Back to Basics: Primary Immune Deficiencies: Windows into the Immune System

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BACK TO BASICS

A review of the scientific foundations of current clinical practice

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Primary Immune Deficiencies: Windows into the Immune System

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Objectives

After completing this article, readers should be able to:

1. Describe the basic role of the innate and adaptive immune systems in host defense.
2. Recognize the clinical features of the various categories of primary immune deficiencies.
3. List the screening laboratory tests that can define the primary immune deficiencies.
4. Discuss the general approaches to immune reconstitution for treating primary immune deficiencies.

Introduction

The inherited immune deficiencies have been invaluable instructors, extending our understanding of the contribution of components of the immune system to host defense. The information provided by studying these disorders also has generated new avenues of therapy, applications of which have influenced the treatment of a range of other human diseases. Currently, more than 120 genetic defects are associated with immune deficiency, and it appears that these numbers will continue to grow. This expansion of knowledge is being driven, in part, by clinicians becoming more aware of the subtleties of immune function and linking clinical phenotypes to potential immune deficiencies. This article focuses on the range of human immune deficiencies in the context of the underlying immunologic defects and associated infections. This link between components of the immune system and protection from infection to various categories of microorganisms serves as the basis for developing current approaches to therapy. Space constraints limit this discussion; readers are referred to major textbooks that deal specifically with immune deficiencies for in-depth discussions of these disorders. (1)

Better understanding of the immune deficiencies requires a basic understanding of the immune system and its division into two major components: innate and adaptive immunity. The former is a phylogenetically more primitive system that responds without the requirement of prior exposure. The functional components of innate immunity include cellular components as well as circulating and secreted proteins (Fig. 1). An innate immune host response is activated by direct contact with specific microbial products, which include lipopolysaccharide, cell wall components, and microbial nucleotides that can activate monocytes and macrophages directly via toll-like receptors specific to the different microbial products. The lymphoid member of the innate immune system is the natural killer cell, which is capable of destroying

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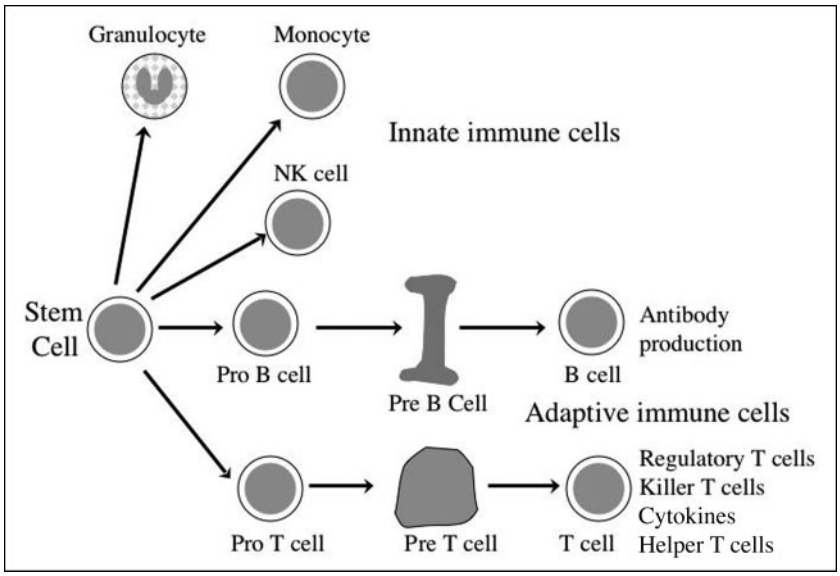

Figure 1. Cells involved in the immune response separated into those involved primarily in the innate response and those in the adaptive response. All cells shown are derived from the pluripotent hematopoietic stem cell resident in the human bone marrow. NK=natural killer

certain target cells directly and secretes soluble mediators, cytokines, and chemokines. These cellular products are secreted during an innate immune response to promote the inflammatory response and to provide a link to the adaptive immune system. Certain microbial products also can activate the complement system directly, providing another means of enhancing inflammation as well as generating opsonic activity to promote ingestion and elimination of microbes by phagocytic cells of the innate system (granulocytes and macrophages).

The adaptive immune response contrasts with the innate system in terms of its specificity directed at the inducing antigen (eg, microorganism). The central players in this system are T and B lymphocytes, each expressing antigen-specific receptors (Fig. 1). The immunologic response following foreign antigen stimulation requires both cell-cell interactions and the release of cytokines and chemokines. Initial antigen exposure generates a primary response tailored specifically to the offending foreign substance. A time lag follows initial antigen interaction until the response is activated and antigen-specific memory cells are generated. Memory cells hasten and magnify the immune response on antigen reencounter (a secondary or anamnestic response). This process is the foundation of protection by vaccination.

The adaptive immune system, thus, is divided into two arms. One is defined by T lymphocytes (cellular immunity) that provide helper, regulatory, and effector functions. The other is the humoral immune system, which depends on B lymphocytes as the source of specific antibodies (immunoglobulins [Igs]).

There is a major distinction between T and B lymphocytes at the level of cellular interaction with foreign antigen. B lymphocytes bind unprocessed (native) antigen; T lymphocytes can interact only with small peptide fragments of the intact antigen when these are bound to cell surface human leukocyte antigen (HLA) molecules (Fig. 2). Antigenic peptides bound to HLA class II molecules (HLA-DR, -DP, or -DQ) interact specifically with CD4 T cells; antigenic peptide presented on HLA class I molecules (HLA-A, -B, -C) bind to CD8 T cells. This pattern of antigen presentation to T cells is significant because HLA class I is expressed on virtually all nucleated cells; HLA class II is expressed only on specific antigen-presenting cells (APCs). Thus, antigen presentation to CD4 T cells is restricted to a specific cell type (APC); antigen presentation to CD8 T cells includes all nucleated cells under the appropriate circumstances. The advantage to this system is that CD8 T lymphocytes are the source of cytotoxic effector T cells, which are capable of destroying virtually any cell that has undergone an undesirable internal change, such as viral infection (associated with expression of viral antigenic peptides). In contrast, the CD4 T lymphocytes can interact only with APCs displaying antigenic peptides that typically are derived from extracellular sources such as microbes (bacteria, fungi) that require ingestion and processing. The CD4 T-lymphocyte interaction with antigen-expressing APCs typically takes place in the lymph node. Specific characteristics distinguish naïve T cells (ie, those cells that have not previously interacted with specific antigen) from memory T cells, and these characteristics are critical in directing the cell traffic patterns.

The inflammatory process resulting from an adaptive immune response involves the secretion of a number of cytokines and chemokines. These critical soluble mediators exert their functions by binding to unique cell surface receptors, many of which are actually expressed by cells of the immune system. Such

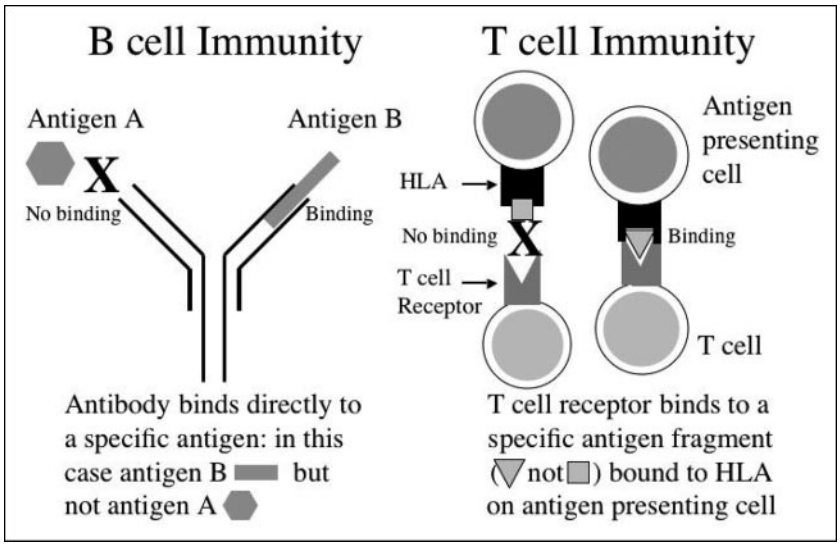

Figure 2. Lymphocyte–antigen interaction. Immunoglobulins, whether secreted or on the surface of B cells, bind to specific whole antigen; T cells bind to peptide fragments of specific antigens displayed (expressed) by human leukocyte antigen (HLA) molecules. There is an additional level of selectivity such that CD4 T lymphocytes bind only to antigenic peptides displayed by HLA class II molecules found only on specific antigen-presenting cells. In contrast, CD8 T lymphocytes bind to antigenic peptides displayed by HLA class I molecules found on nucleated cells.

secretory products are critical to the differentiation and maturation of immune cells and, thus, are central to the inflammatory response. In addition, certain cytokines induce the production and release of specific hematopoietic cells (eg, granulocyte colony-stimulating factor).

Additional complexity is found in T lymphocytes initially observed in experimental models and now confirmed in human studies. On antigen presentation, CD4 lymphocytes can differentiate into at least two functional subsets (Fig. 3). T helper 1 (Th1) lymphocytes facilitate a delayed type hypersensitivity response that features interferon-gamma and interleukin (IL)-12 production with monocyte infiltration. In contrast, the alternative response involves T helper 2 (Th2) lymphocytes that produce IL-4 and IL-5 and generate a response characterized by IgE production and eosinophilic infiltration. Thus, the cytokine output of the CD4 T lymphocyte determines its T helper status and dictates the resulting type of inflammatory response.

Primary immune deficiencies are categorized according to the division of labor within the immune system by grouping the disorders based on the primary cellular target of the defect. Immune deficiencies involving the adaptive immune system are separated further into those primarily affecting T lymphocyte (cellular) immune function and those primarily affecting B lymphocyte (humoral) immune function. The defects of innate immunity are considered together as a group, although some are primarily cellular abnormalities and others are soluble protein defects. These separations fail to take into account the significant interdependency of the components of the immune system but remain the main approach for categorizing primary immune deficiencies.

It is important to note that this discussion does not consider the various secondary immune deficiencies induced by specific immunosuppressive drugs, infectious agents (eg, human immunodeficiency virus), and malnutrition. Certainly, these various conditions must be considered when developing the differential diagnosis for a patient who has recurrent or chronic infections.

Cellular Immune Deficiencies

The primary immune deficiencies resulting from defects in T-lymphocyte function are characterized by increased susceptibility to infections produced by opportunistic organisms, including cytomegalovirus (CMV), *Candida* sp, and *Pneumocystis jiroveci*. (2)(3) Within the cellular immune disorders is a group of defects designated as severe combined immunodeficiency (SCID), which

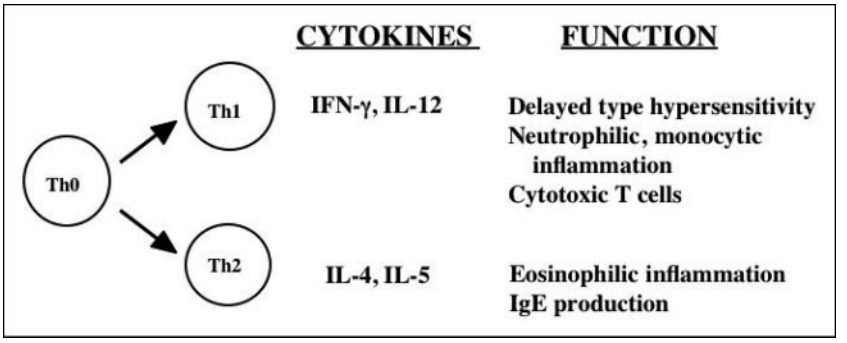

Figure 3. Distinction between T helper cell subsets: Th1 cells produce interferon-gamma and interleukin (IL)-12; Th2 cells produce IL-4 and Il-5.

Table 1. Forms of Severe Combined Immunodeficiency (SCID)

Lymphocyte Phenotype	Defect	Inheritance
T−/B−/NK−	Adenosine deaminase deficiency	AR
T−/B−/NK+	Antigen receptor defect	
	RAG1/2 deficiency	AR
	Artemis deficiency	AR
T−/B+/NK−	Cytokine receptor family defect	
	Common gamma chain deficiency	XL
	JAK3 deficiency	AR
T−/B+/NK+	IL-7 receptor deficiency	AR

−=absent, +=present, AR=autosomal recessive, XL=X-linked recessive, IL=interleukin

share the primary feature of a complete absence of lymphocyte function. The immunologic defect that all forms of SCID have in common is the absence of functioning T lymphocytes (Table 1). Affected patients typically present during infancy with a history of failure to thrive, chronic diarrhea, and recurrent opportunistic infections. Without immunologic reconstitution through bone marrow or stem cell transplantation, most affected patients die within 2 years of birth. Because a favorable outcome following immunologic reconstitution is strongly linked to the initiation of therapy prior to the development of significant infections, early identification of patients and diagnosis of the condition are crucial. (4) During early infancy, most patients who have SCID exhibit lymphopenia, making an absolute lymphocyte count a useful screening test when compared with age-appropriate normal ranges (ie, the lower limit for the absolute lymphocyte count during infancy is 2,500 to 3,000 cells/mm^3). However, a normal lymphocyte count does not exclude SCID.

The underlying genetic basis of most affected patients now can be determined with genetic testing. The general categories of these global immune defects are outlined in Table 1. Results of genetic testing provide the opportunity for genetic counseling and the potential for prenatal diagnosis and carrier screening. It is important to recognize that when SCID is a diagnostic consideration, no blood products should be administered without prior irradiation. This caution is necessary to prevent a possible graft versus host reaction that can be fatal and is mediated by the immunologically competent lymphocytes (graft) contained within blood products (including packed red blood cells) that attack the immunodeficient infant (host). In addition, any setting in which a T-lymphocyte defect is suspected represents an absolute contraindication to the administration of a live vaccine (eg, oral polio vaccine, bacillus Calmette-Guérin) because this exposure could result in fatal systemic infection.

A significant number of additional disorders that have primary cellular defects are beyond the scope of this discussion; readers are referred to specialized textbooks for additional information. (1) Four of the more commonly discussed T-lymphocyte disorders, however, are reviewed.

DiGeorge syndrome is a complex disorder that involves dysmorphogenesis of the third and fourth pharyngeal pouches. The primary targets of this disruption are the parathyroids (hypocalcemia), the great vessels (eg, interrupted aortic arch), the heart (eg, tetralogy of Fallot, ventricular septal defect, trucus arteriosus), the face (short philtrum, hypertelorism, low-set ears, mandibular hypoplasia, cleft palate), and the thymus (dysplasia). (5) The degree of thymic dysplasia varies widely, creating a significant range in the degree of the immunologic defect, from essentially absent T lymphocytes (signifying thymic aplasia and complete DiGeorge syndrome) to virtually no abnormality. Most patients have a hemizygous deletion of 22q11.2 (rarely hemizygous deletion of 10p13), (5) but normal karyotyping does not rule out this diagnosis. Thymic transplantation appears most successful in patients who have complete DiGeorge syndrome that involves significant T-lymphocyte deficiency. (6)

X-linked hyper-IgM syndrome had been considered a B-lymphocyte disorder until its genetic basis was identified in the early 1990s. At that time, the underlying defect was found to be in the gene encoding a protein, CD40 ligand (CD40L), that is expressed by CD4 T lymphocytes following activation. (2) This ligand is a critical surface molecule that binds to the CD40 surface receptor expressed on B lymphocytes and provides a critical signal for switching from IgM to IgG, IgA, or IgE production. The combination of CD40-CD40L binding and specific cytokine signals dictates the Ig class (IgG, IgA, or IgE) secreted. Consequently, B cells from patients who have this disorder can make IgM but cannot produce IgG, IgA, or IgE. The laboratory findings correspond with normal-to-elevated IgM concentrations associated with very low IgG, IgA, and IgE levels. This situation

explains the clinical history of recurrent sinopulmonary infections with encapsulated bacteria, a phenotype very similar to conventional antibody deficiencies. However, the risk of infection with *P jiroveci* and less frequently with other opportunistic organisms that include CMV, *Cryptococcus,* and *Mycobacterium* also is significant. The explanation for this susceptibility is linked to defective interaction between CD4 T lymphocytes and CD40-expressing macrophages (and perhaps B cells), suggesting that the macrophage may be critical in controlling infections caused by certain opportunistic microbes. Thus, a defect affecting a surface protein expressed normally following activation of CD4 T lymphocytes explains the combination of recurrent infections that typifies antibody deficiencies together with a pattern of recurrent opportunistic infections involving *P jiroveci.* Affected patients have additional associated complications, including neutropenia, severe liver disease, and development of malignancy. The standard therapeutic approach is Ig replacement with intravenous gamma globulin and *P jiroveci* prophylaxis.

Wiskott-Aldrich syndrome (WAS) is an X-linked disorder featuring the triad of eczema, thrombocytopenia, and immunodeficiency. (7) Affected patients typically present early in life, with complications of thrombocytopenia, including excessive bleeding following circumcision, bloody diarrhea, or excessive bruising and petechiae. The low platelet count is associated with the distinctive finding of small platelets, which contrasts with the large platelets in idiopathic thrombocytopenia purpura. The immunologic problems associated with WAS usually begin with recurrent sinopulmonary infections involving encapsulated bacteria. Later, infections with opportunistic organisms, including herpesviruses and *P jiroveci,* may develop. Patients often develop autoimmune disease and have an extremely high rate of lymphoma that frequently develops in extranodal sites. This complication is the most common cause of death.

Immunologically, there is a defect in antibody production to carbohydrate antigens progressing to a more global antibody deficiency as well as T-lymphocyte dysfunction that explains the increased susceptibility to opportunistic infections. The genetic basis of WAS is a defect in the gene encoding the WAS protein (WASp) that is involved in actin polymerization. Interestingly, defects in the gene also can present with X-linked thrombocytopenia, so the clinical phenotype associated with WASp defects varies. (7) Patients usually are treated with intravenous immune globulin (IVIG) to minimize bacterial infections, but the only curative therapy is bone marrow or stem cell transplantation from a matched donor. (4)

Ataxia-telangiectasia (AT) is a complex autosomal recessive disorder associated with neurologic, cutaneous, and endocrine abnormalities in addition to immunologic dysfunction. (2) Affected patients typically present during early childhood with regression in motor milestones. Such regression heralds the beginning of neurologic deterioration that is followed by the development of telangiectasias (3 to 6 y of age) and recurrent sinopulmonary infections involving encapsulated bacteria in most patients. The immunologic findings include depressed IgA levels, variably decreased IgG levels, and T-lymphocyte deficiency. AT is the result of mutations affecting the *ATM* gene, thus affecting a protein that is involved in DNA repair. As a result, patients have an increased risk of malignancy and increased radiation sensitivity. There is no effective therapy for this disorder.

Humoral Immune Deficiencies

As a group, the antibody deficiencies represent more than 50% of the primary immune deficiencies and, therefore, are the most common immune disorders seen. The typical clinical presentation is recurrent sinopulmonary infections with encapsulated bacteria, including *Streptococcus pneumoniae* and *Haemophilus influenzae* (Table 2). (3)(8) The primary antibody deficiencies seen in early childhood include an expanding list of defects that interfere with

Table 2. Clinical Presentation of Primary Immune Deficiencies

Category of Disorder	Typical Infectious History
Cellular immune defect	Recurrent opportunistic infections
Humoral immune defect	Recurrent sinopulmonary infections with encapsulated bacteria
Neutrophil defect	Recurrent bacterial and fungal infections involving the skin and organs
Interferon-gamma/interleukin-12 pathway defect	Recurrent atypical myobacterial (includes bacillus Calmette-Guérin), *Salmonella* infections
Complement defect	
Early components	Recurrent sinopulmonary infections with encapsulated bacteria
Terminal components	Recurrent *Neisseria* infections

B-lymphocyte development. (9) Among these is the best known disorder, X-linked agammaglobulinemia (XLA), also known as Bruton agammaglobulinemia. Recently, a number of autosomal recessive genetic defects have been described that have a clinical phenotype similar to XLA. In all of these disorders, the clinical manifestations typically do not appear until 4 to 6 months of age due to initial protection afforded by maternal IgG transferred to the fetus in utero during the third trimester. All congenital agammaglobulinemia disorders are associated with very low-to-absent B-lymphocyte numbers due to the underlying defect that prevents normal B-cell development. XLA is due to a defect in the *BTK* gene that codes for the protein Bruton tyrosine kinase, a signaling molecule necessary for early B-cell development. In the absence of B cells, serum Ig (IgG, IgA, IgM, IgE) concentrations are very low, and lymphoid tissues (including tonsils) are reduced in size. Patients who have XLA have an additional infectious risk, enteroviral meningoencephalitis, that most commonly is associated with echovirus infection. Previously, with routine administration of live oral polio vaccine, patients who had XLA were at increased risk for developing paralytic polio associated with vaccine strains. With the advent of IVIG therapy, allowing the administration of higher doses of IgG, the frequency of enteroviral meningoencephalitis in XLA appears to have decreased. Arthritis can be seen in patients who have XLA and often is a product of infections with *Ureaplasma* or *Mycoplasma* strains, a complication that may require aggressive antibiotic therapy in addition to Ig replacement.

Immunodeficiency with hyper-IgM associated with primary B-cell defects represents at least three different disorders that have distinctive genetic defects compared with the T-cell disorder X-linked hyper-IgM syndrome that was discussed previously. (10) One of these is similar phenotypically to the X-linked syndrome and is due to an autosomal recessive defect in the B cell (and macrophage) surface receptor CD40. Two additional autosomal recessive disorders also specifically target the proteins critical to the Ig switch process in the B cell. Affected patients present with an infection history similar to the other primary antibody deficiencies and do not have opportunistic infections. A hallmark clinical feature in these patients is marked lymphoid hypertrophy in addition to the antibody deficiency. Therapy in these disorders also involves Ig replacement.

An anaphylactic reaction to intravenous immune globulin in the setting of absolute IgA deficiency is a risk.

The most common clinically significant antibody deficiency disorder is common variable immunodeficiency (CVID). (11) Patients who have CVID may present during childhood, although the disease most often is diagnosed in adulthood. The serum Ig concentrations may not distinguish patients who have CVID from those who have congenital antibody deficiencies, but most CVID patients do have circulating B lymphocytes. The clinical spectrum in CVID encompasses frequent gastrointestinal symptoms, including malabsorption and chronic diarrhea (infectious and noninfectious), as well as radiographic findings of nodular lymphoid hyperplasia. In addition, patients have an increased incidence of autoimmune manifestations, including arthritis, autoimmune hematologic disorders, and achlorhydria associated with pernicious anemia. There also may be a systemic granulomatous disease that has features similar to sarcoidosis. Finally, patients have a documented increased incidence of malignancy, including lymphoid malignancies and gastric carcinoma. CVID is a heterogeneous disorder that recently has been associated with at least four different genetic defects in a minority of affected patients. Treatment consists of replacement therapy with IVIG, although interest is increasing in using subcutaneous administration rather than the intravenous route in certain patients. (12) This change relates to the lower adverse effect profile and the potential for home therapy with subcutaneous administration.

IgA deficiency is the most common primary immunodeficiency, having an incidence as high as 1:600 according to screening studies using blood bank donors. (8) However, only a small proportion of patients who have this defect have recurrent infections; thus, most IgA-deficient individuals do not have a symptomatic primary immunodeficiency. Often, the symptomatic cases also are found to have defects in one or more IgG subclasses. The incidence of systemic autoimmune disease within

this patient group is increased. It has been reported that extended HLA typing has identified a common restricted haplotype in a number of IgA deficiency and CVID patients. It also is common to find IgA deficiency and CVID in the same pedigree.

IgA deficiency is not an indication for replacement Ig therapy unless there is an additional IgG antibody defect because the commercial Ig products contain little or no IgA. There also is no evidence that infused Igs are secreted by mucosal tissues. In addition, an anaphylactic reaction in the setting of absolute IgA deficiency related to the presence of circulating anti-IgA antibodies is a risk. These autoantibodies can react with minute amounts of IgA present in some commercial Ig preparations and in other blood products. The capacity to screen effectively for this potential complication is controversial and emphasizes the need for careful medical observation when initiating immune globulin replacement therapy.

Other forms of primary antibody deficiency include IgG subclass deficiency and selective antibody deficiency. These relatively rare conditions result from a more limited defect in antibody production. The need for replacement Ig therapy for these conditions is controversial and should be decided in consultation with an experienced specialist. The reader is referred to the specialty textbooks for in-depth discussions of these conditions. (1)

Innate Immune Defects

The primary immune deficiencies resulting from defects in the innate immune system are far less common than those affecting adaptive immunity. The following discussion focuses on congenital disorders affecting phagocytic function, the more recently described disorders affecting the interferon-gamma/IL-12 signaling pathway, and complement deficiencies (Table 2).

Chronic granulomatous disease (CGD) is a phagocytic cell disorder associated with a defect in oxidative metabolism. (13) Four underlying genetic defects produce CGD, and all result in the inhibition of a specific enzyme complex (NADPH oxidase) that impairs killing of certain microbes within the cell. The most frequent form of CGD is inherited as an X-linked disorder; the other three forms are autosomal recessive disorders. CGD is diagnosed by demonstrating defective oxidase activity in granulocytes by using either the dihydrorhodamine flow cytometry test or the nitroblue tetrazolium test. The clinical findings include recurrent infections by a selected group of bacteria and fungi (*Staphylococcus aureus*, *Burkholderia cepacia*, *Serratia* sp, *Nocardia* sp, *Aspergillus* sp, *Candida* sp). The most common infections are deep abscesses, pneumonia, lymphadenitis, osteomyelitis, and systemic infection. In addition, affected patients develop granulomas that may result in urinary retention and bowel obstructions, complications that respond well to corticosteroids. The standard therapy for CGD consists of prophylaxis with trimethoprim/sulfamethoxazole and itraconazole. In addition, subcutaneous interferon-gamma therapy has been shown in a placebo-controlled trial to reduce the frequency and severity of infections.

Leukocyte adhesion deficiency type 1 (LAD1) is the best characterized and most frequent of the rare group of disorders affecting cell adhesion. (13) The fundamental defect is decreased movement of leukocytes to inflammatory sites. LAD1 is an autosomal recessive disorder caused by mutations in the gene encoding the adhesion molecule CD18, a protein found in three different dimeric adhesion molecules (the beta-2 integrins). The defect in CD18 either prevents or decreases the expression of the beta-2 integrins, preventing or decreasing the tight adhesion of leukocytes to the vascular endothelium. The diagnosis of LAD1 is established by demonstrating, typically using flow cytometry, the decrease or absence of CD18 expression on leukocytes. The clinical consequence of this disorder varies according to the severity of the defect and includes delayed separation of the umbilical cord, persistent leukocytosis, gingivitis, and periodontitis. Recurrent infections typically affect the skin, lungs, gastrointestinal tract, and perirectal area with *S aureus* and gram-negative bacilli. The infections often are necrotic and characterized by absence of pus. Bone marrow or stem cell transplantation is the only curative therapy, but transplantation generally is reserved for patients who have the most severe form of LAD1 associated with complete absence of CD18 expression. (2)

The most common infections in patients who have chronic granulomatous disease are deep abscesses, pneumonia, lymphadenitis, osteomyelitis, and systemic infection.

Defects in the interferon-gamma/IL-12 pathway represent a group of disorders that only has been appreciated and characterized recently. (14) Patients typically present with chronic atypical mycobacterial infections that are resistant to long-term, multidrug therapy. The clinical phenotype includes patients who have a variety of defined conditions, including defects affecting either chain of the interferon-gamma receptor, the intracellular signaling proteins linked to the receptor, IL-12 production by monocytes and macrophages, and the IL-12 receptor expressed by T lymphocytes. These findings clearly establish that interferon-gamma stimulation of macrophages is critical for destroying this family of microbes. In addition, the production of IL-12 by the macrophage provides critical positive feedback, inducing T lymphocytes to produce more interferon-gamma. However, a number of patients have the same clinical phenotype but have no defined defect, suggesting that additional insights will be gained by further study. An experimental trial of interferon-gamma therapy has demonstrated that this is a useful adjunct to intensive antimicrobial therapy in certain patients who have a functioning interferon-gamma receptor.

Complement deficiencies represent the least common of all primary immune deficiencies. They are inherited as autosomal recessive disorders and can be categorized into two major groups. Deficiencies affecting the early components (C1 through C4) of the classic complement pathway often present with recurrent sinopulmonary infections due to encapsulated bacteria and are associated with an increased incidence of systemic autoimmune disease. Deficiencies affecting the terminal components (C5 through C9) of the complement cascade are associated with recurrent *Neisseria* infections and an increased risk of meningitis. These conditions are screened for by observing the absence of complement activity in the total hemolytic complement assay (CH50). There is no specific therapy for these disorders.

Table 3. Screening Laboratory Tests for Immune Deficiencies

Category of Possible Disorder	Screening Tests
Cellular immune defect	Absolute lymphocyte count HIV test
Humoral immune defect	Quantitative immunoglobulins Natural antibodies (eg, isoagglutinins) HIV test
Neutrophil defect	Absolute neutrophil count × 3 Neutrophil morphology
Complement defect	Total hemolytic complement (CH50)

Therapy of Immune Deficiencies

The therapeutic approach to primary immune deficiencies is targeted to the underlying condition. Patients who have SCID and other serious T-lymphocyte deficiencies typically require bone marrow or stem cell transplantation to reconstitute their immune systems. Transplantation has evolved into a highly successful form of therapy but continues to have clearly defined and serious risks, and as such, remains reserved for life-threatening cellular immune deficiencies. (4) Current options beyond matched sibling donors include matched unrelated donors identified through a national marrow registry, haploidentical parental donors, and cord blood stem cells. These procedures are most successful when performed by centers that have extensive experience in treating immune deficiencies.

Patients who have SCID related to a deficiency in the enzyme adenosine deaminase (ADA) (Table 1) can be treated with bovine ADA modified with polyenthylene glycol (PEG-ADA). As noted previously, patients who have complete DiGeorge syndrome have undergone successful T-lymphocyte reconstitution with thymic transplantation. (5) Treatment of T-lymphocyte disorders by using gene therapy remains an attractive objective but has not yet proven to be a safe therapeutic approach.

Treatment of humoral immune deficiencies relies on antibody replacement with immune serum globulin. (12) The goal is to maintain adequate trough levels of IgG (typically targeted at 500 to 600 mg/dL [5.0 to 6.0 g/L]), which generally translates into administering 400 to 600 mg/kg every 3 to 4 weeks. It also is important to remember that treatment for an antibody deficiency is a lifetime commitment because spontaneous resolution of documented primary humoral immune deficiencies is very rare. Ultimately, each patient needs to be managed individually, and it is best to work with a specialist to develop the optimal treatment. For children, the dosing plan must be adjusted to accommodate growth. The objective is to prevent recurrent infections to protect the lungs from damage leading to bronchiectasis, the most serious long-term consequence of antibody deficiencies. The most common adverse reactions associated with IVIG

therapy include backache, abdominal pain, nausea, chills, and headache. These generally can be controlled by decreasing the infusion rate or by administering premedication. Subcutaneous administration of immune serum globulin appears to decrease the incidence of adverse effects and may allow a patient to tolerate therapy with less discomfort. The most serious adverse effect is the immediate anaphylactic (anaphylactoid) reaction already discussed, making it mandatory that Ig replacement therapy be initiated under careful medical supervision. Additional serious but rare adverse effects include aseptic meningitis, renal failure, and immune hemolysis.

Management approaches for patients who have defects in innate immunity are evolving and include prophylaxis directed at bacterial and fungal infections along with cytokine (eg, interferon-gamma) administration as adjunctive therapy. Because of their complexity, it is critical to address the conditions together with an experienced specialist. (15)

Summary

The primary immune deficiencies have provided valuable insights into many features of the immune response. The critical clinical message is to be vigilant when a patient has infections that are too frequent, affect unusual sites, or are caused by atypical organisms. Such circumstances should prompt consideration of a primary or secondary immunodeficiency. When immunodeficiency is suspected, screening laboratory tests may help clarify the diagnosis (Table 3), but generally it is best to consult with a specialist to evaluate and treat the immunodeficient patient. (15)

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. Which of the following is involved in adaptive immunity?

   A. Antigen-presenting cells.
   B. Complement system.
   C. Granulocyte oxidase activity.
   D. Monocyte adhesion.
   E. Natural killer cells.

2. A 4-month-old boy is admitted to the intensive care unit after a seizure caused by hypocalcemia. He has a history of chronic diarrhea, failure to thrive, and recurrent candidal diaper dermatitis. Physical examination shows low-set ears and a III/VI holosystolic heart murmur at the lower sternal borders. Which of the following is the *best* therapeutic approach for this child's immune dysfunction?

   A. Bone marrow transplantation.
   B. Daily prophylaxis with trimethoprim-sulfamethoxazole.
   C. Interferon-gamma therapy.
   D. Monthly immunoglobulin (Ig) infusions.
   E. Thymic transplantation.

3. A 16-month-old boy is brought to your clinic for an evaluation. His mother reports that he has had more than 10 episodes of otitis media and one hospitalization for pneumonia. Her only other complaint is that he bruises easily. On physical examination, you note multiple bruises and patches of eczema over his arms and legs. Of the following, the *most* likely diagnosis is:

   A. Ataxia-telangectasia.
   B. Chronic granulomatous disease.
   C. Combined variable immunodeficiency.
   D. Wiskott-Aldrich syndrome.
   E. X-linked agammaglobulinemia.

4. For which of the following diseases is Ig replacement *most* appropriate?

   A. Chronic granulomatous disease.
   B. DiGeorge syndrome.
   C. Isolated IgA deficiency.
   D. Severe combined immunodeficiency.
   E. X-linked hyper-IgM syndrome.

5. You are evaluating a 4-month-old boy who has had three prior abscesses caused by *Staphylococcus aureus*. He also has a history of a urinary tract infection caused by *Serratia marcescens*. He currently has an abscess on his buttock, which is draining copious pus. You suspect an immunodeficiency because of his recurrent infections. Which of the following laboratory tests is *most* likely to confirm the diagnosis?

   A. Absolute lymphocyte count.
   B. IgG subclass measurement.
   C. IgM measurement.
   D. Leukocyte CD18 expression on flow cytometry.
   E. Nitroblue tetrazolium test.

Back to Basics: Primary Immune Deficiencies: Windows into the Immune System

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