128 Approach to the Child with Recurrent Infections

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Introduction

Newborns exhibit a physiological immature immune system. As they grow and interact with the environment, they encounter pathogens for the first time that trigger their immune system to mount a response and to develop an immunological memory. It is common for children to experience frequent infections; however, a concern should arise when these infections become severe, refractory to therapy, recurrent, or caused by unusual organisms. In this case, the physician should consider the possibility of an underlying primary immunodeficiency disorder (PID).

Primary immunodeficiencies are inherited disorders of the immune system function that predispose affected individuals to an increased rate and severity of infection, immune dysregulation with autoimmune disease, and malignancy. There are over 100 distinctive genetic disorders that have been identified up to date, but less than 20 probably account for more than 90% of cases.

They are classified according to the principle immunologic mechanisms that are disrupted. These subdivisions include humoral, cellular deficiencies, combined immunodeficiencies that affect both humoral and cellular mechanisms, phagocytic, and compliment system defects.

Individual immunodeficiencies are rare, but altogether they occur in as many as 1 in 2,000 live births. Of all the previously mentioned immune system components, antibody deficiencies account for about half of all primary immunodeficiency disorders (PIDs).

It is important for a physician faced with a child with recurrent infections to first consider other medical conditions, potentially resulting in secondary immunodeficiency and other anatomical or biochemical conditions predisposing to infection. Once those have been excluded, or are not considered sufficient to explain the observed degree of infectious susceptibility, the physician should proceed in a stepwise manner to search for a diagnosis of PID.

Knowing the principal clinical manifestations of each subtype of PID provides a useful way to narrow down the differential diagnoses (◉ *Table 128.1*). In general, the initial evaluation is guided by the clinical presentation. Screening tests are applied followed by advanced tests as indicated. Early diagnosis and therapy are key for improved survival and better quality of life for immunodeficient patients. It is therefore important to have an approach to identify those patients and effectively direct them to the appropriate route.

Classification of Primary Immunodeficiency

The immune system is a large organization of many interdependent cell types that work cooperatively to defend the human body from invading organisms such as bacteria, viruses, parasites, and fungi.

Inherited disorders of the immune system are classified according to the arm of the immune system that they predominantly affect. Immunity is subdivided into two major components, the *innate* "nonspecific" and the *adaptive* "specific." The former is characterized by its faster and immediate maximal generic response with no resulting immunologic memory. It is provided by the surface barrier of the skin and the mucous membranes. In addition, the inflammatory process attracts leukocytes by the release of cytokines that is triggered by injured cells. *The complement system* is the major humoral component of the innate immune response. It is a biochemical cascade that attacks the surfaces of foreign cells and is named so for its ability to "complement" the killing of pathogens by antibodies. Finally, the *Cellular Barriers* "Leukocytes" act like independent, single-celled organisms and are the second arm of the innate system. The innate leukocytes include the phagocytes (macrophages, neutrophils, and dendritic), mast cells, eosinophils, basophils, and natural killer cells. These cells identify and eliminate pathogens, either by attacking larger pathogens through contact or by engulfing and then killing microorganisms. Innate cells are also important mediators in the activation of the adaptive immune system. PIDs due to genetic defects in neutrophil development, toll-like receptor signaling and

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Table 128.1

Primary immunodeficiency disorders: examples of typical clinical presentations (Adapted from Elsevier © with permission. Bonilla FA, Bernstein IL, Khan DA et al. (2005) Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 94(5):S1–S63

Category of immunodeficiency and examples	Characteristic presentation
Antibody deficiencies	
XLA, ARA, CVID, SIGAD, IGGSD, SAD, THI, hypogam	Recurrent sinopulmonary infections with encapsulated bacteria
Cellular deficiencies	
IL-12/IFN-γ axis	Atypical mycobacterial and salmonella infections
AIRE mutations	Mucocutaneous candidiasis and autoimmune endocrinopathy
Combined deficiencies	
SCID	Failure to thrive, diarrhea, opportunistic infection, rash
Wiskott–Aldrich syndrome	Thrombocytopenia with bleeding and bruising, eczema, recurrent infection with encapsulated organisms
Ataxia telangiectasis	Chronic sinopulmonary disease, cerebellar ataxia, oculocutaneous telangiectasis, malignancy
DiGeorge syndrome	Hypocalcemic seizures due to hypoparathyroidism, cardiac disease, abnormal facies, infection
CD40 ligand deficiency	Recurrent, serious pyogenic infections (also opportunistic infections)
Phagocyte defects	
Chronic granulomatous disease	Deep-seated infection, abscess with granuloma formation
Leukocyte adhesion deficiency	Recurrent serious bacterial infections, delayed separation of the umbilical cord, poor wound healing, lack of pus
Hyper-IgE syndrome	Chronic dermatitis, recurrent serious infection of lungs with pneumatoceles, skin infections, bone fragility, failure to shed primary teeth
Complement deficiencies	
Early classical pathway components	Autoimmune disease and bacterial infections
Late components	Neisserial infection
C3 and regulatory components	Recurrent infections with encapsulated bacterial

Abbreviations: *AIRE* autoimmune regular, *ARA* autosomal recessive agammaglobulinemia, *CVID* common variable immunodeficiency, *hypogam* hypogammaglobulinemia, *IFN-γ* interferon-γ, *IGGSD* IgG subclass deficiency, *IL*-12 interleukin 12, *SAD* specific antibody deficiency, *SCID* severe combined immunodeficiency, *SIGAD* selective IgA deficiency, *THI* transient hypergammaglobulinemia of infancy, *XLA* X-linked agammaglobulinemia

complement reveal the protective role played by the innate immune system.

The second major component of the immune system is the adaptive immunity. It exhibits brisker and more specific responses on second and subsequent encounters to foreign antigen. It can also provide long-lasting protection through its capacity of immunologic memory. The responses are carried out by lymphocytes. There are two broad classes of such responses, antibody responses and cell-mediated immune responses, and they are carried out by different classes of lymphocytes, called B-cells and T-cells, respectively. T- and B-lymphocytes are the main self-defense weapons of this system. Unlike innate immune responses, the adaptive responses are highly specific to the particular pathogen that induced them.

Humoral or antibody deficiency is the most common type of PID and accounts for approximately 60% of all primary immunodeficiency. Five to ten percent of affected individuals have abnormalities of cell-mediated immunity (T-Cells), while a further 20–25% have combined defects of both humoral and cellular function. Disorders of phagocyte account for approximately 10–15% of all PIDs, while Complement deficiency is the rarest, comprising less than 2% of all PIDs.

Another classification for PID is presented by the International Union of Immunological Societies Expert

Committee on Primary Immunodeficiencies, published in 2009 by Notarangelo et al. It includes a detailed list of all the identified PIDs and their genetic basis. It serves as a useful reference for the immunologist. The classification adopted in this chapter is meant to facilitate the approach for the general pediatrician.

Clinical Features of Primary Immunodeficiency

History and Examination

In evaluating a child with recurrent infection, it is critical as much as possible to document carefully the foci of infections, the organisms, and the response to treatment. This is necessary to distinguish infectious disease from others noninfectious conditions such as allergic diseases. Any other conditions that may increase the patient's susceptibility to infection, including congenital defects, allergy, and metabolic disorders, should be considered when appropriate.

Careful evaluation of the family history of a similar condition can be helpful in determining the likelihood of PID. Consanguinity is suggestive of autosomal recessive diseases. Several PIDs are X-linked; a history of male infection or unexplained infective deaths in infancy or early childhood on the maternal side of the family is significant. Death from infection in infancy is highly suggestive of severe combined immunodeficiency (SCID) and should be taken seriously even in families where there is no consanguinity. The age at onset of infections of unusual frequency or severity may yield important insights into possible underlying immune deficiencies. In addition, pregnancy history, previous blood transfusions and vaccination history are also important. The latter is important from the diagnostic perspective of which antigens the patient's immune system has been exposed to, and secondarily important to document live vaccines that may become pathogenic in the immunocompromised host.

Growth parameters and the general state of health of the child should be evaluated as children with cell-mediated immunodeficiency tend to appear chronically unwell and have features of malnutrition. Ear examination with attention to the tympanic membranes should be carefully inspected for evidence of acute inflammation or scarring. Examination of the lymphatic system for the presence/absence and size of the lymph nodes, spleen and tonsils is important. The skin should also be examined for vascular abnormalities as well as rashes, which may or may not be infectious, due to malnutrition or graft-versus-host disease.

Humoral Immunodeficiency

Antibody deficiency is the most common form of PID. Among its subtypes, selective IgA deficiency (SIGAD) is very common, affecting approximately 1 in 500. Most patients with SIGAD are asymptomatic.

The principle clinical manifestations of humoral immunodeficiency are recurrent bacterial infections of the respiratory tract. These infections tend to be recurrent, pyogenic, and present after 6 months of age. On average, the majority of maternally acquired Immunoglobulin G (IgG) has disappeared by 6 months of age. IgG production begins shortly after birth and reaches adult levels by the fifth year of life. The common organisms infecting these children are polysaccharide-encapsulated organisms, such as *Haemophilus influenzae* and *Streptococcus pneumonia*. In general, patients with disorders of the humoral immune system tend to grow well; failure to thrive is not a feature of these diseases. An overview of selected humoral immunodeficiencies is presented in (*Table 128.2*).

Cellular Immunodeficiency

Cellular immunodeficiency accounts for 5–10% of PIDs. When T-cell function is impaired, antibody formation is also affected. Children suffering from defects of the cell-mediated immune system are predisposed to developing viral, bacterial, fungal, and parasitic infections. Infective organisms are mostly intracellular, such as *Mycobacteria* and *Salmonella*. They usually present between 3 and 6 months of age. A major feature of this group is failure to thrive associated with persistent diarrhea and malabsorption. Other features include diseases due to BCG vaccine, disseminated TB, and severe herpes infections. These children may also present with skin rashes and chronic, persistent candidal infection of the nail, skin, and mucous membranes, as seen in Chronic Mucocutaneous Candidiasis (CMCC). A list of cellular immunodeficiencies is presented in *Table 128.3*.

Combined Immunodeficiency

It comprises 20–25% of PIDs. This is a heterogeneous group, characterized by the presence of T- and B-cell dysfunction, often associated with decreased numbers of T lymphocytes and immunoglobulin levels. The "combined" nature of these immune deficiencies results from

Table 128.2
Characteristic features of selected humoral immunodeficiency

Humoral deficiency	Age of onset	Infections	Characteristic features
XLA	>6 months	Otitis media, sinusitis, and pneumonia	Absence of lymph nodes and tonsils Agammaglobulinemia and very low/absent B-cell count
		CNS infection with ECHO-virus	Paralytic polio with live vaccine Absence of BTK protein
CVID	Recurrent infection in children >2 years	Otitis media, sinusitis, pneumonia, bronchitis, and enteric infection	GI tract (20–25%): lymphonodular hyperplasia, IBD, and malabsorption Autoimmune diseases (20%): AIHA, ITP, seronegative arthritis, and vasculitidis Lymphoproliferative disorders: splenomegaly and peripheral lymphadenopathy Malignancies: NHL and gastric cancer
SIGAD	>4 years	Viral, otitis media, sinopulmonary infection and GI infection	Serum IgA level <0.07 g/L with normal IgG and IgM levels GI: Crohn's, UC, and celiac disease Atopy: allergies and asthma Autoimmune: lupus-like illness and arthritis Malignancies: GI and lymphoid malignancies later in life

Abbreviations: *XLA* X-linked agammaglobulinemia, *ECHO* enterocytopathic human orphan, *BTK* bruton tyrosine kinase, *CVID* common variable immunodeficiency, *GI* gastrointestinal, *IBD* inflammatory bowel disease, *AIHA* autoimmune hemolytic anemia, *ITP* idiopathic thrombocytopenic purpura, *NHL* Non-Hodgkin lymphoma, *SIGAD* selective IgA deficiency, *UC* ulcerative colitis

Table 128.3
Diseases of cellular immunodeficiencies

Defect of the IL-12/IFN-γ axis
IFN-γ receptor α chain
IFN-γ receptor β chain
IL-12 p40
IL-12 receptor β1 chain
Signal transducer and activator of transcription 1
CMCC
CD16 deficiency
Idiopathic CD4+ T Lymphocytopenia
NK cell deficiency due to unknown defect
Cellular immunodeficiency, unspecified

Abbreviations: *IL* interleukins, *INF* interferon, *CMCC* chronic mucocutaneous candidiasis, *NK* natural killer, *CD* cluster differentiation

the inability of T-cells to provide immunological "help" to the antibody producing B-cells or a direct impact on B-cell development, resulting in the combined clinical features of both T-cell and B-cell dysfunction. Patients with Combined Immunodeficiency (CID) present within the first few months of life with recurrent, persistent, or severe bacterial, viral, or fungal infections. Failure to thrive, diarrhea, and rashes are frequently seen features. Common

pathogens are most often seen, in addition to nonpathogenic organisms (opportunistic infections). Infections usually do not remain localized; disseminated disease is frequent in those patients.

It is critical to deal with even a suspicion of severe combined immunodeficiency (SCID) as a medical emergency because of the rapidity with which these infants succumb to life-threatening infections, and early management is life saving.

Newborn screening provides a promising method for identifying these children as early as possible. The feasibility of newborn screening for SCID has been demonstrated by Baker et al. in their experience in Wisconsin. *Table 128.4* presents features of some CIDs.

Phagocytic Cell Disorders

This entity constitutes approximately 10–15% of all PIDs. It includes defects in neutrophil and monocyte maturation and differentiation, chemotaxis, phagocytosis, and intracellular killing. Phagocytic cell defects may present with deep-seated abscesses due to infections with *Staphylococcus aureus* or gram-negative organisms such as *Klebsiella pneumonia*, *Serratia*, and *Proteus* species. These individuals are also predisposed to fungal infections, especially *Aspergillus fumigatus* pneumonia. Infections of the skin and viscera can also be manifestations of a phagocytic cell disorder. *Table 128.5* displays some of the characteristic features of selected phagocytic cell disorders.

Complement Disorders

Complement disorders account for a small percentage of PIDs (less than 2%) and may coexist with autoimmune diseases, such as systemic lupus erythematosus (SLE). The clinical features of these disorders vary depending on which complement proteins are affected. The complement system consists of 30 proteins that work synergistically in defending against invading organisms. Of these complement proteins, the commonest is deficiency of C1 inhibitor causing hereditary angioedema, but not infection. A deficiency of C2 is associated with SLE-like syndrome, vasculitis, dermatomyositis, and predispose individuals to recurrent bacterial infections. C3 is the most abundant protein of the complement system. Its products play

Table 128.4
Characteristic features of selected combined immunodeficiency

CID	Age of onset	Infections	Characteristic features
SCID	3–9 months	Pneumonia, septicemia, gastrointestinal	Absence of lymphoid tissue and thymus Failure to thrive and diarrhea Skin disorders and GVHD (due to maternal T-Cells) Disseminated BCG infection. Chronic hepatitis and neutropenia
WAS	<6 months	Otitis media, pneumonia, skin (herpes)	Triad: eczema, thrombocytopenia, and immune deficiency Recurrent and severe infections Autoimmune disease: colitis, vasculitis, and glomerulonephritis EBV-related B-cell lymphoma 10–15%. Average age 10 years
DiGeorge syndrome	Birth	Pneumonia and gastrointestinal	Cardiac abnormality, abnormal facies, thymic aplasia, cleft palate, and primary hypoparathyroidism 80–90% associated with 22q11.2 deletion
CD40 and CD40-L Deficiency (previously known HIgM)	Infancy	Pneumonia, otitis media, gastrointestinal, soft tissue	Gastrointestinal complaints with malabsorption associated with cryptosporidium infection and cholangitis Lymphoid hyperplasia Chronic anemia and neutropenia

Abbreviations: *SCID* severe combined immunodeficiency, *GVHD* graft-versus-host disease, *BCG* Bacillus Calmette–Guérin, *WAS* Wiskott–Aldrich syndrome, *EBV* Epstein–Barr virus, *HIgM* hyper-IgM

Table 128.5
Characteristic features of selected phagocyte disorders

Phagocyte disorders	Age of onset	Infections	Characteristic features
CGD	Infancy	Skin, pneumonia, perianal abscess, osteomyelitis, multiple ulcers infected with *Serratia* species in young adults	Granulomatous abscesses: lungs, lymph nodes, skin, liver, bones, and brain Hepatosplenomegaly, dermatitis, pneumonitis, suppurative lymphadenitis Obstructive granulomas in the GU and GI systems
HIES (Job syndrome)	Early childhood	Pneumonia, skin, otitis media, mastoiditis	Markedly elevated serum IgE and eosinophilia Severe papular and pruritic rash, becomes lichenified. Coarse facies Hyperextensible joints, polyarticular arthritis, reduced bone density, and recurrent fractures Recurrent pneumonia with pneumatocele formation Cold abscesses
LAD	Early in life	Cellulitis, abscesses, bacterial and fungal respiratory tract infection	Significant neutrophilia, recurrent infections, along with absence of pus formation LAD type I: poor wound healing, delayed separation of the umbilical cord LAD type II: pulmonary infections and chronic severe periodontitis. Characteristic facies, growth and developmental delay, and mental retardation
CHS	–	Pyogenic, affect mainly skin and respiratory tract	Partial oculocutaneous albinism and pleomorphic neurologic manifestations; cognitive impairment, photophobia, nystagmus, and central and peripheral neuropathies. Giant Azurophilic granules are characteristic Lymphoproliferative disorder known as the accelerated phase causing lymphadenopathy, hepatosplenomegaly, and bone marrow failure

Abbreviations: *CGD* chronic granulomatous disease, *GU* genitourinary, *HIES* hyper-IgE syndrome, *LAD* leukocyte adhesion deficiency, *CHS* Chediak–Higashi syndrome

an important role in chemotaxis, opsonization, and regulation of the complement cascade. Deficiency of C3 predisposes affected individuals to severe pyogenic infections. Disorders of the terminal complement cascade (C6 through C9) are associated with predisposition to Neisserial meningitis.

Laboratory Investigations

Laboratory investigations are heavily relied on to reach a specific diagnosis of PID. Before proceeding with immunological tests, basic tests should be applied to detect any electrolyte or metabolic imbalances the child may have due to intractable diarrhea, or malabsorption. A complete blood count with a differential, as well as a coagulation profile is essential. Efforts must also be made to identify any infection the patient may have.

The history and physical examination findings serve as a guide to which investigations to start with. The general rule is that screening tests are applied first followed by advanced tests. *Table 128.6* serves as an outline for this approach.

Consultation with physicians experienced in the diagnosis of PIDs is essential wherever uncertainty regarding evaluation occurs, to aid in reaching an accurate diagnosis as quickly as possible, and enable directed therapy. Wherever possible, diagnosis at the molecular level is desirable to establish a clear diagnosis and permit accurate genetic counseling. It also assists in better defining of genotype-phenotype association and to identify candidates for gene-specific therapies.

Table 128.6

Laboratory tests for evaluation of immunodeficiency (Adapted with permission from Elsevier ©. Bonilla FA, Bernstein IL, Khan DA et al. (2005) Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 94(5):S1–S63)

B-cell function
Screening tests Serum immunoglobulin levels Serum specific antibody titers Advanced tests Antibody response to booster immunization Flow cytometry to enumerate B-cells In vitro immunoglobulin production in response to mitogen In vitro immunoglobulin production in response to anti-CD40 and cytokines Antibody response to immunization with ϕ X174
Cellular immune function
Screening tests Flow cytometry to enumerate T-cells and natural killer cells Cutaneous delayed hypersensitivity Advanced tests Enzyme assays (ADA, PNP) FISH for 22q11 and 10p11 deletion In vitro proliferative response to mitogens and antigens Natural killer-cell cytotoxicity Cytokine production in response to mitogen or antigen stimulation Expression of surface markers after mitogen stimulation
Phagocytic cell function
Screening tests Blood cell count with differential Neutrophil staining, morphology Advanced tests Oxidase function (dihydrorhodamine, nitroblue tetrazolium, chemiluminescence) Flow cytometry for adhesion molecules Chemotaxis Phagocytosis Enzyme assays (myeloperoxidase, G6PDH) WBC turnover Bacterial or fungal killing Bone marrow biopsy
Complement function
Screening tests CH_{50} (total hemolytic complement activity) AH_{50} (alternative pathway hemolytic activity) Advanced tests Level or function of individual complement components Chemotactic activity of complement split products
General
Advanced tests Molecular methods including southern, northern, and western blots, PCR/SSCP, DNA fingerprinting, and nucleotide sequencing

Abbreviations: *ADA* adenosine deaminase, *FISH* fluorescent in situ hybridization, *G6PDH* glucose-6-phosphate dehydrogenase, *PCR* polymerase chain reaction, *PNP* purine nucleoside phosphorylase, *SSCP* single-strand conformation polymorphism, *WBC* white blood cell

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