# Immunodeficiency

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Introductory article

Article Contents



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Immunodeficiency is a condition caused by one or more immune system defects and is characterized clinically by increased susceptibility to infections with consequent severe, acute, recurrent or chronic disease. An immunodeficiency disorder should be considered in anyone with infections that are unusually frequent, severe and resistant; without a symptom-free interval; from an unusual organism or with unexpected or severe complications. Immunodeficiencies may be either primary or secondary.

## Definitions of Immunodeficiency

### Primary immunodeficiencies

The primary immunodeficiencies are classified into four main groups depending on which component of the immune system is deficient: B cells, T cells, phagocytic cells or the complement cascade. **See also**: Complement; Lymphocytes

The overall incidence of symptomatic primary immunodeficiency (other than selective immunoglobulin (Ig) A deficiency) is estimated as 1 in 10 000; about 400 new cases occur each year in the United States. Since many primary immunodeficiencies are hereditary or congenital, they appear initially in infants and children; about 80% of those affected are under 20 years old and, owing to X-linked inheritance of many syndromes, 70% occur in males.

Of the primary immunodeficiencies, B-cell-associated antibody defects predominate; selective IgA deficiency (usually asymptomatic) may occur in 1 in 400 people. Excluding asymptomatic IgA deficiency, B-cell defects still account for 50% of the primary immunodeficiencies, but another 15% involve antibody deficiency due to T-cell abnormalities. T-cell defects account for about 30% (with about 5% purely due to T-cell deficiencies such as DiGeorge Syndrome), phagocytic deficiencies account for 15% and complement deficiencies account for 5%. T-cell defects include several disorders with associated B-cell (antibody) defects, which are understandable since B and T cells originate from a common precursor stem cell and, in addition, T cells influence B-cell function. Phagocytic diseases include disorders in which the primary defect is one of cell movement (chemotaxis) and those in which the primary defect is one of microbicidal activity. A classification of primary immunodeficiencies is shown in **Table 1** for phagocytic disorders, **Table 2** for lymphocytic disorders and **Table 3** for complement disorders. **See also**: Immunodeficiency, Primary: Affecting the Adaptive Immune System; Immunodeficiency, Primary: Affecting the Innate Immune System

### Secondary immunodeficiencies

Secondary immunodeficiency is an impairment of the immune system resulting from an infection, medications or malignancy in a previously normal person. The impairment is often reversible if the underlying condition or illness resolves. Secondary immunodeficiencies are considerably more common than primary immunodeficiencies and occur in many hospitalized patients. Nearly every prolonged serious illness interferes with the immune system to some degree. A classification of the secondary immunodeficiencies is shown in **Table 4**. **See also**: Immunodeficiency: Secondary

## Diagnosis of Immunodeficiency

### Clinical presentation

The most common manifestation of immunodeficiency is frequent infections, usually beginning with recurrent respiratory infections. Most immunodeficient patients eventually develop severe bacterial infections that persist, recur or lead to complications (e.g. sinusitis, chronic otitis and bronchitis often follow repeated episodes of sore throat). Bronchitis may progress to pneumonia, bronchiectasis and respiratory failure, the most common cause of death in these patients. Infections with opportunistic organisms (e.g. *Pneumocystis carinii* or *Cytomegalovirus*) may occur, particularly in patients with T-cell deficiencies.

Infection of the skin and mucous membranes also is common. Resistant thrush (oral candidial infection) may be the first sign of T-cell immunodeficiency. Oral ulcers and periodontitis also are noted, particularly in granulocytic disorders.

Other common symptoms include diarrhoea, malabsorption and failure to thrive. The diarrhoea may be noninfectious or associated with *Giardia lamblia*, *Rotavirus*, *Cytomegalovirus* or *Cryptosporidium*. In some patients, the diarrhoea may be exudative with loss of serum proteins and lymphocytes. Less common manifestations of immunodeficiency include haematological abnormalities (autoimmune haemolytic anaemia, leucopenia, thrombocytopenia), autoimmune disorder (vasculitis, arthritis, endocrinopathies) and central nervous system disease (chronic encephalitis, slow development, seizures). **See also**: Autoimmune Disease: Pathogenesis; Immune Haemolytic Anaemia; Malabsorption

**Table 1** Phagocytic disorders

| Disorder | Defect | Associated findings |
|---|---|---|
| *Neutropenic disorders* | | |
| Reticular dysgenesis | Bone marrow failure | Severe bone marrow hypoplasia with neutropenia and lymphopenia |
| Cyclic neutropenia | Bone marrow defect | Severe infections when neutropenic for 3–5 days in 21 day cycle |
| Severe congenital neutropenia or Kostmann's (AR) | Bone marrow failure | Usually die in infancy of severe infections |
| Myelokathexis and WHIM syndrome (AD) | Bone marrow myelokathexis | Warts, hypogammaglobulinaemia, infections, and myelokathexis causing neutropenia |
| Shwachman–Diamond syndrome (AR) | Bone marrow failure | Neutropenia due to bone marrow failure, pancreatic insufficiency |
| Familial benign neutropenia (AD) | Neutropenia | No increased risk for infections |
| *Defects in microbicidal activity* | | |
| Chronic granulomatous disease (XL or AR) | Oxidative enzyme defect | Lymphadenopathy, cutaneous abscesses, liver abscesses, pneumonia |
| Myeloperoxidase deficiency (AR) | Enzyme defect | Often asymptomatic but sometimes fungal infections |
| Chediak–Higashi syndrome (AR) | Granule formation defect | Oculocutaneous albinism, giant granules in leucocytes, neuropathy |
| Glucose-6-phosphate dehydrogenase deficiency (XL) | Enzyme defect | Haemolytic anaemia, recurrent infections |
| Glutathione synthetase deficiency | Enzyme defect | Haemolytic anaemia, recurrent infections, neutropenia |
| *Defects of cell movement* | | |
| Hyperimmunoglobulinaemia E syndrome | Elevated IgE, chemotactic defect | Eczema, dermatitis, pneumonia, abscesses |
| Leucocyte adhesion defects type I (AR) | Lack CD18 β chain on surface | Prolonged attachment of umbilical cord, leucocytosis, periodontitis, infections |
| Leucocyte adhesion defects type 2 (AR) | Lack sialyl X Lewis selectin | Periodonitis, abscesses, pneumonia, neutrophilia |
| Neutrophil actin dysfunction | Actin dysfunction | Recurrent infection, neutrophilia |
| Localized juvenile periodontitis | Chemotactic defect | Severe periodontitis with alveolar bone loss starting at puberty |
| Specific granule deficiency | Specific granules absent, abnormal nuclei | Prolonged cutaneous infections, lung abscesses, mastoiditis |

*Note*: ACD, autosomal codominant; AD, autosomal dominant; AR, autosomal recessive; Ig, immunoglobulin and XL, X-linked; WHIM, warts, hypogammaglobulinaemia, infections, myelokathexis.

## Associated history

If there is a family history of early death, similar disease, autoimmune illness, allergy, early malignancy or consanguinity, then a pedigree chart will help to identify a hereditary pattern.

The age of onset may also help in diagnosis. Patients with T-cell disorders are usually present at under 6 months of age. Onset of illness at around 6 months of age, when transplacentally acquired maternal antibodies have disappeared, suggests congenital antibody deficiency. Patients with phagocytic disorders often develop symptoms in infancy but sometimes are not diagnosed until later in childhood. **See also**: Placental Immune Defences – Protection Against Rejection and Infection

## Physical findings

Patients with immunodeficiency often appear chronically ill, with pallor, malaise, malnutrition and a distended abdomen. Rashes, vesicles, pyoderma, eczema, petechiae, alopecia or telangiectasia may appear on the skin, and conjunctivitis is common. Cervical lymph nodes and adenoid and tonsillar tissue are typically absent in some B- or T-cell immunodeficiencies, despite a history of recurrent throat infections. However, the lymph nodes may be enlarged and draining in patients with phagocytic disorders. The tympanic membranes often are scarred or perforated, and the nostrils may be excoriated and crusted, indicative of purulent nasal discharge. Postnasal drip and nocturnal cough suggest chronic sinusitis. Rales and

**Table 2** Lymphocytic disorders

| Disorder | Defect | Associated findings |
|---|---|---|
| *B-cell (antibody) deficiencies* | | |
| X-linked agammaglobulinaemia (Bruton) | Tyrosine kinase defect | B lymphocytes absent, pyogenic infections, arthritis |
| Autosomal recessive agammaglobulinaemia (AD) | Cannot form IgM heavy chain | No pre-B or B cells, pyogenic infections |
| Hyper-IgM syndrome (XL) | Absence of CD40 ligand on T cells | Neutropenia, lymphadenopathy, sclerosing cholangitis, pneumonia |
| IgA deficiency | Lack IgA | Autoimmunity, respiratory or food allergy, respiratory infection |
| IgG subclass deficiencies | Low IgG subclass | IgA deficiency, recurrent respiratory infections |
| IgM deficiency | Low IgM | Recurrent infections, autoimmunity |
| Common variable immunodeficiency | Defect in B cells | Autoimmunity, B cells present with low immunoglobulins, recurrent infections |
| Transient hypogammaglobulinaemia of infancy | Slow maturation | Prematurity, recurrent infections |
| Specific antibody deficiency with normal immunoglobulins | Poor response to polysaccharide | Recurrent infections |
| *Predominant T-cell deficiency* | | |
| DiGeorge anomaly | Defect in chromosome 22 | Hypocalcaemia, peculiar facies, aortic arch and heart abnormalities |
| Chronic mucocutaneous candidiasis | Poor response to candida | Endocrinopathies, fungal and bacterial infections |
| Nezelof syndrome | T cell abnormal | Bronchiectasis, increased IgE levels |
| *Severe combined T- and B-cell immunodeficiency (SCID)* | | |
| Reticular dysgenesis | Bone marrow defect | Severe neutropenia and lymphopenia, early death |
| Adenosine deaminase deficiency (AR) | Enzyme defect | Decreased T and B cells, skeletal abnormalities |
| Nucleoside phosphorylase deficiency (AR) | Enzyme defect | Severely low T cells, neurologic disease |
| X-linked SCID | Defect in IL-2 receptor $\gamma$ chain | Severely low T cells |
| Jak-3 deficiency (AR) | Defect in tyrosine kinase Jak 3 | Low T cells, normal B cells |
| Zap 70 deficiency | Defect in tyrosine kinase ZAP-70 | Very low CD8 cells |
| CD3-TCR deficiency | Defective CD3 chains | Various forms depending on chain that is defective |
| RAG deficiency (AR) | Defect in DNA-binding proteins from genes RAG 1 or RAG 2 | Low T and B cells |
| Omenn syndrome | RAG mutations | Severe infections, diarrhoea, erythroderma, elevated IgE |
| Artemis mutation | DNA repair defect | Low T and B cells, radiation sensitivity |
| TAP deficiency (MHC class I deficiency) | HLA class I defect | Very low CD8 cells, normal B cells |
| MHC class II deficiency | HLA class II defect | Low CD4 cells, normal B cells |
| Griscelli syndrome | Myosin protein defect | Very decreased cellular immunity, pigmentary defects |
| *Other lymphocyte disorders* | | |
| Ataxia–telangiectasia (AR) | DNA repair defect | Dermatitis, neurological deterioration, infections |
| Wiskott–Aldrich syndrome (XL) | WAS protein defect | Eczema, thrombocytopenia, infections, malignancy |
| Short-limbed dwarfism | RNAase protein defect | Cartilage–hair hypoplasia, infections |
| XL lymphoproliferative syndrome | Lymphocyte signalling protein defect | *Epstein–Barr virus* infection, often fatal |
| ALPS | Defective apoptosis | Lymphadenopathy, autoimmunity, malignancies |
| IPEX syndrome ((XL) | FOXP3 mutation | Severe diarrhoea, diabetes, rash, thyroid disease |

*Note*: ACD, autosomal codominant; AD, autosomal dominant; ALPS, autoimmune lymphoproliferative syndrome; AR, autosomal recessive; DNA, deoxyribonucleic acid; HLA, human leucocyte antigen, Ig, immunoglobulin; IL-2, interleukin 2; IPEX, immunodeficiency, polyendocrinopathy, enteropathy, X-linked; MHC, major histocompatibility complex; RAG, recombination-activating genes; RNAase, ribonuclease; TAP, transporter antigen presentation; TCR, T cell receptor; WAS, Wiskott–Aldrich syndrome and XL, X-linked.

wheezes are often present on auscultation of the lungs. The liver and spleen are frequently enlarged. Muscle mass and fat deposits of the buttocks are diminished. In infants, there may be excoriation around the anus as a result of chronic diarrhoea or a candidial rash. Neurological examination may reveal delayed developmental milestones or ataxia.

A characteristic constellation of findings permits a tentative clinical diagnosis in a number of immunodeficiency

**Table 3** Complement disorders

| Disorder | Associated findings |
|---|---|
| C1, C4, C2 deficiency (AR) | Systemic lupus erythematosus-like syndrome, glomerulonephritis |
| C3 deficiency | Pyogenic infections |
| C5 | Bacterial infections |
| C6, C7, C8, C9 (AR) | *Neisseria* infection |
| C1 inhibitor deficiency (AD) | Angioedema, systemic lupus erythematosus |
| Factor H deficiency (ACD) | Haemolytic–uraemic syndrome, glomerulonephritis |
| Factor D deficiency (ACD) | Pyogenic infections |
| Properin deficiency (XL) | *Neisseria* infections |
| Mannose-binding lectin deficiency | Increased bacterial infections due to lack of complement activation |

*Note*: ACD, autosomal codominant; AD, autosomal dominant; AR, autosomal recessive; and XL, X-linked.

syndromes: newborns with DiGeorge anomaly typically exhibit infections, hypocalcaemia, peculiar facies and congenital heart disease; boys with Wiskott–Aldrich syndrome typically suffer from pyogenic infections, eczema and bleeding manifestations; children with ataxia–telangiectasia develop recurrent sinopulmonary infections, ataxia and telangiectasia in early childhood; and patients with hyperIgE syndrome develop severe eczema and severe pulmonary infections.

## Laboratory screening studies

Screening tests for immunodeficiency can be performed in most offices and include a complete blood count (CBC) with differential and platelet count; determination of IgG, IgM and IgA levels; assessment of specific antibody function and evaluation for infections with appropriate cultures. **See also**: Antibody Classes

The CBC will establish the presence of anaemia, thrombocytopenia, lymphopenia, neutropenia or leucocytosis. A total lymphocyte count of less than $1500\,pL^{-1}$ is suggestive of T-cell immunodeficiency. The peripheral blood smear should be examined for the presence of Howell–Jolly bodies and other unusual red blood cell forms suggestive of asplenia or poor splenic function. The granulocytes may show morphological abnormalities such as the large granules of the Chediak–Higashi syndrome and absence of granules in specific granule deficiency. **See also**: Spleen: Consequences of Lack of Function

Ig levels also are part of the initial screen, and values must be interpreted with care because of marked alterations with age; all infants aged 2–6 months are hypogammaglobulinaemic by adult standards. A total IgG level of less than $400\,mg\,dL^{-1}$ with normal screening functional antibody test results usually excludes antibody deficiency. A total Ig level of less than $200\,mg\,dL^{-1}$ usually indicates significant antibody deficiency. IgM function may be estimated by isoagglutinin titres (antiA and/or antiB). Antibodies to these and certain bacterial polysaccharides are selectively deficient in certain disorders (e.g. Wiskott–Aldrich syndrome, IgG2

**Table 4** Secondary immunodeficiency disorders

| Predisposing factors | Specific factors |
|---|---|
| Premature and newborn infants | Physiological immunodeficiency due to immaturity of the immune system |
| Hereditary and metabolic diseases | Chromosome abnormalities (e.g. Down syndrome) |
| | Uraemia |
| | Diabetes mellitus |
| | Malnutrition, vitamin and mineral deficiency |
| | Protein-losing enteropathies |
| | Nephrotic syndrome |
| | Myotonic dystrophy |
| | Sickle-cell disease |
| Immunosuppressive agents | Radiation |
| | Immunosuppressive drugs, corticosteroids |
| | Antilymphocyte or antithymocyte globulin |
| | Anti-T-cell monoclonal antibodies |
| Infectious | Congenital infections (rubella) |
| | Viruses (measles, varicella, human immunodeficiency virus, cytomegalovirus, *Epstein–Barr virus*) |
| | Acute bacterial disease |
| | Severe mycobacterial or fungal disease |
| Infiltrative and haematological | Histiocytosis |
| | Sarcoidosis |
| | Hodgkin disease and lymphoma |
| | Leukaemia, myeloma |
| | Agranulocytosis and aplastic anaemia |
| Surgery and trauma | Burns |
| | Splenectomy |
| | Anaesthesia |
| Miscellaneous | Systemic lupus erythematosus |
| | Chronic active hepatitis |
| | Alcoholic cirrhosis |
| | Ageing |
| | Anticonvulsant drugs |
| Graft-versus-host disease | |

subclass deficiency). In the immunized patient, specific antibody titres to *Haemophilus influenzae* type B, hepatitis B, rubella virus, tetanus or diphtheria antigens can be used to estimate IgG function. An adequate antibody level to one or more of these antigens or a higher-titre antibody response following reimmunization is evidence against antibody deficiency. Finally, screening should include a search for chronic infection. The sedimentation rate often is raised, usually in proportion to the degree of infection. Appropriate radiographs (chest, sinus) and cultures should be obtained. **See also**: *Hepatitis B Virus*; *Rubella Virus*

If the results of all these screening tests are normal, immunodeficiency (particularly antibody deficiency) can usually be excluded. However, if chronic infection is documented, if the history is unusually suspicious or if the results of screening tests are positive, advanced tests must be performed.

## Tests for B-cell (antibody) deficiency

If Ig levels are very low (total less than 200 mg $dL^{-1}$), a diagnosis of antibody deficiency is established and other procedures are indicated only to define the exact illness and to identify other immunological defects. If Ig levels and pre-existing antibody titres are low but not absent, the antibody responses to one or more standardized antigens should be assessed. Antibody titres are obtained before and 3–4 weeks after immunization with tetanus toxoid or diphtheria vaccine to test for protein antigen responsiveness, or after immunization with pneumococcal or meningococcal vaccine to test for polysaccharide antigen responsiveness. Responsiveness to polysaccharide antigens, however, does not usually occur until 2 years of age. An inadequate response (less than a 4-fold rise in titre) is suggestive of antibody deficiency regardless of total Ig levels.

If Ig levels are low, B-cell enumeration is performed by assessing the percentage of lymphocytes reacting with fluoresceinated antibodies to B cell-specific antigens (e.g. CD19, CD20) as assessed by flow cytometry. Normally, 10–20% of peripheral blood lymphocytes are B cells.

Next, serum levels of IgG subclasses should be obtained. IgG subclass determinations are indicated if IgG levels are normal or near normal but antibody function is deficient. Selective deficiencies of one of the four subclasses may be present. High and low levels of IgD and IgE may occur in some antibody deficiency syndromes. IgE levels may be high in chemotactic disorders, partial T-cell immunodeficiencies, allergic disorders and parasitism. **See also**: Allergy

Other laboratory tests for B-cell deficiencies are indicated in certain circumstances. A lymph node biopsy (sometimes preceded by immunization in the adjacent extremity) is indicated in the presence of lymphadenopathy to exclude malignancy or infection. If rapid IgG catabolism or IgG loss through the skin or gastrointestinal tract is suspected, an IgG survival study may be indicated. The illnesses in which the genetic defect has been identified, the mutant gene or mutant gene product can be identified (e.g. Bruton tyrosine kinase gene in X-linked agammaglobulinaemia; CD40 ligand in hyper-IgM syndrome) by special laboratory testing. **See also**: Immunodeficiency Disorders due to Antibody Deficiency (B-lymphocyte Disorders)

## Tests for T-cell deficiency

Profound and prolonged lymphopenia usually suggests a T-cell immunodeficiency. Chest radiography is a useful screening test in infants. An absent thymic shadow in the newborn period suggests T-cell deficiency, particularly if the radiograph is obtained before the onset of infection or other stress that may shrink the thymus. **See also**: The Thymic Niche and Thymopoiesis

Delayed hypersensitivity skin tests are valuable screening tests after the age of 2 years. The following antigens are used: mumps, *Candida* (1:100), fluid tetanus toxoid (1:10) and *Trichophyton*. Nearly all adults and most immunized infants and children will react to one or more of these antigens with erythema and induration ($>5$ mm) at 48 h. The presence of one or more positive delayed skin test results generally confirms an intact T-cell system.

The most valuable advanced test in cellular immunodeficiency is T-cell and T-subset (helper/inducer and suppressor/cytotoxic) enumeration, usually performed by flow cytometry using T-cell-specific monoclonal murine antibodies. A T-helper cell (CD4) count lower than 500 cells per pL is highly suggestive of a T-cell immunodeficiency, and a CD4 count below 200 cells per pL indicates a profound T-cell immunodeficiency. The ratio of CD4/CD8 (helper/suppressor) cells should be greater than 1.0; reversal of this ratio also suggests T-cell immunodeficiency (e.g. in acquired immune deficiency syndrome (AIDS), a decline in the CD4/CD8 ratio indicates progressive immunological impairment). Monoclonal antibodies also are available to identify activated cells (human leucocyte antigen (HLA)-DR, CD25), natural killer cells (CD16 and CD56) and immature T-cell (thymocyte) antigens (CD1). **See also**: Acquired Immune Deficiency Syndrome (AIDS); T Lymphocytes: Cytotoxic; T Lymphocytes: Helpers

Another useful advanced test measures the ability of the patient's lymphocytes to proliferate and enlarge (transform) when cultured in the presence of mitogens, irradiated allogeneic mononuclear cells (in the mixed leucocyte reaction) or antigens to which the patient has been exposed previously. With these stimuli, normal lymphocytes undergo rapid division, which can be assessed morphologically or by uptake of radioactive thymidine into dividing cells. Patients with T-cell immunodeficiency have low or absent proliferative responses in proportion to the degree of immune impairment. Special tests also assess lymphokine production after mitogen or antigen stimulation.

Different types of cytotoxicity (natural killer, antibody-dependent or cytotoxic T cell) are measured using different tumour cell or virus-infected target cells. In some forms of combined immunodeficiency, enzymes of the purine pathway (adenosine deaminase, nucleoside phosphorylase) are deficient and can be assayed using the patient's erythrocytes. HLA typing can be valuable for assessing the

presence of two populations of cells (chimaerism) due to cells from the mother or from a blood transfusion, and for excluding deficiencies of HLA antigens (bare lymphocyte syndrome).

### Tests for phagocytic cell deficiency

An investigation is indicated when a patient with a convincing history of immunodeficiency has normal B- and T-cell immunity. Recurrent staphylococcal infections, perianal abscesses and delayed umbilical cord detachment with marked leucocytosis are suggestive of a phagocytic defect.

Initial screening with a CBC may reveal neutropenia but serial blood counts (at twice-weekly intervals) may be necessary to rule out cyclic neutropenia. Other testing may include determination of IgE concentration, which is raised in the hyper-IgE syndrome. A nitroblue tetrazolium (NBT) dye reduction test will test for chronic granulomatous disease (CGD), the most common phagocytic disorder. The NBT test is based on the increased oxidative burst activity of granulocytes following activation with reduction of colourless NBT to blue formazan due to the release of oxygen radicals. CGD can also be diagnosed by flow cytometry using the dye dihydrorhodamine which changes fluorescence when exposed to oxygen radicals. Carriers of the X-linked form of CGD will have a partial response. Granulocytes can also be tested for the presence or absence of myeloperoxidase by special staining techniques. **See also**: Neutropenia

A chemotactic abnormality can be assessed by an *in vitro* assay in which migration of granulocytes or monocytes is measured, using a special chemotactic chamber (Boyden) or an agarose plate; cell movement towards a chemoattractant (complement fragments, chemotactic peptide) is assessed.

Next, phagocytosis is tested by measuring uptake of latex particles or bacteria by isolated granulocytes or monocytes. Microbial killing is then assessed by mixing the patient's granulocytes in fresh serum with a known number of live bacteria, followed by serial quantitative bacterial assays over a 2-h period. **See also**: Phagocytosis: Techniques

Other specialized tests define phagocytic defects: assays of granulocyte mobilization after administering corticosteroids, adrenaline (epinephrine) or endotoxin; assays for granulocyte oxidant products (hydrogen peroxide, superoxide) and assays for specific granulocyte adhesions proteins such as CD11/CD18.

### Tests for complement deficiency

A complement abnormality is screened by measuring the total serum complement activity (CH50) and serum C3 and C4 levels. Low levels of any of these should be followed by titration of the classical and alternative complement pathways and the measurement of individual complement components. Monospecific antisera or sensitized erythrocytes and solutions that contain all components except for the one to be assessed are used to measure complement components.

Antisera also are available to measure complement control proteins. Deficiency of C1 inhibitor is associated with hereditary angioedema, and deficiency of factor I (C3 inhibitor) is associated with C3 deficiency with C3 hypercatabolism. Assays of serum opsonic activity, serum chemotactic activity or serum bactericidal activity can be used to test complement function indirectly. **See also**: Complement

## Infections in Immunodeficient Patients

Recurrent infections are the primary feature of immunodeficiency diseases. Opportunistic infections are caused by organisms often present in the environment that usually do not cause significant infections in patients with intact immune systems, such as *Pneumocystis* and some fungi. These opportunistic infections usually occur in patients with primary T-cell deficiencies or AIDS. However, the more common pathogens, such as *Staphylococcus*, are also opportunistic as they may result in life-threatening infections in these immunodeficient patients. **See also**: AIDS: Clinical Manifestations

The type of infection may suggest the nature of the immunodeficiency. Infections with major Gram-positive organisms (pneumococci, streptococci) are noted in antibody (B-cell) immunodeficiencies. Severe infections from viruses, fungi and other opportunistic organisms are common in cellular (T-cell) immunodeficiencies. Recurrent staphylococcal and Gram-negative infections are common in phagocytic deficiencies. Recurrent *Neisseria* infection is characteristic in patients with complement component deficiencies. **Table 5** lists pathogens associated with specific immunodeficiency diseases. **See also**: Infections in the Immunocompromised Host

## Treatment of Immunodeficiency

General management of patients with immunodeficiency requires an extraordinary amount of care to maintain optimal health and nutrition, to manage infections, to prevent emotional problems related to the illness and to cope with costs. Patients should be protected from unnecessary exposure to infection, should sleep in their own beds and preferably have their own rooms. Killed vaccines should be given regularly if there is evidence of some antibody function. The teeth should be kept in good repair.

Antibiotics are life saving for treating infections; selection and dosage are identical to those used normally. However, because immunodeficient patients may succumb rapidly to infection, fever and other manifestations of infection are assumed to be secondary to bacterial infection,

**Table 5** Infections in immunodeficient patients

| Disorder | Pathogens |
|---|---|
| *Phagocytic disorders* | |
| Congenital or cyclic neutropenia | Bacteria, Gram-positive and Gram-negative |
| Leucocyte adhesion deficiency | Fungus (*Candida, Aspergillus*) |
| Chediak–Higashi syndrome | *Staphylococcus aureus* is predominant pathogen with increased susceptibility to other bacteria and fungi as in neutropenia |
| HyperIgE syndrome | *Staphylococcus aureus* is predominant pathogen<br>Other Gram-positive and Gram-negative bacteria<br>Fungi (*Candida albicans, Aspergillus*) |
| Chronic granulomatous disease | Bacteria, catalase-positive including *Staphylococcus aureus, Serratia marcescens, Salmonella, Burkholdia cepacia, Nocardia*<br>Fungus (*Aspergillus*) |
| Myeloperoxidase deficiency | *C. albicans* |
| *B-cell (antibody) disorder* | |
| X-linked agammaglobulinaemia (Bruton) | Bacteria, Gram-positive and Gram-negative<br>Viruses (echo, coxsackie, adenovirus)<br>Parasites (*Giardia*) |
| Common variable immunodeficiency | Similar to Bruton disease, plus *Cryptosporidium* |
| HyperIgM syndrome | Similar to Bruton disease, plus opportunistic organisms |
| IgA deficiency | Common viral and bacterial respiratory pathogens<br>*Giardia* |
| IgG subclass deficiency | Encapsulated bacteria (*Streptococcus pneumoniae, Haemophilus influenzae*) |
| Transient hypogammaglobulinaemia of infancy | Common bacterial respiratory pathogens |
| *T-cell and severe combined immune deficiency disorders* | |
| DiGeorge syndrome (highly variable with regard to degree of immunodeficiency) and severe combined immune deficiency (often more severe than DiGeorge syndrome) | *Candida* spp. (thrush common)<br>Bacteria (common and opportunistic) including *Streptococcus pneumoniae, Pseudomonas aeruginosa, Mycobacteria* spp.<br>Viruses (*Herpes simplex virus, Cytomegalovirus, Varicella-zoster virus*)<br>Protozoa (*Pneumocystis carinii, Crytosporidium*) |
| Wiskott–Aldrich syndrome | Bacteria (encapsulated) including *H. influenzae, Streptococcus pneumoniae*<br>*Candida* spp.<br>Viruses (*Cytomegalovirus, Herpes simplex virus*, *Varicella-zoster virus*, *Epstein–Barr virus*, virus causing molluscum contagiosum) |
| Ataxia–telangiectasia | Bacteria (more common pathogens) |
| Chronic mucocutaneous candidiasis | Fungi (*Candida, Histoplasma*)<br>Bacteria, (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *H. influenzae, Nocardia*)<br>Viruses (*Herpes simplex virus, Varicella-zoster virus*)<br>*Giardia* |
| *Complement disorders* | |
| C1, C4, C2, C3 | Bacteria (encapsulated) including *Streptococcus pneumoniae* and *H. influenzae* |
| C5, C6, C7, C8, C9 | *Neisseria meningitidis* (meningitis)<br>Disseminated gonococcal infection |
| Properidin | *N. meningitidis* |

and antibiotic treatment has begun immediately. Throat, blood or other cultures are obtained before most therapies; these are especially useful subsequently when the infection does not respond to the initial antibiotic and when the infectious organism is unusual.

Continuous prophylactic antibiotics often are beneficial, particularly when there is the risk of sudden overwhelming infection (e.g. Wiskott–Aldrich syndrome, asplenic syndromes); when other forms of immune therapy are unavailable (e.g. in phagocytic disorders) or insufficient (e.g. recurrent infection in agammaglobulinaemia despite Ig therapy) and when there is a high risk for a specific infection (e.g. *P. carinii* in cellular immunodeficiency disorders). Prophylactic therapy with antifungal agents, such as itraconazole or voriconazole, has been used in some patients with phagocytic disorders (e.g. CGD and hyper-IgE syndrome).

Antivirals, including amantadine or rimantidine for influenza, aciclovir for herpes infection (including *Varicella zoster*) and ribavirin for respiratory syncytial virus, may be life saving in immunodeficient patients with viral infections. **See also**: Herpesviruses (Human); Respiratory Syncytial Virus

Ig is effective replacement therapy in most forms of antibody deficiency. The largest intramuscular dose at one site is 10 mL in adults and 5 mL in children; accordingly, multiple injections at various sites may be necessary. High doses of intravenous Ig ($400–800\,mg\,kg^{-1}\,month^{-1}$) can be given and are beneficial to some antibody-deficient patients not responding well to conventional doses, particularly those with chronic lung disease. The aim with high-dose intravenous Ig is to keep IgG trough levels in the normal range (i.e. $>500\,mg\,dL^{-1}$). Slow subcutaneous infusions of 10–16% Ig given at weekly intervals has also been needed to deliver high-dose Ig therapy (i.e. more than $400\,mg\,kg^{-1}\,month^{-1}$) in patients with adverse reactions to intravenous infusions or poor venous access.

Other therapies, including immunologically enhancing drugs (isoprinosine), biological agents (transfer factor, interleukins) and hormones (thymic), have been of limited value in treating cellular or phagocytic immunodeficiencies, although interferon $\gamma$ is the only cytokine specifically approved for treatment of a primary immunodeficiency (e.g. CGD). Enzyme replacement with bovine adenosine deaminase conjugated to polyethylene glycol (PEG-ADA) has benefited patients with adenosine deaminase deficiency. **See also**: Interferons: Therapeutic Uses

Stem cell transplantation can often achieve complete correction of immunodeficiency. In severe combined immune deficiency (SCID) and its variants, bone marrow transplantation from an HLA-identical, mixed leucocyte culture-matched sibling has resulted in restored immunity in over 300 cases. In patients with intact or partial cellular immunodeficiency (e.g. Wiskott–Aldrich syndrome), prior immunosuppression must be given to ensure engraftment. When a matched sibling donor is unavailable, haplo-identical (half-matched) bone marrow from a parent can be used. Under these circumstances, mature T lymphocytes that will cause graft-versus-host (GVH) disease must be removed from the parenteral marrow before its administration. Alternatively, bone marrow from a matched but unrelated person identified through the International Bone Marrow Transplant Registry can be used. It is also possible to harvest CD34 stem cells from the peripheral blood of donors by leucopheresis followed by isolation of CD34 cells. Umbilical cord blood can also be used as a source of stem cells, from an HLA-matched sibling or banked HLA-compatible cord blood.

Fetal thymus transplants, thymic epithelial cell transplants and fetal liver transplants have been used with occasional success. Several patients with severe DiGeorge syndrome have been successfully treated with paediatric thymuses recovered at cardiac surgery.

Gene therapy involves transferring a normal gene into the bone marrow cells of the patient whose defective gene has been identified. Patients with adenosine deaminase deficiency, X-linked SCID, and CGD have been successfully treated with gene therapy but there is a risk of developing leukaemia or lymphoma.

## Further Reading

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