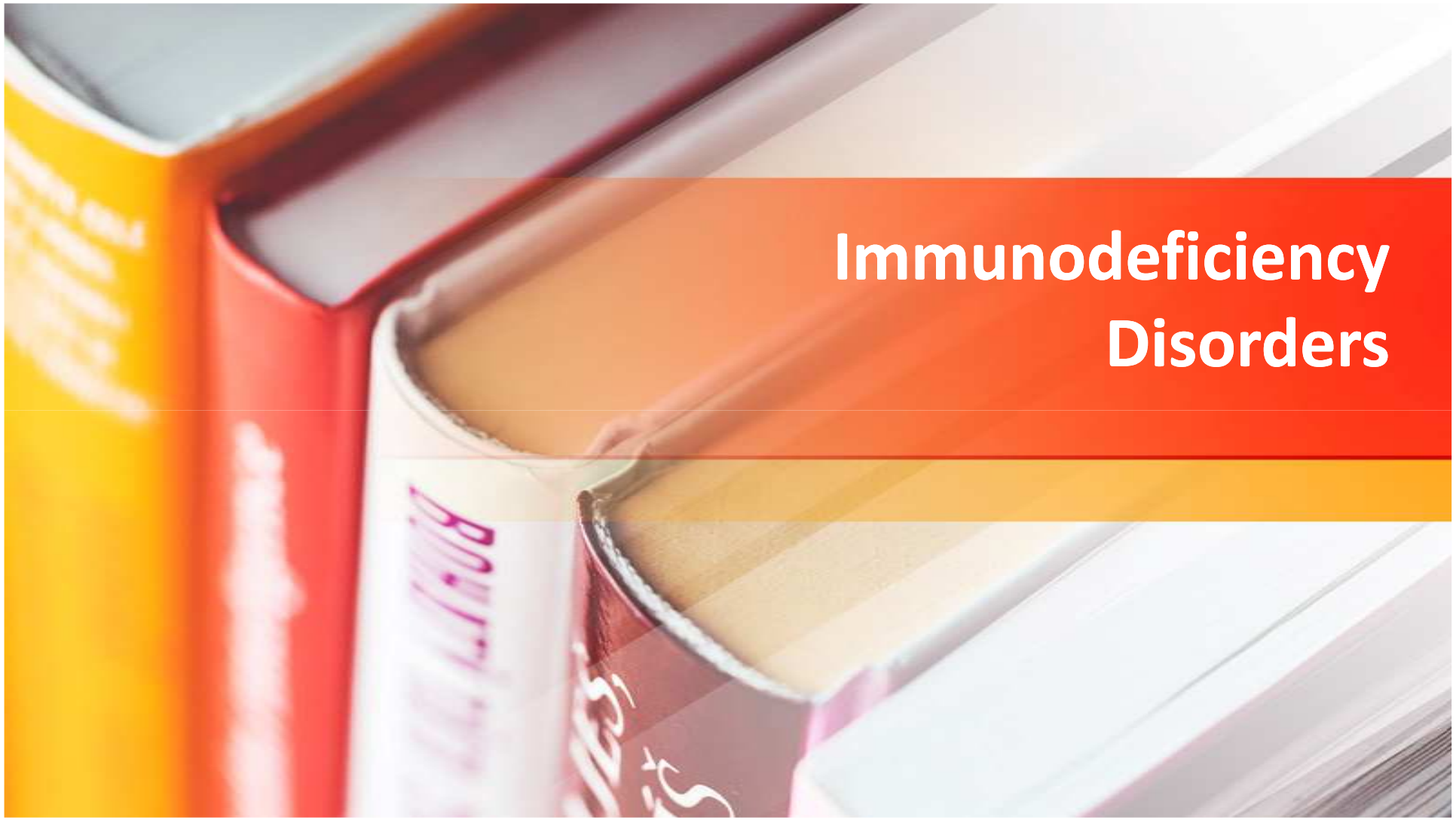

Immunodeficiency Disorders

Learning objectives

By the end of this session student should be able to know

- Primary immunodeficiency and
- Secondary immunodeficiency diseases.

DEFINITION AND CLASSIFICATION

- Immunodeficiency - state where the defence mechanisms of the body are impaired, leading to enhanced susceptibility to microbial infections as well as to certain forms of cancer.
- Immunodeficiency diseases are broadly classified as:
  - Primary immunodeficiency
  - Secondary immunodeficiency

PRIMARY IMMUNODEFICIENCY DISEASES

Humoral immunodeficiency (B cell defects)	
1	Bruton disease (X-linked agammaglobulinemia)
2	Common variable immunodeficiency
3	Isolated IgA deficiency
4	Hyper-IgM syndrome
5	Transient hypogammaglobulinemia of infancy
Cellular immunodeficiencies (T cell defects)	
1	DiGeorge syndrome (Thymic hypoplasia)
2	Chronic mucocutaneous candidiasis
3	Purine nucleoside phosphorylase (PNP) deficiency

Combined immunodeficiencies (B and T cell defects)	
1	Severe combined immunodeficiencies • Cytokine receptor mutation • Adenosine deaminase (ADA) deficiency
2	Wiskott-Aldrich syndrome
3	Ataxia telangiectasia
4	Nezelof syndrome

PRIMARY IMMUNODEFICIENCY DISEASES

Disorders of phagocytosis	
1	Chronic granulomatous disease
2	Myeloperoxidase deficiency
3	Chediak-Higashi syndrome
4	Leukocyte adhesion deficiency
5	Lazy leukocyte syndrome
6	Job's syndrome or Hyper-IgE syndrome
7	Tuftsin deficiency
8	Shwachman's disease
Disorders of complement*	
1	Complement component deficiencies
2	Complement regulatory protein deficiencies

Infections in Immunodeficiencies

Pathogen Type	T-Cell Defect	B-Cell Defect	Granulocyte Defect	Complement Defect
Bacteria	Bacterial sepsis	Streptococci, Staphylococci, Haemophilus influenzae	Staphylococci, Pseudomonas Nocardia	Neisseria, Other pyogenic infections
Viruses	Cytomegalovirus, Epstein-Barr virus, Severe varicella, Chronic infections with respiratory and intestinal viruses	Enterovirus encephalitis	-	

Infections in Immunodeficiencies

Pathogen Type	T-Cell Defect	B-Cell Defect	Granulocyte Defect	Complement Defect
Fungi	Candida, Pneumocystis jirovecii	-	Candida, Aspergillus	Neisseria, Other pyogenic infections
Parasites	-	Giardiasis	-	
Special features	Aggressive disease with opportunistic pathogens, failure to clear infections	Recurrent sinopulmonary infections, Sepsis, chronic meningitis	-	

Bruton disease (X-linked agammaglobulinemia)

- Failure of pre-B cells to differentiate into immature B cells in the bone marrow.
- Due to absence of an enzyme called *Bruton's tyrosine kinase (*transformation of pre-B cell into immature B cell) → Total absence of B cells and plasma cells in the circulation.
- Pre-B cells are found in normal numbers in bone marrow and the T-cell-mediated responses are also normal.
- Cytoplasm of pre B cell may have incomplete immunoglobulins.

Bruton disease (X-linked agammaglobulinemia)

- X linked, primarily in males; nevertheless, sporadic cases have been described in females.
- Secondary infections are seen after 6 months of age, when maternal antibodies are depleted.
  - Recurrent bacterial infections (e.g., *Haemophilus influenzae, Streptococcus pneumoniae, or Staphylococcus aureus*) leading to acute and chronic pharyngitis, sinusitis, otitis media, bronchitis, and pneumonia.
  - Viruses that are cleared by neutralizing antibodies- e.g. enteroviruses
  - Parasites which are usually resisted by secretory IgA- e.g. *Giardia lamblia.*
- Autoimmune diseases (such as SLE and dermatomyositis) also occur in up to 20% of cases.

Common Variable Immunodeficiency

- Heterogeneous group of both sporadic and inherited forms of the disease.
- Hypogammaglobulinemia, increased susceptibility to infection, autoimmune disorders (hemolytic anemia, pernicious anemia), as well as lymphoid tumors.

Common Variable Immunodeficiency

- The clinical manifestations are superficially similar to those of Bruton diseases; but differ in the following aspects:
  - Both sexes are affected equally
  - Onset of symptoms is much later, in the second or third decade of life.
  - B cell development defect.
  - Diagnosis is usually one of exclusion (after other causes of immunodeficiency are ruled out); the basis of the immunoglobulin deficiency is variable (hence the name).
  - Intrinsic B-cell defects, deficient T-cell help, or excessive T-cell suppressor activity.

Isolated IgA deficiency

- Most common, affects about 1 in 700 white individuals.
- Weakened mucosal defences due to IgA deficiency predispose patients to recurrent sinopulmonary infections and diarrhea.
- Significant (but unexplained) association with autoimmune diseases.

Isolated IgA deficiency

- Pathogenesis:
  - Block in the terminal differentiation of IgA-secreting B cells to plasma cells (due to altered T-cell production of cytokines or intrinsic B-cell defect).
  - The levels of other immunoglobulins are usually normal or even excess.

Hyper-IgM syndrome

- X-linked disorder - due to a defect in *isotype class switch over* of B cells.
- Class switch over depends upon two signals generated by helper T cells which influence the B cells-
  - T_H cell induced cytokine
  - Signal generated due to direct contact through the interaction of CD40 molecules on B cells with CD40 ligand (CD40L) on T_H cells.

Hyper-IgM syndrome

- Mutations in either CD40L or CD40 genes; prevent the T- and B-cell interaction – blocks the class switch over → lack of synthesis of other classes of antibodies.
- Deficiency of IgG - defect in opsonization and complement activation (predisposes to recurrent pyogenic infections) and IgA deficiency leads to increased recurrent sinopulmonary infections and diarrhea.

Hyper-IgM syndrome

- Excess IgM antibodies → autoimmune hemolytic anemia, thrombocytopenia, or neutropenia.
- Patients with defect in CD40L are more susceptible to *Pneumocystis jirovecii* infection.
- X linked- Hyper-IgM syndrome is X-linked in 70% of the cases affecting males; in the remaining patients, the precise mutations have not been fully characterized.

Transient Hypogammaglobulinemia of Infancy

- Occurs due to an abnormal delay in the initiation of synthesis IgG (or some time IgA or IgM).
- Some infants IgG synthesis is delayed (usually starts by 2 mo) leading to defect in opsonization or complement activation resulting in recurrent otitis media and respiratory infections;
- Spontaneous recovery occurs usually by 18-24 months of age.
- Interestingly, these infants show a normal antibody response against vaccines.

DiGeorge syndrome (thymic aplasia)

- Results from a congenital defect in thymic development leading to defect in T-cell maturation.
- Infants are extremely vulnerable to viral, fungal, intracellular bacterial and protozoan infections.
- Pathogenesis- In 90% of cases, there occurs a deletion affecting chromosome 22q11 which leads to developmental malformation affecting the third and fourth pharyngeal pouches in embryonic life.
- Thymus, parathyroid glands, and portions of the face and aortic arch become defective.

DiGeorge syndrome (thymic aplasia)

- There may be associated:
  - Parathyroid gland hypoplasia resulting in neonatal tetany and hypocalcemia
  - Anomalies of the heart and the great vessels (Fallot's Tetralogy).
  - Characteristic facial appearance
- Treatment- Thymus transplantation has been found to be successful in restoration of immune function. In others (with partial defects), immunity may improve spontaneously with age.

Chronic mucocutaneous candidiasis

- Represents an impaired cell-mediated immunity against *Candida albicans* leads to superficial infections of the skin, mucous membranes, and nails.
- Do not show increased susceptibility to other infections but often associated with endocrinopathies and autoimmune disorders.
- Transfer factor therapy, along with amphotericin B has been reported to be effective.

Purine nucleoside phosphorylase deficiency

- Autosomal recessive disorder (chromosome 14),
- Characterized by deficiency of an enzyme of purine metabolism called purine nucleoside phosphorylase (PNP).
- PNP is a key enzyme required for purine degradation; catalyzes the conversion of guanosine to hypoxanthine.
- Deficiency leads to elevated deoxy-GTP levels resulting in T-cell toxicity. However, B cells are not affected.
- T cell depletion predisposes to increased susceptibility to infection and autoimmune disorders.

Severe combined immunodeficiencies (SCID)

- Represents groups of genetically distinct syndromes; all having in common, defects in both humoral and cell-mediated immune responses.
- ***Types of genetic defect in SCID include:***
  - Mutation in cytokine receptor - Approximately 50-60% of the cases of SCID are X-linked (seen in males).
  - Results from mutations in the gene encoding the common γ chain shared by the cytokine receptors for IL-7 and others (IL-2, IL-4, IL-9, and IL-15).
  - Defective IL-7 receptor - defect in survival and expansion of immature B- and T-cell precursors in the bone marrow.
  - Defect in IL-15 receptor - deficiency of NK cell.

Severe combined immunodeficiencies (SCID)

- *Adenosine deaminase (ADA)* deficiency - Most common, ADA deficiency leads to accumulation of deoxyadenosine which is toxic to rapidly dividing immature T lymphocytes.
- *RAG Mutation*- Recombinase-activating genes (RAG) defect blocks the development of T and B cells.

Severe combined immunodeficiencies (SCID)

- *Jak3 mutation*- Jak3, an intracellular kinase mutation is another way of blocking the cytokine receptor signalling.
- *Class II MHC deficiency*-Mutations that impair the expression of class II MHC molecules prevent the development of CD4+ T cells. This condition is also called the *bare lymphocyte syndrome.*

Severe combined immunodeficiencies (SCID)

- ***Infections- A***ffected infants are susceptible to severe recurrent infections by a wide array of pathogens, including *Candida, Pneumocystis*, cytomegalovirus, and *Pseudomonas.*
- ***Treatment-*** Bone marrow transplantation. Gene therapy replacing the mutated genes has been successful in X linked cases.

Wiskott-Aldrich syndrome (WAS)

- X-linked recessive disease.
- Characterized by immunodeficiency with thrombocytopenia, eczema.
- Severity of WAS increases with age.
- First manifests itself by defective responses to bacterial polysaccharides and by lower IgM levels.
  - IgG levels are usually normal.
  - Paradoxically the levels of IgA and IgE are often elevated.
- Other T and B cell responses are normal initially, but with increase of age, there are recurrent bacterial infections and a gradual loss of humoral and cellular responses.

Wiskott-Aldrich syndrome (WAS)

- Prone to develop non-Hodgkin B-cell lymphomas.
- Bloody diarrhea secondary to thrombocytopenia.
- ***Pathogenesis:***
  - Genetic defect is due to a mutation in the gene encoding Wiskott-Aldrich syndrome protein (WASP) present in precursor lymphoid cells of bone marrow.
  - Cytoskeletal glycoprotein (sialophorin or CD43), required for actin polymerization.

Ataxia Telangiectasia

- Difficulty in maintaining balance while walking (cerebellar ataxia)
- Appearance of broken capillaries (telangiectasia) in the eyes and choreoathetoid movements (usually noticed in infancy).
- Deficiency of IgA and sometimes IgE.
- Profound sinopulmonary infections
- Primary defect - kinase involved in regulation of the cell cycle.

Nezelof syndrome

- Autosomal recessive.
- Cellular immunodeficiency resulting from thymus hypoplasia.
- In some patients, B cells are normal, whereas in others a B-cell deficiency is secondary to the T-cell defect.
- Affected individuals suffer from chronic diarrhea, viral and fungal infections, and a general failure to thrive.

DISORDERS OF PHAGOCYTOSIS
Chronic granulomatous disease (CGD)

- **Pathogenesis:**
  - Involves inherited defects in the gene encoding components of oxidase system.
  - E.g. Nicotinamide adenine dinucleotide phosphate (NADP) oxidase of phagocyte which breaks down hydrogen peroxide to generate free oxygen radicals (O_2^-) that are involved in microbial killing.
  - Decreased oxidative burst which predisposes to recurrent bacterial infections. CGD is a genetic disease that runs in family in two forms:
- X linked form (more common, 70%) - membrane component of phagocyte oxidase is defective.
- Autosomal recessive form- cytoplasmic component of phagocyte oxidase is defective.

DISORDERS OF PHAGOCYTOSIS
Chronic granulomatous disease (CGD)

- **Manifestations-**
  - Bacteria involved in the recurrent infections are catalase positive; pyogenic pathogens such as staphylococci, *Pseudomonas* and coliforms.
  - Excessive inflammatory reactions that result in gingivitis, swollen lymph nodes, and non-malignant granulomas (lumpy subcutaneous cell masses).
  - Nitroblue tetrazolium reduction test (NBT) is used for screening to detect deficiency of NADPH oxidase activity.

Myeloperoxidase deficiency

- Common genetic disorder characterized by deficiency in either quantity or function, of myeloperoxidase, an enzyme produced by neutrophils.
- Patients present with immune deficiency and recurrent infections, especially with *Candida albicans*.

Chediak-Higashi syndrome

- Autosomal recessive disease.
- Defective fusion of phagosomes and lysosomes in phagocytes which leads to increased susceptibility to recurrent and severe pyogenic infections.
- Abnormalities in melanocytes leading to albinism (lack of skin and eye pigment)
- Abnormalities in cells of the nervous system (associated with nerve defects), and
- Platelets abnormalities, causing bleeding disorders.
- Aggressive but non-malignant infiltration of organs by lymphoid cells.

Chediak-Higashi syndrome

- **Pathogenesis:**
  - *Mutation in a protein called LYST (r*egulate lysosomal trafficking).
  - Impairs the targeting of proteins to secretory lysosomes, which makes them unable to lyse bacteria.
  - Phagocytes from patients with this immune defect contain *giant granules* but do not have the ability to kill bacteria.

Leukocyte adhesion deficiency (LAD)

- Autosomal recessive disorder.
- Defect in the adhesion of leukocytes which results in poor leukocyte chemotaxis particularly neutrophil, inability to form pus and neutrophilia. Predisposes to various infections
  - **Leukocyte adhesion deficiency 1**- Mutations in β2 integrin subunit (CD18), of the leukocyte cell adhesion molecule (chromosome 21).
  - **Leukocyte adhesion deficiency 2**- Mutations in fucosyltransferase required for synthesis of sialylated oligosaccharide which is a selectin ligand.

Lazy leukocyte syndrome

- Idiopathic condition due to defect in neutrophil chemotaxis.
- Increased pyogenic infections such as gingivitis, abscess formation, pneumonia and neutropenia.

Job's Syndrome (Hyper IgE syndrome)

- Characterized by eczema, recurrent staphylococcal skin abscesses, recurrent lung infections (pneumatocele), eosinophilia and high serum levels of IgE.
- Defect in neutrophil chemotaxis.
- Most cases are sporadic, but some familial cases of Hyper IgE Syndrome have been reported, with either an autosomal dominant (AD) or autosomal recessive (AR) mode of inheritance.
  - Autosomal dominant cases are linked to mutations in the STAT3 gene
  - Autosomal recessive cases are due to mutations in DOCK8 gene

Tuftsin deficiency

- Tuftsin is a tetrapeptide (Thr-Lys-Pro-Arg) produced primarily in the spleen, by the cleavage of the Fc-portion of the heavy chain of IgG.
- Stimulates the bactericidal activity of phagocytes.
- Tuftsin deficiency, either hereditary or following splenectomy.
- Increased susceptibility to certain capsulated organisms such as *H. influenzae*, pneumococci, and meningococci.

Shwachman's syndrome

- Rare congenital disorder characterized by neutropenia, exocrine pancreatic insufficiency, bone marrow dysfunction, skeletal abnormalities, and short stature.

SECONDARY IMMUNODEFICIENCIES

- Secondary effects of other diseases such as-
  - Malnutrition (due to inadequate immunoglobulin synthesis)
  - Aging (suppression of immune system with age)
  - Patients with several infections that supresses immune system causing lymphocyte depletion, e.g. HIV (human immunodeficiency virus) infection.
  - Underlying cancers (particularly those of the bone marrow and blood cells (leukemia, lymphoma, multiple myeloma),
  - Underlying proteinuric renal diseases– leads to loss of immunoglobulins
  - Sarcoidosis
  - Patients on immunosuppressive medications
  - Patients receiving chemotherapy or radiation therapy for malignancy