



Immunodeficiency



A. Introduction

Recurrent infections of the respiratory tract (e.g., lungs, sinuses, ears, nose and throat) are common clinical presentations of patients that are often referred to an allergist/immunologist for evaluation. Many patients who have received multiple courses of antibiotics for frequent sinus infections, colds, chest infections, ear infections and sore throats are evaluated yearly for defects of the immune system. In most cases, these infections turn out to be due to respiratory allergy or simply frequent infections. However, in a few cases, a specific immunodeficiency will be diagnosed and the resulting treatment may be lifesaving.

Immunologically deficient individuals can be categorized into two major groups. One group suffers from a specific defect that originates in the immune system, defined as a primary immunodeficiency (e.g., x-linked agammaglobulinemia). In contrast, immunodeficiency that is a consequence of a disease process not directly related to the immune system (e.g., kidney disease associated with nephrotic syndrome and loss of immunoglobulin) is defined as a secondary immunodeficiency.

B. Primary immunodeficiencies

Primary immunodeficiency may result from defects in the production of circulating antibodies (humoral immunological defense system) or from a cellular defect in the immune system, which would include defects in sensitized T-cells and/or macrophages. Combined immunodeficiency indicates the existence of defects in both the humoral and cellular arms of the immune system.

Once considered rare diseases involving severely ill individuals, primary immunodeficiencies now appear to be more common than previously thought. In fact, the estimated frequency of the most common immunodeficiency—selective IgA immunodeficiency (SIgAID)—is 1 of 500 people (See Table 1)

Initially, an immunodeficiency disorder associated with mild clinical symptoms might go undiagnosed (See Table 2 for 10 warning signs of immunodeficiency). However, over time, immunodeficiency can lead to recurrent and/or severe infections that respond poorly to conventional

therapy. Therefore, early diagnosis of immunodeficiency can limit severe damage due to poorly controlled infection and might be life-saving. Genetic counseling of family members may be invaluable in decision-making once the potential risks are understood.

C. Immune defects

The immune system defends the body from infection through a series of complex interactions involving **antibodies, plasma cells, sensitized T- and B-cells, circulating complement proteins, soluble mediators (cytokines), neutrophils, macrophages and dozens of other mediators and cellular components involved in immunoregulation.** Deficiency or defects in any part of an immune response can impair the body's ability to protect itself against invading viruses, bacteria, fungi, or parasites resulting in an increased chance of severe infection (See Figure 1).

Primary immunodeficiencies (Table 1) result from genetic, developmental, or acquired defects, whereas secondary immunodeficiencies (Table 3) are due to other medical diseases that damage the immune system. For example, chronic disease of the gastrointestinal tract can lead to a protein losing enteropathy, resulting in decreased circulating antibodies. Another example would be the AIDS virus, which damages cellular components of the immune system, leading to recurrent infections.

The immune system can be defined (a) in terms of its components (e.g., antibodies, T-cells, etc.) or (b) by its type of response to foreign antigens, referred to as either **innate** or **adaptive**.

The **innate immune response** is based on the presence of preformed antibodies and sensitized cells that can immediately attack foreign antigens or invading organisms early in the process of infection. In contrast, the **adaptive immune response** develops slowly, as antigen exposure induces immunological changes that take days to weeks to achieve optimum results. Fortunately, the innate response fights infection early, giving the adaptive system time to develop a stronger response.

The **adaptive immune response** is much more specific and potent than the innate immune response, thus resulting in far more

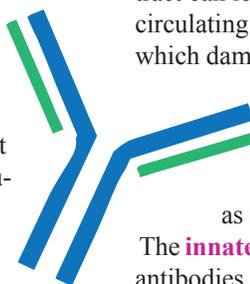


Table 1:

Incidence of primary immunodeficiency states

Type	Incidence
Selective IgA immunodeficiency	1:300-700
Selective IgM immunodeficiency	1:600
Common variable immunodeficiency	1:75,000
Severe combined immunodeficiency	1:100,000
X-linked agammaglobulinemia	1:100,000
Chronic granulomatous disease	1:500,000

Table 2: Primary Immunodeficiency 10 Warning Signs

1. Eight or more new ear infections within one year
2. Two or more serious sinus infections within one year
3. Two or more months on antibiotics with little effect
4. Two or more pneumonias within one year
5. Failure of an infant to gain weight or grow normally
6. Recurrent, deep skin or organ abscesses
7. Persistent thrush in mouth or elsewhere on skin after age 1
8. Need for intravenous antibiotics to clear infections
9. Two or more deep-seated infections
10. A family history of primary immunodeficiency

specific and potent antibodies and sensitized cells that can more effectively attack antigens present in invading viruses and bacteria. Following exposure to an antigen, the immune system adapts its response by developing increasingly specific and effective antibodies and sensitized cells. In time, clones of these cells begin to develop, thus enhancing the immune response.

The secondary adaptive immune response will occur more quickly if there has been prior exposure and the immune system is primed to produce the necessary cells and specific antibodies. This quickened response is known as the amnestic response, indicating the presence of immunologic memory and its role in rapidly activating the adaptive response.

This specific—or adaptive—immune system is mediated by T- and B-lymphocytes and their cytokines, adaptive antibodies (IgG), and specifically sensitized cells.

At this time, more than 120 genetic defects in the immune system have been identified and there are still more to be defined.

Clinically, immunodeficiency diseases are broadly characterized by defects of B-lymphocytes (50% of cases), defects of combined T- and B- lymphocytes (20-30% of cases), unique T-cell defects, phagocyte defects (18% of cases) and complement deficiencies (2% of cases). The type and site of infection often indicates the probable type of immunodeficiency (Tables 4 and 5). For example, B-cell or humoral (antibody) defects mostly result in susceptibility to bacteria (sino-pulmonary infections, enteroviruses and parasites). In contrast, T-cell-mediated defects often result in increased susceptibility to opportunistic organisms (e.g., *P. carinii*), viruses and fungi. Additionally, phagocytic defects usually result in pyogenic (bacterial) infections involving the sinuses, lungs, skin and lymph nodes. Complement deficiencies are associated with pyogenic infections, sepsis and recurrent meningitis, caused by encapsulated bacteria.

D. Recognizing immunodeficiency

A detailed history, physical examination and laboratory studies will help differentiate frequent infections due to common risk

factors (e.g., daycare attendance; frequent exposure to school-age children; exposure to cold temperatures; allergies or passive smoke exposure) from a primary immunodeficiency due to a specific immune defect.

Early in the course of immunodeficiency, the pattern of symptoms of recurrent infection may be mild or intermittent, often attributed to other causes such as allergies. However, persistence of these symptoms should raise suspicion of the presence of immunodeficiency (See Table 2).

E. Immunodeficiency and its co-morbidities

1. Gastrointestinal symptoms. Although many patients with primary immune deficiencies present with recurrent and chronic respiratory infections, gastrointestinal disorders are also commonly diagnosed in immunodeficient patients. The combination of recurrent respiratory infections along with gastrointestinal symptoms may also prompt immunologic screening. It should be noted that infection with *Giardia lamblia* and bacterial overgrowth

When should immunodeficiency be considered?

Frequent upper respiratory symptoms may not represent an immunodeficiency, but rather, the occurrence of recurrent individual viral upper respiratory infections. On the other hand, prolonged symptoms from repeated infections (such as sinusitis) might be due to inadequate treatment with multiple short courses of oral antibiotics. Other patients who complain of constant colds may actually suffer from allergic rhinitis. The appearance of densities or infiltrates on a chest x-ray may represent atelectasis due to asthma rather than true infiltrates resulting from pneumonia. Unlike atelectasis, infiltrates due to infection are usually associated with fever, changes in white blood cell counts, positive sputum (Gram stain or culture), or serological evidence that supports the diagnosis of bacterial pneumonia.

Patients with unusually severe infections requiring parenteral antibiotics, prolonged or multiple courses of antibiotics for a single infection, or surgical intervention such as incision and drainage of abscesses or removal of seriously infected tissue should also undergo a screening evaluation in order to exclude immunodeficiency.

Lastly, patients with unusual or opportunistic infections (or those with unusually severe symptoms or excessively high or prolonged fever to seemingly common organisms) should also be evaluated for immunodeficiency.

in the small intestine are frequently observed in patients with antibody deficiencies.

2. Autoimmune disease may be limited to a single tissue or organ, or may be more global in nature (e.g., autoimmune hemolytic anemia and systemic lupus erythematosus or rheumatoid arthritis). Gastrointestinal symptoms in immunodeficient patients may be secondary to autoimmune disease (e.g., inflammatory bowel disease, lymphoid hyperplasia, Celiac disease, atrophic gastritis with pernicious anemia) or infections (*Giardia lamblia*, rotavirus, cryptosporidiosis).

3. Proliferative disorders and/or solid malignancies like gastric carcinoma may also be a feature of some primary immunodeficiencies, especially the B-cell disorders (common variable hypogammaglobulinemia, CVH, SIgAID).

4. Family history of immunodeficiency, autoimmune disease and/or infantile death may help predict immunodeficiency. Primary immunodeficiencies—especially B-cell defects are familial and often arise in the setting where other family members have autoimmune diseases, especially rheumatoid arthritis, SLE or autoimmune

hematologic disorders.

5. Adverse reactions to vaccines or transfusions may also be indicative of an underlying immunodeficiency. For example, anaphylactic reactions to blood or blood products can occur in patients with selective IgA immunodeficiency due to IgE antibodies directed against IgA present on unwashed, transfused red cells. Patients with B-cell deficiencies or severe combined immunodeficiencies may experience infections or adverse reactions to live attenuated vaccines—including live oral polio vaccine or even exposure to individuals vaccinated with live viruses, which could lead to the development of paralytic polio.

F. Patient evaluation

1. The patient history

A patient's history of past infections helps determine the appropriate laboratory tests required to identify and explain the patient's symptoms. The pattern of infection might be helpful in identifying the probable immune defect. For example, infections with encapsulated extracellular bacterial pathogens—particularly of the respiratory tract—are suggestive of defects in antibody production.

Non-invasive mucosal infections may particularly suggest isolated IgA deficiency. While infections with opportunistic pathogens, (protozoa and fungi) and severe or recurrent infections due to chicken pox or herpes may suggest defects in cell-mediated immunity. Deficiencies in the complement system may lead to failure to clear bacteria promptly from the blood stream, resulting in bacteremia/sepsis, or hematogenously disseminated infections such as osteomyelitis (See Table 4).

The seriousness of the immunodeficiency can be supported by the frequency of absence from school or work, hospitalizations, emergency room visits and disability resulting from infection-related

illness. The family history should include questions about infection among siblings and preceding generations. In particular, families with a history of premature deaths of male infants should raise suspicion of x-linked immune deficiencies.

2. The physical exam

The physical exam in patients with primary immunodeficiencies is often normal, but cases of identifiable physical abnormalities may offer clues to defects in host defenses. The initial exam should include assessment of general appearance. Children with underlying immunodeficiencies may fail to thrive in early childhood, or older children may look chronically ill and/or appear underweight or have dysmorphic features. Repeated pyogenic infections may lead to permanent scars of the eardrums or the skin. Digital clubbing may imply serious pulmonary damage from repeated infections. The presence or absence of tonsils, lymph nodes or splenic tissue may be helpful in identifying B-cell disorders.

Conversely, the presence of palpable lymph nodes and easily visible tonsils essentially excludes x-linked agammaglobulinemia.

In contrast, the presence of cervical or peripheral adenopathy, splenomegaly, or hepatomegaly may suggest common variable immunodeficiency (CVID), human immunodeficiency virus (HIV), chronic granulomatous disease (CGD), or other abnormalities. Abnormalities involving the skin may point to an immunodeficiency. For example, certain skin rashes like eczema, thrush, vitiligo, persistent warts, and molluscum contagiosum may also be indicative of an underlying primary immunodeficiency.

3. Common sense laboratory testing for immunodeficiency (See Table 6).

■ Generally, patients with T-cell disorders have opportunistic infections, whereas patients with antibody, phagocytic cell or complement deficiencies usually have recurrent infections due to encapsulated bacteria.

■ Screening for primary immunodeficiency is not currently performed at birth. Fortunately, many immunologic defects can be easily as

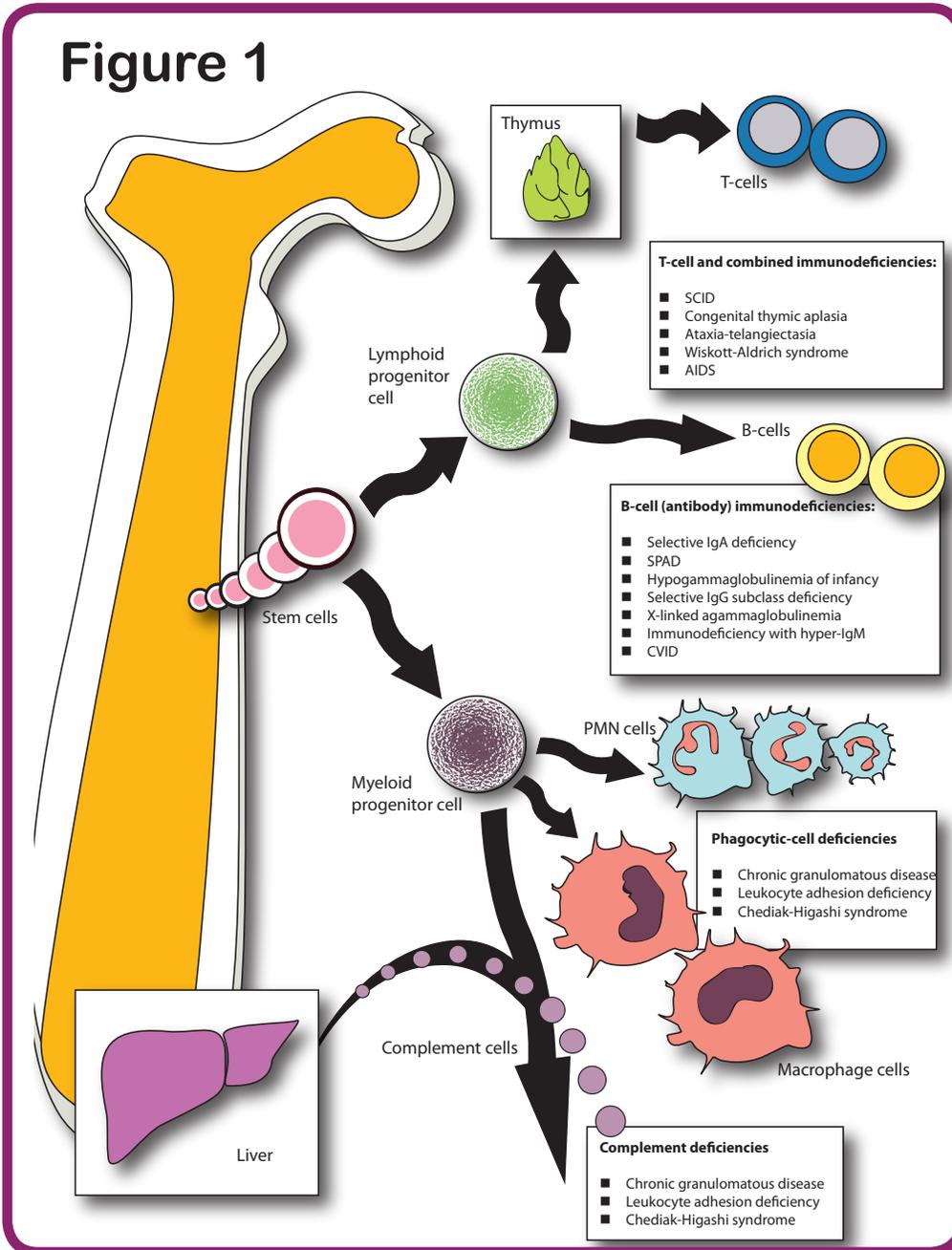


Table 3

Common causes of secondary immunodeficiency

- Malnutrition
- HIV
- Malignancy
- Immunosuppressive drugs
- Immunomodulatory agents
 - Rituximab (affecting B-cells)
 - Infliximab, etanercept, adalimumab, anakinra (affecting cellular immunity)
- Drug-induced hypogammaglobulinemia:
 - Certain antiepileptics (e.g., diphenhydantoin, carbamazepine, valproate)
- Protein loss (especially if presenting with low IgG but normal IgA and IgM):
 - Nephrotic syndrome, protein-losing enteropathy, severe burns
- Metabolic disease
 - Diabetes, severe liver disease, uremia

sessed with a simple blood count. For example, a complete blood cell count with differential with a normal absolute neutrophil count will rule out congenital or acquired neutropenia.

■ If the patient's absolute lymphocyte count is normal, a severe T-cell defect is unlikely.

■ General blood chemistry panels often reveal low total protein but normal albumin in agammaglobulinemia due to very low gammaglobulin levels. A low uric acid level may be indicative of Adenosine deaminase (ADA) deficiency or purine nucleoside phosphorylase deficiency, while a low serum calcium level may suggest DiGeorge Syndrome due to associated hypoparathyroidism.

■ Normal quantitative immunoglobulins will rule out most B-cell immunoglobulin deficiencies.

■ It is also possible that clinically significant antibody deficiency may be present even with normal levels of all classes of immunoglobulins. Therefore, specific antibody production should be assessed in patients with a history of recurrent bacterial infections, particularly of the respiratory tract.

■ Antibody response to vaccination is required for functional antibody deficiencies (e.g., selective anti-polysaccharide antibody deficiency). Measurements of antibodies against tetanus and diphtheria toxins and several pneumococcal polysaccharides as well as H. influenzae type-B polysaccharide are quite helpful in this area. Lack of a significant rise in specific antibody titers after immunization and/or failure to achieve protective levels indicates that the patient is unable to mount specific antibody responses and therefore has an immunodeficiency.

■ A total hemolytic complement assay (the CH-50, a functional assay) is the most cost-effective test for assessing complement deficiency.

■ A cost-efficient test for T-cell function is the anergy panel (skin testing) for assessing T-cell function. An anergy panel consists of intradermal skin testing to common recall antigens (candida, trichophyton and tetanus). If the test is positive (significant induration and erythema), then virtually all primary T-cell defects are excluded, thus limiting the need for more expensive in-vitro tests such as lymphocyte phenotyping (T-cell enumeration by flow cytometry) and lymphocyte proliferation responses to mitogen and/or antigen challenge.

■ If a phagocytic defect is suspected, especially in an individual with staphylococcal gram-positive infections, screening with a neu-

trophil oxidative burst by flow cytometry should be performed. Detailed laboratory analysis in patients suspected of phagocyte disorders should include assessment of neutrophil chemotaxis and the oxidative respiratory burst that accompanies phagocytosis.

■ Genetic testing may ultimately be required for definitive diagnosis in some cases and for genetic family counseling.

Specific examples of immunodeficiency disorders and B-cell disorders

A. X-linked immunodeficiency

(also called XLA, Bruton's agammaglobulinemia, sex-linked agammaglobulinemia) XLA was the first defined primary immunodeficiency. A rare x-linked genetic disorder, XLA is more common in males. XLA patients do not generate mature B-cells resulting in antibody immunodeficiency. Patients with untreated XLA are prone to develop serious and even fatal infections. A genetic mutation has occurred at the Bruton's tyrosine kinase gene which leads to a severe block in B-cell development resulting in a marked reduction of immunoglobulin (antibody) production in the serum. Patients typically present in early childhood with recurrent bacterial infections, particularly with extracellular, encapsulated bacteria such as pneumococcus. XLA is treated by infusion of human IgG antibody. Treatment with pooled gamma globulin can usually reduce the severity and number of infections through passive immunity offered by IVIG administered every 3 or 4 weeks.

b. Common variable hypogammaglobulinemia

CVH is characterized immunologically by IgG, IgA and IgM levels less than 2 standard deviations below age-adjusted means. In adults, IgG levels must be less than 400 mg/dl (normal range 600-1600 mg/dl). T- and B-cell numbers in the peripheral blood are normal and T cell function is normal. There is a reduced antibody response to antigen challenge.

Clinically, the disease begins between ages 15 and 40 and equally affects males and females. Recurrent sino-pulmonary infections, bacterial conjunctivitis, bronchiectasis, pulmonary granulomas and malabsorption (secondary to G.lambdia) are the common presentations of this immunodeficiency. Leukemia, lymphoma, gastric cancer, autoimmune disease (rheumatoid arthritis, SLE, vitiligo, hemolytic or pernicious anemia), and upper and lower respiratory allergies are often associated with this defect. Treatment includes replacement gamma globulin therapy with rotating antibiotics in those with relapsing respiratory infections.

c. Selective IgA Immunodeficiencies (SIgAID)

This is the most common immunodeficiency. SIgAID refers to the ab-

Table 4: Sites of Infections

Otitis media, recurrent mastoiditis	B-cell deficiency
Sinusitis	B-cell deficiency
Pneumonia bronchiectasis	B-cell deficiency
Meningitis	B-cell deficiency
Sepsis	B-cell deficiency
	Neutrophil/phagocyte defects
Skin infections	B-cell deficiency
	Neutrophil/phagocyte defects
Gingivitis/stomatitis	Neutrophil/phagocyte defects
Organ abscesses	Neutrophil/phagocyte defects
Lymphadenitis	Neutrophil/phagocyte defects

Table 4: Microbiology of Infections

sence of IgA antibodies in serum, typically less than 5 mg/dl (normal range 80-500 mg/dl) with normal IgG and IgM levels. Over time, SIgAID may evolve into a pan-hypogammaglobulinemic state consistent with common variable hypogammaglobulinemia. The T- and B-cell numbers in the peripheral blood are normal and T-cell function is usually normal.

Clinically, many individuals are asymptomatic, but some have symptoms similar to common variable hypogammaglobulinemia, allergies, autoimmune disease (rheumatoid arthritis, SLE/Celiac disease), recurrent sino-pulmonary disease and bronchiectasis. Antibodies (IgE and IgG) against IgA may develop in some patients with SIgAID which in turn leads to an increased incidence of anaphylactic reactions to the IgA present in transfused blood or blood products. Anaphylaxis from blood products can be diminished by screening IgA-deficient patients for the presence of anti-IgA antibodies. Blood transfusion from IgA-deficient donors will be tolerated in IgA-deficient patients with circulating anti-IgA antibodies. Patients with SIgAID do not require gammaglobulin replacement, since they don't lack IgG and immunoglobulin infusions don't contain replacement IgA.

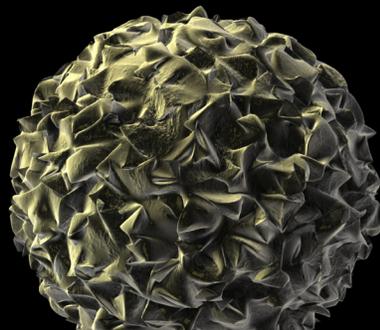
d. Selective IgM immunodeficiencies (SIgMID)

SIgM immunodeficiency appears to be increasingly recognized and its prevalence appears to be increasing to the point that it may be among the most common of immunodeficiencies. SIgMID patients typically have IgM levels less than two standard deviations below age-adjusted norms (usually less than 50 mg/dl in adults with a normal range of 52-71 mg/dl). Serum IgA and IgG levels are normal. T- and B-cell numbers are normal and T-cell function is normal.

In a retrospective analysis and literature review (Dunsky, E.; Goldstein, M.; *Annals of Allergy, Asthma and Immunology*. 2006;97:717-730.) from our practice, the clinical features of SIgMID in adults and children were characterized. Clinical features are similar to SIgAID with a range of presentations from an asymptomatic state to recurrent sino-pulmonary infections, bronchiectasis, allergies, asthma, autoimmune disease and surprisingly idiopathic anaphylaxis, chronic urticaria and angioedema. These latter three disorders have not been reported with increased frequency in any other B-cell immunodeficiencies. Some patients may require gamma globulin replacement, but most will not benefit.

e. Selective polysaccharide antibody deficiencies (SPAD) T-cell

These individuals have normal quantitative immunoglobulin levels, however, they demonstrate a selective defect in their antibody response to polysaccharide vaccination (e.g., strep pneumoniae, *H. influenza* and *N.*



Site Mycobacteria

Encapsulated organisms

(*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Nisseria*)

Catalase-positive organisms

(*Staph aureus*, *Klebsiella*, *Serratia*)

Viruses

Herpes, varicella, CMV

Enteroviruses (echovirus, Coxsackie)

Fungi

Candida
Aspergillus

Parasites

Giardia lamblia
Toxoplasma gondii

Opportunistic infections

Pneumocystis carinii
Cryptosporidium

Defect

T-cell deficiency
N-K cell defect
IL-12

B-cell or complement deficiency

Neutrophil/phagocyte defects (CGD)

T-cell deficiency
IL-12/ NK cell defects

B-cell deficiency

T-cell deficiency
T-cell or phagocyte defects

B-cell deficiency
T-cell deficiency

T-cell deficiency
T-cell deficiency

meningitis). Functionally, SPAD patients have an increased incidence of infections (e.g., pneumonia, meningitis, otitis media and sepsis). This disease can be demonstrated by a lack of response to unconjugated polysaccharide vaccine in patients with normal quantitative immunoglobulin levels. Patients with SPAD rarely require gamma globulin replacement.

f. T-cell disorders

Severe combined immunodeficiency (SCID). This disorder is extremely rare, with only about 30-50 new cases per year. Immunologically, it is characterized by failure of stem cells to differentiate into T-cells and B-cells. Infants with SCID have very few lymphocytes in their peripheral blood and have no or few lymphocytes in their lymphoid tissue. In some cases, lymphocytes are present but fail to express major histocompatibility complex molecules. Genetically, this is more common in male infants because over 50% of cases are caused by a genetic defect on the X-chromosome. The remaining cases are due to autosomal recessive genes on other chromosomes. More than half of these cases have a gene deficiency of adenosine deaminase (ADA) or purine nucleoside phosphorylase.

Clinically, patients who have SCID are susceptible to all microbial infections, but most notably rotavirus, *Candida albicans* and *P. carinii*. They have chronic diarrhea, pneumonia, failure to thrive and may have progressive infections if immunized with live organisms. The symptoms occur in early childhood and prove fatal within the first year of life if untreated with bone marrow

transplantation or gene therapy (ADA deficiency).

- **Congenital thymic aplasia (DiGeorge Syndrome)**

Patients with DiGeorge syndrome have a failed development of the thymus and parathyroid glands. Newborns often suffer from hypocalcemic tetany during the first 24 hours of life. They also suffer from a number of other congenital defects involving the heart, kidneys and other organs. Children have distinct facial features with wide-set eyes and low-set notched ears. There are few or no T-cells, B-cells, or plasma cells. Total immunoglobulin levels may be normal but immunization does not result in adequate antibody production.

- **Ataxia-telangiectasia**

This disorder is inherited as an autosomal recessive trait and presents in early childhood. Patients typically display a wobbly gait, have telangiectasia appearing on their eyes and skin by age 6 and suffer from severe sino-pulmonary infections. They may also have other neurologic, endocrine, hepatic and cutaneous symptoms.

- **Wiskott-Aldrich Syndrome**

This is an x-linked disorder affecting males who have thrombocytopenia and progressive T-cell dysfunction. Their serum contains increased levels of IgA and IgE, with normal levels of IgG, and reduced levels of IgM. Clinically, these patients usually suffer from eczema, pyogenic and opportunistic infections.

g. Phagocytic cell deficiencies

Most of the defects of phagocytic cells present with recurrent bacterial infections. There are several stages along the process of phagocytosis which may be impaired, including: cell motility, adherence and inability to phagocytize and kill micro-organisms. These phagocytic disorders include chronic granulomatous disease, leukocyte adhesion deficiency and Chediak-Higashi syndrome.

- **Chronic granulomatous disease (CGD)**

Chronic granulomatous disease (CGD) is defined by the inability of neutrophils to kill ingested micro-organisms stemming from defective nicotinamide adenine dinucleotide phosphate oxidase enzyme. These enzymes allow for the generation of super oxide ions and hydrogen peroxide, which are necessary for the intracellular survival of the bacteria and leads to granuloma formation. Children who have chronic granulomatous disease are susceptible to pneumonia, lymphadenitis and abscesses in the skin, liver and other viscera. The patients suffer from infections often due to organisms of low virulence such as staphylococcus epidermitis, serratia marcescens and aspergillus. Diagnosis of this disease may be made by a neutrophil respiratory burst assay done by flow cytometry.

- **Leukocyte adhesion deficiency**

As a result of a genetic defect, phagocytes cannot adhere to vascular epithelium expressing intracellular adhesion molecule-1 and thus cannot migrate out of blood vessels into areas of infection. The process results in an elevated blood neutrophil count and an inability to form pus effectively. In patients who have leukocyte adhesion deficiency severe bacterial infections can spread rapidly from within the mouth and the GI tract. Patients with this disorder have been successfully treated with bone marrow transplantation.

- **Chediak-Higashi Syndrome**

Patients with this illness have partial albinism and recurrent pyogenic infections with staphylococcus and streptococcus. The prognosis is poor, with most children dying early. Defective neutrophil chemotaxis, phagocytosis and intracellular killing results from defects in micro-tubules and an inability of enzymes to release their granules.

h. Complement deficiencies

The complement system consists of over 20 glycoproteins and is a major effector component of the humoral branch of the immune system. Mechanisms dependent on complement activation include: opsonization, which promotes phagocytosis of particular antigens, recruitment and activation of immunologically active cells at sites of inflammation, processing and clearance of immune complexes as well as direct lysis of target cells including viruses.

Complement deficiencies—although uncommon—have been described for each complement component. Complement deficiencies are usually associated with bacterial infections, predominantly sino-pulmonary infections and immune complex disease and angioedema.

Patients lacking any of the complement components may suffer recurrent episodes of meningococemia, meningococcal meningitis and disseminated gonococcal infections.

The total hemolytic complement test (CH-50) may be useful as a screen for complement deficiency. There is no specific treatment for complement component abnormalities. Acute infections are treated with antibiotics and long-term management may include the use of prophylactic antibiotics. Complement proteins cannot be replaced currently except for C-1 esterase deficiency where a blood concentrate has recently been approved for acute episodes of hereditary angioedema due to C-1 esterase deficiency.

Treatment

The principal treatments for primary immunodeficiency include:

1. **Protective isolation**—prevention of infections
2. **Antibiotic prophylaxis** and acute treatment of bacterial/fungal infections
3. **Replacement therapy** for missing humoral or cellular immunologic functions

Although the molecular etiology of many of the primary immunodeficiencies has been reported, gene therapy is not available for except for a few select cases of severe combined immunodeficiency.

1. **Prevention by controlling infection:** Limit the immunodeficient patient's exposure to infectious disease. Remove immunodeficient children from day care or pre-school, avoid others with colds, as well as crowds. In addition, avoid high-risk situations and ensure the patient has received all appropriate vaccines (e.g., conjugated polysaccharide vaccines and annual immunization against influenza). Checking specific antibody titers post immunization can provide assurance of protection.

- Vaccines used to treat immunodeficient patients and their families and close contacts should be killed vaccines, since live vaccines pose a serious risk.
- Prompt and rigorous treatment of apparent bacterial infections associated with sinusitis and bronchitis. Treat adequately with antibiotics until you are certain that the infection has been completely resolved.
- Frequent follow-up visits are needed to assure treatment is truly effective as well to identify infection in its early stage.
- When infection is resistant, prolonged courses of oral antibiotics and/or parenteral treatment may be required.

2. **Prophylactic antibiotic treatment in immunodeficiency**

Prophylactic antibiotic treatment can be carried out with a once-daily dose of trimethoprim-sulfamethoxazole (e.g., half of the total daily dose that would be used for otitis media). Other oral antibiot-

ics, such as ampicillin or a cephalosporin, may also be used, especially in patients who are allergic to sulfonamides, but these may be associated with a higher risk for resistant bacteria. Patients who develop diarrhea or other gastrointestinal side effects, oral thrush, or vaginal candidiasis may be poor candidates for this approach.

3. Immunoglobulin treatment in immunodeficiency

Half or more of all primary immune deficiencies involve defects in antibody production. Patients with X-linked agammaglobulinemia, common variable hypogammaglobulinemia, hyper-IgM syndromes, and other severe immunoglobulin deficiencies often require immunoglobulin replacement. In patients with severe antibody deficiency, lack of efficacy of antibiotics, or when prophylaxis has not been effective, immunoglobulin replacement may be the treatment of choice.

Immunoglobulin therapy is administered mostly by the intravenous route (IVIG), but subcutaneous administration has recently been made available. Since the half-life of IgG is about 21 days, IV infusions are typically administered every three to four weeks, versus subcutaneous infusions which may be given at home at weekly intervals or even more often. The dose and interval of IVIG needs to be optimized to control infections and other symptoms, but it usually ranges from 300 mg/kg/month to 800 mg/kg/month. Higher doses are reserved for patients with chronic lung and/or sinus infections. Serum IgG concentrations are measured just prior to an infusion to determine their trough or low level to ensure adequacy of dosing.

Patients with active acute or chronic infection may experience severe systemic symptoms (e.g., shaking chills, fevers, and/or inflammatory reactions at the site of infection) when initially receiving infusions of IVIG. Therefore, it may be wise to treat the patient with an adequate course of antibiotics prior to initial IVIG infusions.

When initiating treatment with IVIG, we recommend beginning with a slow infusion rate (0.5 mg/kg/min to 1 mg/kg/min)—which would be 0.01 mL/kg/min to 0.02 mL/kg/min of 5% solution—and slowly increase the rate at 30-minute intervals, as tolerated, until a maximum rate of 4 mg/kg/min to 6 mg/kg/min is achieved. The rate should be slowed at the first sign of a reaction. Most non-reactive patients can complete their infusions within a few hours. Some patients may experience adverse reactions during IV infusions. Common symptoms may include: headache, backache, flushing, chills, and

nausea. Severe symptoms might include: dyspnea, wheezing, anxiety, chest pain, and anaphylactoid symptoms.

Severe symptoms are not usually a result of a true anaphylactic reaction, since they are not usually mediated by IgE and are frequently associated with increased rather than decreased blood pressure. Such reactions can be treated by decreasing the rate of infusion and/or by administration of diphenhydramine, corticosteroids, acetaminophen, or aspirin prior to treatment. Patients with consistent patterns of reactions can be kept at slower rates during future treatment and/or pretreated with the previously mentioned medications. In rare cases, pretreatment with corticosteroids (e.g., 0.5 mg/kg to 1 mg/kg of prednisone or intravenous methylprednisolone) may be necessary.

True anaphylaxis is extremely uncommon and has been reported in IgA- deficient patients in which IgE antibodies are present against IgA.

Rare complications of IVIG therapy include aseptic meningitis, thrombotic events, and acute renal failure.

These complications are usually associated with high doses of IVIG (>1,000 mg/kg) which are used for their anti-inflammatory or immunomodulatory effects. Such adverse reactions are rare in patients receiving conventional doses as replacement therapy for immune deficiencies.

Finally, late adverse reactions may include headache, which may have migraine-like features and may be associated with nausea and fever. These reactions may occur up to 48 hours after the infusion and they generally respond to acetaminophen, aspirin, or other non-steroidal anti-inflammatory drugs.

Management of patients with phagocytic dysfunction and complement disorders is best accomplished by treatment of the specific infections, as no replacement therapies have been identified except in the case of hereditary angioedema.

Management of t-cell deficiencies is more difficult, as there is no readily available cure. Bone marrow transplantation and gene therapy have been tried in certain disorders. These aggressive forms of therapy have been associated with various adverse effects. Members of the patient's household should receive regular immunizations with killed vaccinations.

In the future, further definition of gene abnormalities may lead to more effective interventions in immunodeficiency treatment. ■

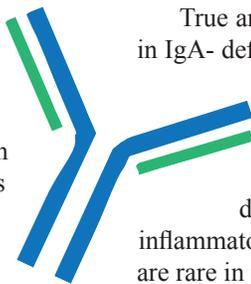


Table 6

Laboratory diagnosis of immunodeficiency states

Immune system defense mechanism	Functional component	Screening tests	Other diagnostic tests
Humoral immunity	B-cell function	Quantitative immunoglobulins	IgG subclass levels Immunization/antibody titers (pneumococcal vaccine, tetanus/diphtheria toxoid)
	Complement system	Total hemolytic complement assay	Evaluation/measurement of individual complement components
Cell-mediated immunity	T-cell function	CBC count with differential	
		Delayed-type hypersensitivity skin tests	Lymphocyte quantitation (T-cells and B-cells)
Innate immunity	Phagocytic function	CBC count with differential	Nitroblue tetrazolium test
			Measurement of chemotaxis, phagocytosis, bacterial killing (research assays)
			Flow cytometry for surface markers and adhesion molecules