifestations of CHS, but it does not prevent progressive neurological deterioration [48].

Gene Therapy

Gene therapy involves introducing normal genetic material into patient's cells to compensate for the abnormal gene. It is currently being investigated in patients with certain SCIDs, such as X-linked SCID and ADA deficiency, especially if no available matched sibling donor [49]. Prospective studies are required to follow the duration of immune reconstitution status post-gene therapy and to document the long-term safety of these gene-transduced cells in human.

Conclusions

The immune system is essential for protection from infectious and noninfectious invaders. This protection is achieved by collaboration between innate and adaptive immunity. Congenital defect in innate or adaptive immunity leads to PID. There are more than 350 PIDs that are classified according to the defective component of the immune system. Although the most common presentation of PID is recurrent

infections, other manifestations are common including allergic disorders, autoimmunity, lymphoproliferation, and cancers. PID patients are at high risk for morbidity and mortality due to the underlying immune defect and the presence of complications. Pulmonary complications and sepsis are the most common indications for PICU care. The management of PIDs varies from medical treatment with IVIG and prophylactic antibiotic to advanced therapies like HCT and gene therapy.

Conflict of Interest The authors declare that they have no conflict of interest.

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