Immunodeficiency

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Immunodeficieny

- Immunodeficiency is failure of immune system to protect against disease or malignency

- Immunodeficiency is of two types
  - Primary
  - Secondary

immunodeficiency

- Primary immunodeficiency is caused by genetic or developmental defects in the immune system. These defects are present at birth but may show up later on in life.
- Secondary or acquired immunodeficiency is the loss of immune function as a result of exposure to disease agents, environmental factors, immunosuppression, or aging

Primary immunodeficiency

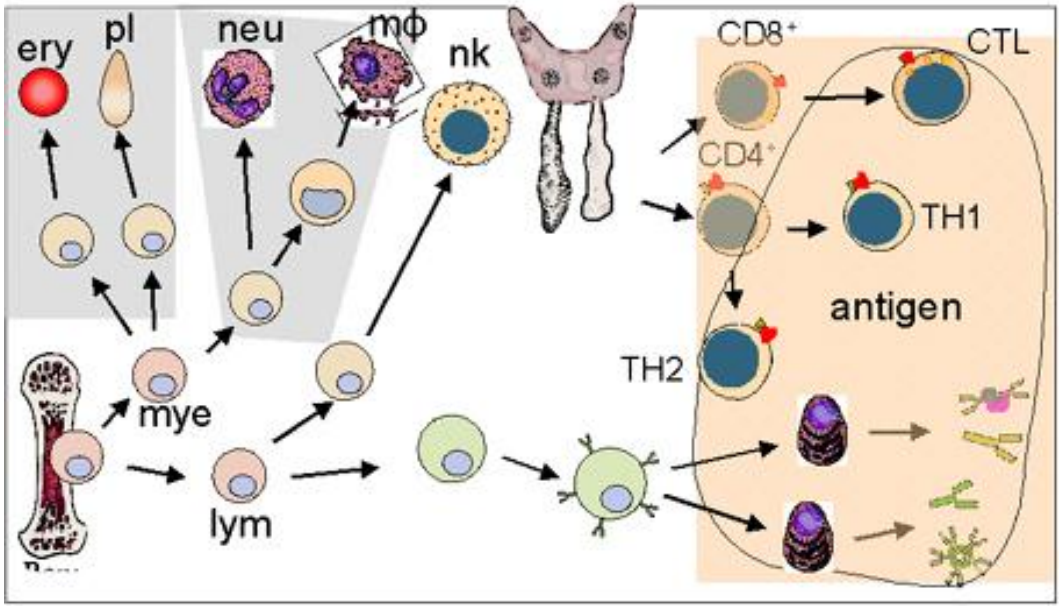
- Individuals with immunodeficiencies are susceptible to a variety of infections and the type of infection depends on the nature of immunodeficiency

Table 1. Characteristic infections of the primary immunodeficiencies

component	primary pathogen	primary site	clinical example
T-cells	intracellular, bacteria viruses, protozoa, fungi,	non-specific	SCID, DiGeorge
B-cells	pneumococcus, streptococcus, haemophilus	lung, skin, CNS	IgG, IgM deficiency IgG, IgM deficiency
	enteric bacteria and viruses	GI, nasal, eye	IgA deficiency
phagocytes	Staphylococcal, Klebsiella Pseudomonas,	lung, skin, regional lymph node	chronic granulomatous disease (CGD)
complement	neisseria, Haemophilus, pneumococcus, streptococcus	CNS lung skin	C3, Factors I and H, late C components

Primary immunodeficiency

- Developmental defects in primary immunodeficiency



- These defects may be in the specific or non-specific immune mechanisms

Deficiency in Specific Immune system

- There are variety of immunodeficiencies which result from defects in stem cell differentiation and may involve T-cells, B-cells, and/or immunoglobulins of different classes and subclasses
- A defect in the early hematopoiesis which involves stem cells results in reticular dysgenesis (defect in development) that leads to general immune defects and subsequent susceptibility to infections

Deficiency in Specific Immune system

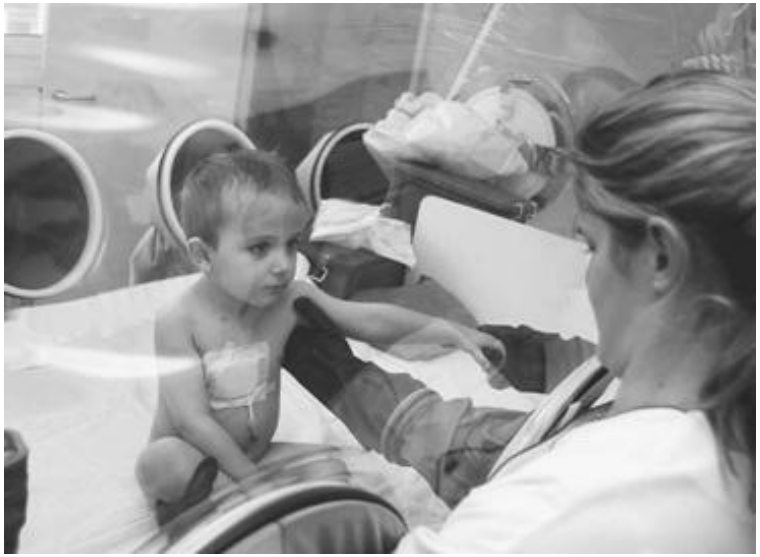
- Lymphoid linage deficiency
  - if the lymphoid progenitor cells are defective, then both the T and B cell lineages are affected and result in the severe combined immunodeficiency (SCID)
  - In about 50% of SCID patients, the immunodeficiency is x-linked whereas in the other half the deficiency is autosomal

SCID

- The *x*-linked severe SCID is due to a defect in the gamma-chain of IL-2 also shared by IL-4, -7, -11 and 15, all of which are involved in lymphocyte proliferation and/or differentiation.
- The autosomal SCIDs arise primarily from defects in adenosine deaminase (ADA) or purine nucleoside phosphorylase (PNP) genes which results is accumulation of dATP or dGTP, respectively, and cause toxicity to lymphoid stem cells
- Other genetic defects leading to SCID include those for RAG1, RAG2 and IL-7-alpha

- SCID patients should not get live vaccines
- Will be cured by bone marrow transplantations / genetherapy

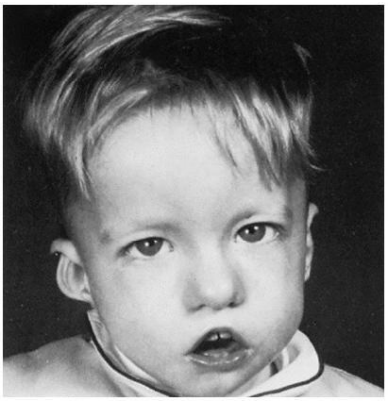
SCID



SCID

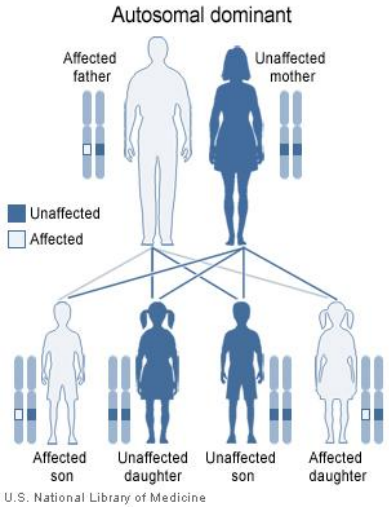
Disorders of T cells

- T cell disorders affect both cell-mediated and humoral immunity making the patient susceptible to viral, protozoal and fungal infections. Even measels vaccine is also fatal in these case
- Digeorge's syndrome
  - The most clearly defined T-cell immunodeficiency and is also known as congenital thymic aplasia/hypoplasia, or immunodeficiency with hypoparathyroidism.
  - The syndrome is associated with hypoparathyroidism, congenital heart disease, low set notched ears and fish shaped mouth

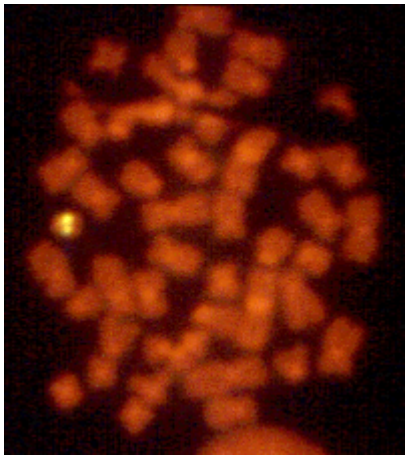


Disorders of T cells

- A thymic graft taken from an early fetus (13 - 14 weeks of gestation) can be used for treatment. Older grafts may result in GVH reaction
- DiGeorge syndrome is autosomal dominant and is caused by a deletion in chromosome 22.



In DiGeorge's syndrome, 22q11.2 deletion is inherited in an autosomal dominant pattern



Deletion of genes in DiGeorge syndrome can be visualized by a fluorescent signal on only one of the two copies of chromosome 22

Disorders of T cells

Ataxia-telangiectasia

Ataxia-telangiectasia is a deficiency of T cells associated with a lack of coordination of movement (ataxis) and dilation of small blood vessels of the facial area (telangiectasis). T-cells and their functions are reduced to various degrees. B cell numbers and IgM concentrations are normal to low. IgG is often reduced and IgA is considerably reduced (in 70% of the cases). There is a high incidence of malignancy, particularly leukemias, in these patients. The defects arise from a breakage in chromosome 14 at the site of TCR and immuinoglobulin heavy chain genes.

Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome syndrome is associated with normal T cell numbers with reduced functions, which get progressively worse. IgM concentrations are reduced but IgG levels are normal. Both IgA and IgE levels are elevated. Boys with this syndrome develop severe eczema, petechia (due to platelet defect and thrombocytopenia). They respond poorly to polysaccharide antigens and are prone to pyogenic infection. Wiskott-Aldrich syndrome is an X-linked disorder (figure 4) due to defect in a cytoskeletal glycoprotein, CD43.

MHC deficiency (Bare leukocyte syndrome)

A number of cases of immunodeficiency have been described in which there is a defect in the MHC class II transactivator (CIITA) protein gene, which results in a lack of class II MHC molecules on their APC. Since the positive selection of CD4 cells in the thymus depends on the presence of these MHC molecules, these patients have fewer CD4 cells and are infection prone. There are also individuals who have a defect in their transport associated protein (TAP) gene and hence do not express the class I MHC molecules and consequently are deficient in $CD8^+$ T cells.

Disorders of B cells

X-linked infantile hypogammaglobulinemia

X-linked hypogammaglobulinemia, also referred to as Bruton's hypoglobulinemia or agammaglobulinemia, is the most severe hypogammaglobulinemia in which B cell numbers and all immunoglobulin levels are very low. The patients have failure of B-cell maturation associated with a defective B cell tyrosine kinase (*btk*) gene. Thus, B cells exist as pre-B cells with H chains but not L chains rearranged. Diagnosis is based on enumeration of B cells and immunoglobulin measurement. Patients have no immunoglobulins and suffer from recurrent bacterial infections.

Transient hypogammaglobulinemia

Children, at birth, have IgG levels comparable to that of the mother. Because the half life of IgG is about 30 days, its level gradually declines, but by three months of age normal infants begin to synthesize their own IgG. In some infants, however, IgG synthesis may not begin until they are 2 to 3 years old. This delay has been attributed to poor T cell help. This results in a transient deficiency of IgG which can be treated with gamma-globulin.

Common variable hypogammaglobulinemia (Late onset hypogammaglobulinemia)

These individuals have deficiencies of IgG and IgA in the 2nd or 3rd decade of their life because B cells fail to differentiate into plasma cells. These patients are susceptible to a variety of pyogenic bacteria and intestinal protozoa. They should be treated with specially prepared gamma-globulin for intravenous use.

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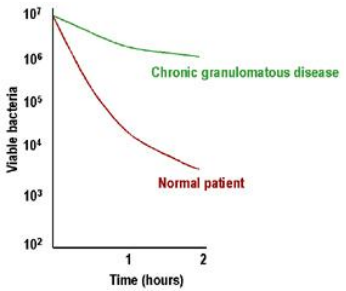
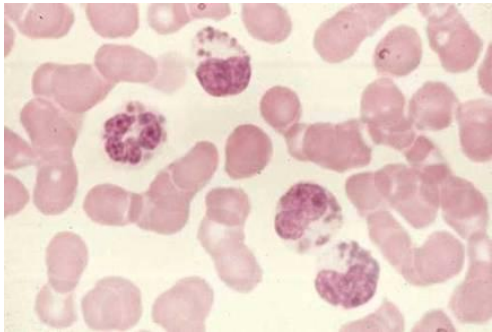
Deficiency in non specific immunity

- Primary immunodeficiencies of the non-specific immune system include defects in phagocytic and NK cells and the complement system.
- **Chronic granulomatous disease (CGD)**
- CGD is characterized by marked lymphadenopathy, hepato-splenomegaly and chronic draining lymph nodes. Leukocytes have poor intracellular killing (figure 5) and low respiratory burst. In majority of these patients, the deficiency is due to a defect in NADPH oxidase (cytochrome b_{558} : gp91^{phox}, or rarely gp22^{phox}) or other cofactor proteins (gp47^{phox}, gp67^{phox}) that participate in phagocytic respiratory burst. These patients can be diagnosed on the basis of poor Nitroblue tetrazolium (NBT) reduction which is a measure of respiratory burst. Interferon-gamma therapy has been successful.



Deficiency in non specific immunity

- **Leukocyte Adhesion Deficiency**
  In this disease, T cells and macrophages lack the complement receptor CR3 due to a defect in CD11 or CD18 peptides and consequently they cannot respond to C3b opsonin. Alternatively there may a defect in integrin molecules, LFA-1 or mac-1 arising from defective CD11a or CD11b peptides, respectively. These molecules are involved in diapedisis (emigration of leucocytes across the endothelium.)and hence defective neutrophils cannot respond effectively to chemotactic signals. Treatment is with bone marrow (devoid of T cells and MHC-matched) transplantation or gene therapy.
- **Chediak-Higashi syndrome**
  Chedial – higashi syndrome is marked by reduced (slower rate) intracellular killing and chemotactic movement accompanied by inability of phagosome and lysosome fusion and proteinase deficiency. Giant lysosomes (intracellular granules) are often seen (figure). The respiratory burst is normal.



Disorders of complement system

- **Disorders of complement system**
  Complement abnormalities also lead to increased susceptibility to infections. There are genetic deficiencies of various components of complement system, the most serious of which is the C3 deficiency which may arise from low C3 synthesis or deficiency in factor I or factor H.

Secondary immunodeficiencies

- **Also called acquired immunodeficiencies**

- **Immunodeficiencies associated with infections**
  Bacterial, viral, protozoan, helminthic and fungal infections may lead to B cell, T cell, PMN and macrophage deficiencies. Most prominent among these is acquired immunodeficiency syndrome (AIDS). Secondary immunodeficiencies are also seen in malignancies.

Secondary immunodeficiencies

- **Immunodeficiencies associated with aging**
  - These include a progressive decrease in thymic cortex, hypo-cellularity of and reduction in the size of thymus, a decrease in suppressor cell function and hence an increase in auto-reactivity, a decrease in CD4 cells functions. By contrast B cells functions may be somewhat elevated.

Secondary immunodeficiencies

- **Immunodeficiencies associated with malignancies and other diseases**
  - B cell deficiencies have been noted in multiple myeloma, Waldenstrom's macroglobulinemia, chronic lymphocytic leukemia and well differentiated lymphomas.
  - Hodgkin's disease and advanced solid tumors are associated with impaired T-cell functions. Most chemotherapeutic agents used for treatment of malignancies are also immunosuppressive.
  - Other conditions in which secondary immunodeficiencies occur are sickle cell anemia, diabetes mellitus, protein calorie malnutrition, burns, alcoholic cirrhosis, rheumatoid arthritis, renal malfunction, *etc*.