MED441
KING SAUD UNIVERSITY

Immunodeficiency disorders

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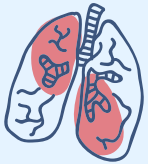
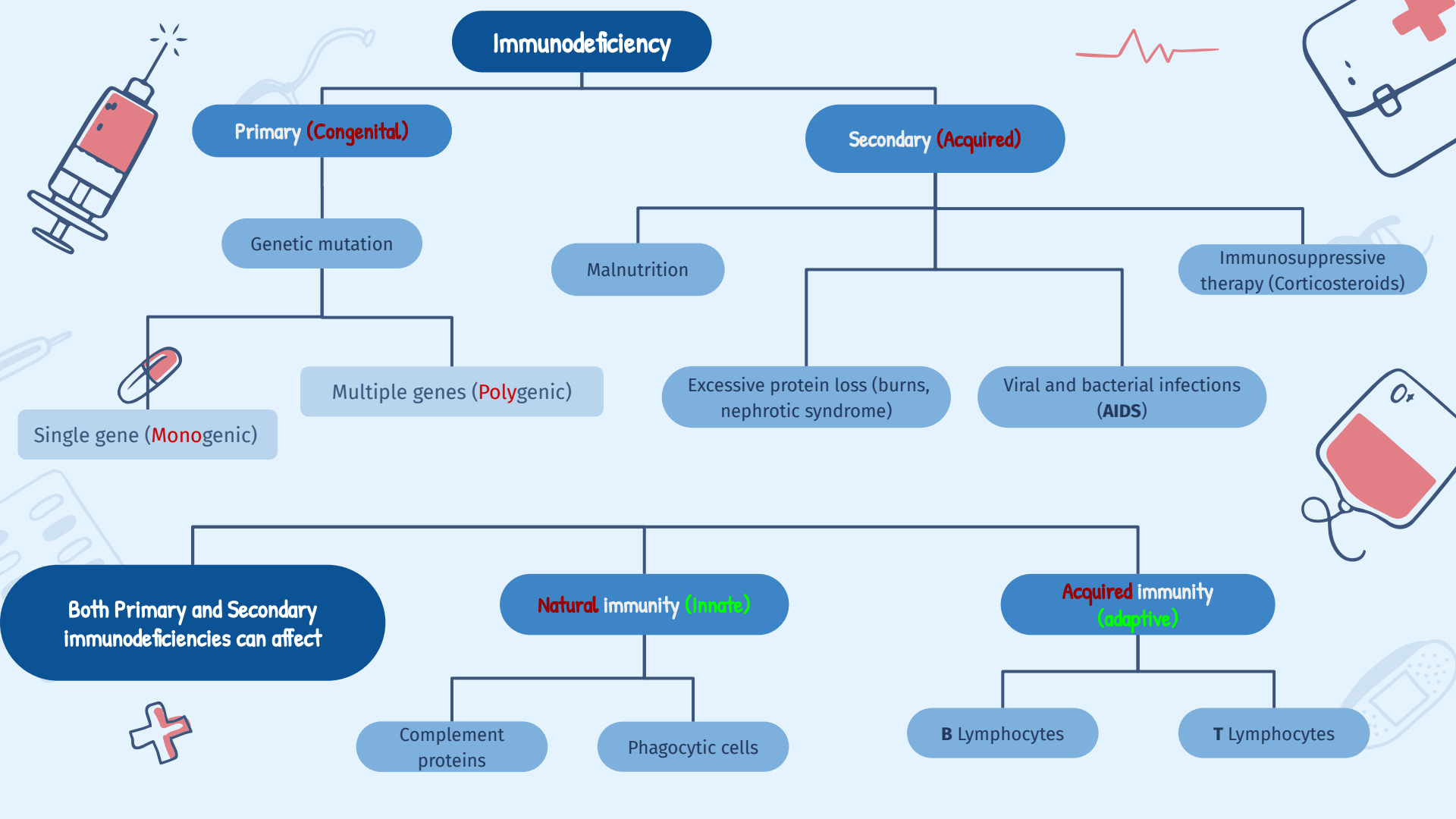
Colour index:
Main text
IMPORTANT
Drs notes
Females slides
Male slides
Extra

Foundation block — Editing file

Objectives:



- Identify that immunodeficiency is due to a defect in the immune function
- Describe the classification of immunodeficiency
- Explain the presentations of different types of immunodeficiencies (e.g. recurrent infections)
- Understand the varieties of immune system deficiencies involving defects in: T cells, B cells, phagocytes and complement
- Know the laboratory investigations for immunodeficiency disorders


Immunodeficiency
Primary (Congenital)
Secondary (Acquired)
Genetic mutation
Malnutrition
Immunosuppressive therapy (Corticosteroids)
Single gene (Monogenic)
Multiple genes (Polygenic)
Excessive protein loss (burns, nephrotic syndrome)
Viral and bacterial infections (AIDS)
Both Primary and Secondary immunodeficiencies can affect
Natural immunity (Innate)
Acquired immunity (adaptive)
Complement proteins
Phagocytic cells
B Lymphocytes
T Lymphocytes

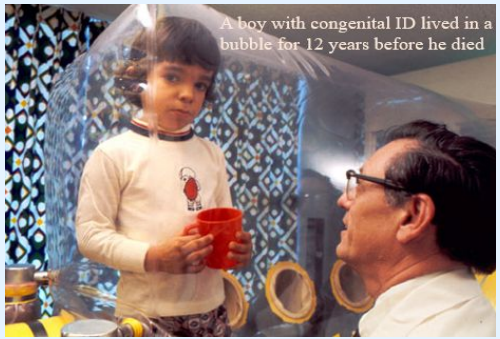
What is Immunodeficiency?

Immunodeficiency is a state in which the ability of the immune system to fight infectious disease is compromised or entirely absent

A person who has an immunodeficiency is called 'Immunocompromised'

Caused by opportunistic microbes

Opportunistic microbes: usually non- pathogenic microbes, but they become pathogenic when the host is weak and immunocompromised.



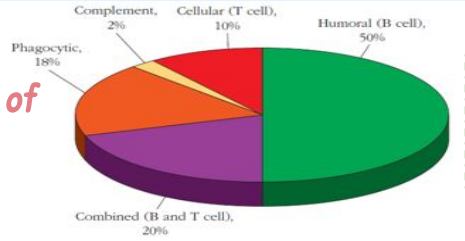
Immunodeficiency (ID) is considered present when infections are:

01 Frequent and severe

02 Resistant to antimicrobial therapy

03

Distribution of primary ID



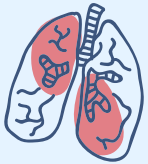
For example: defect of Humoral B cell (adaptive immunity) is the most common (50%)

Our focus for the rest of the lecture

Pattern of infections and symptoms associated with **Primary ID**

Disorder	Opportunistic infections	Other symptoms
Antibody	Sinopulmonary (pyogenic bacteria) Gastrointestinal (enterovirus, giardia)	Autoimmune diseases (autoantibodies, inflammatory bowel disease
Cell-mediated immunity	Pneumonia (pyogenic bacteria, pneumocystis carinii, viruses) Gastrointestinal (viruses), mycoses of Skin and mucous membranes (fungi)	N/A
Complement	Sepsis and other blood-borne infections (streptococci, pneumococci, neisseria)	Autoimmune diseases (systemic lupus erythematosus, glomerulonephritis
Phagocytosis	Skin abscesses, reticuloendothelial infections (staphylococci, enteric bacteria, fungi, mycobacteria)	N/A
Regulatory T cells	N/A	Autoimmune disease

T-cell Defects



- ★ It is a deletion of small piece of chromosome 22.
- ★ It is associated with impaired immune system and developmental delays.

DiGeorge Syndrome primary (Congenital Thymic Aplasia)

A congenital defect that is marked by in general:

- → Absence or underdevelopment of the Thymus gland (hypoplasia).
- → Hypoparathyroidism. They function to control the normal metabolism and the blood level of the calcium.
- → Facial abnormalities.
- → Cardiovascular abnormalities

Management of DiGeorge syndrome

Fetal thymus tissue graft transplant (14 weeks old)

We can also treat Calcium deficiency to avoid epilepsy.

Features of DiGeorge syndrome

Children may present with tetany

In the complete form:

- → Extreme susceptibility to viral protozoal, and fungal infections.
- → Profound depression of T-cell numbers.
- → Absence of T-cell responses.

B-Cell Defects (Gammaglobulinemia)

Team 439:

Why? Because the T cells are not affected. only B cells work in the case of bacterial infection and T cells work in cases of viral infections.

1

Patients with B-cell defects are subject to recurrent bacterial infection BUT display normal immunity to most viral and fungal infections.

2

Diverse spectrum ranging from:

- Complete absence of **B**-cells and plasma cells.
- Low or absent immunoglobulins
- Selective absence of certain immunoglobulins.

3

Genetic Transmission

- Autosomal recessive.
- X-linked disease:
  - Females : carriers (normal).
  - Males : manifest the disease.

Management of immunoglobulin deficiencies:

Periodic intravenous immunoglobulin (IVIG) reduces infectious complications.

B-cell Defects (Gammaglobulinaemias)

X-linked agammaglobulinemia (XLA) or Bruton's hypogammaglobulinemia (Congenital disease)

- The most common type, 80% to 90%.
- Defect in Bruton Tyrosine Kinase **(BTK)**.
- The defect involves a block in maturation of pre- B- cells to mature B-cells in bone marrow.

Agammaglobulinemia is a group of inherited immune deficiencies characterized by a low concentration of antibodies in the blood due to the lack of particular lymphocytes (B) in the blood and lymph

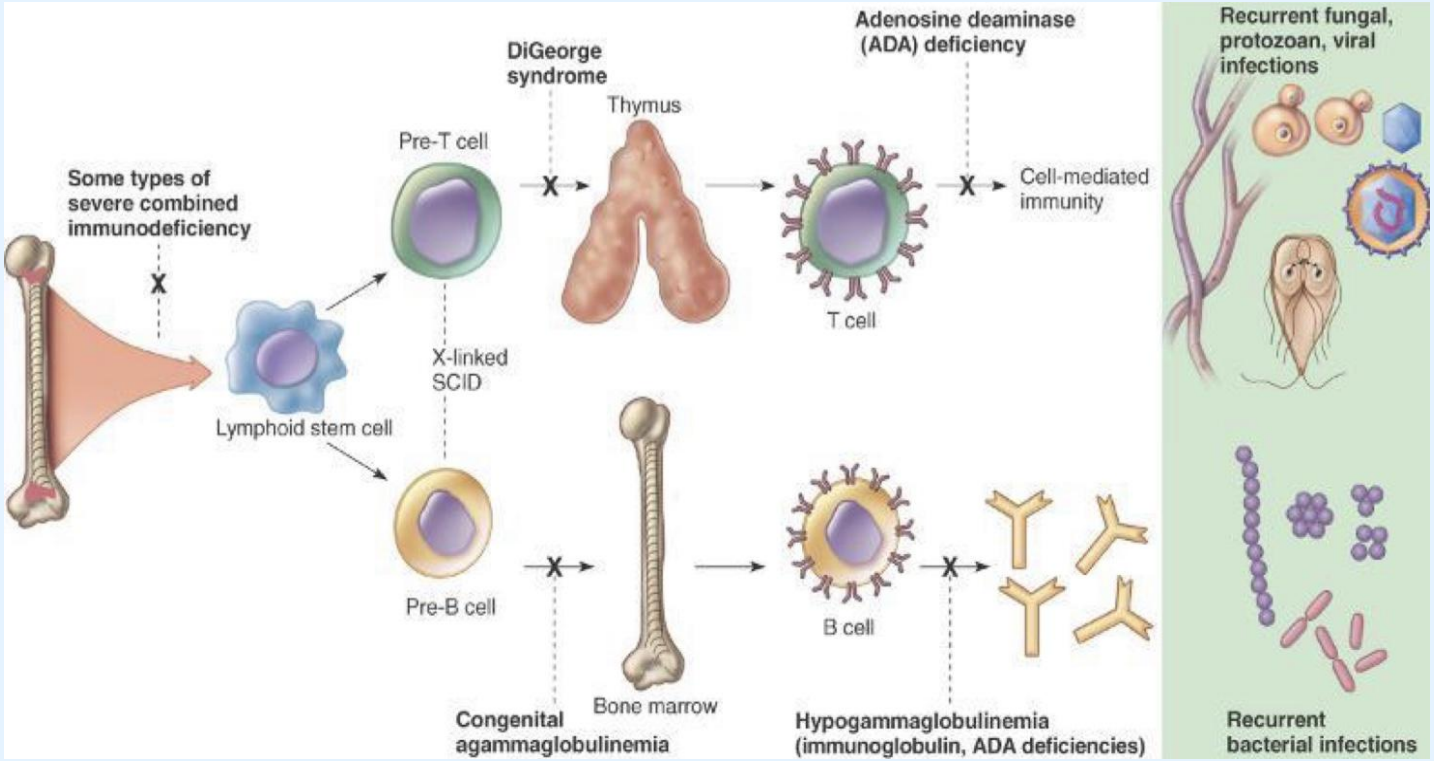
Features of XLA:

- Reduced B-cell counts to 0.1 % (normally 5%-15%)
- Absence of Immunoglobulins
- Affected children suffer from recurrent pyogenic bacterial infections

Selective immunoglobulin deficiency rare (Congenital disease)

- IgA deficiency (1:700)
- Most are asymptomatic: but may have increased incidence of respiratory tract infections (R.T.I)
- Some have recurrent R.T.I and gastrointestinal tract symptoms

Summary

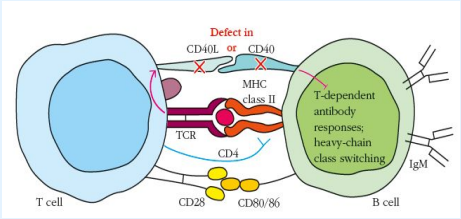

Some types of severe combined immunodeficiency
X
Lymphoid stem cell
Pre-T cell
DiGeorge syndrome
Thymus
Adenosine deaminase (ADA) deficiency
Cell-mediated immunity
T cell
X-linked SCID
Pre-B cell
Bone marrow
B cell
Congenital agammaglobulinemia
Hypogammaglobulinemia (immunoglobulin, ADA deficiencies)
Recurrent fungal, protozoan, viral infections
Recurrent bacterial infections

B-cell Defects (Gammaglobulinaemias)

X- linked hyper-IgM Syndrome (Congenital disease)

Characterized by:

- Defective CD40L/CD40 interaction B cell class switching fails.
- Variable IgM levels most frequently high.
- Low IgG, IgA & IgE. Team 439:(remember the word AGE)



Male slides

Common Variable Immunodeficiency Disorders

Disorders of unknown etiology

Characterized by:

- Presentation in childhood or later in life.
- Recurrent respiratory tract infections due to immunodeficiency.
- Reduction in the levels of one or more antibody isotype with normal B cell numbers.
- Impaired B-cell responses to antigen.

Both T and B cells defects

Severe Combined Immunodeficiency (SCID)

- Congenital
- Increased susceptibility to : viral , fungal, bacterial protozoal infectious (starting at 3 months of age) SCID found mainly in babies from 3-6 months
- causes:

Enzyme deficiencies :

1.ADA (adenosine deaminase) deficiency

-Catalyzes conversion of adenosine or deoxyadenosine to inosine or deoxyinosine , respectively (Which interferes with DNA synthesis).

only found in boys slide

2.PNP (purine phosphorylase) deficiency

-Toxic metabolites accumulate in T and B cells.

- Management :

1.Infusion of purified enzymes.

2.Gene therapy

★ Boys Slide

Both T and B cells defects

Severe Combined Immunodeficiency (SCID) Cont.

- Reticular Dysgenesis (RD)
  - Initial hematopoietic cell development is blocked by defects in the adenylate kinase 2 gene (AK2)
  - Apoptosis of myeloid and lymphoid precursors
  - Severe reductions in circulating leukocytes
  - Impairment of both innate and adaptive immunity
  - Susceptibility to infection by all types of microorganisms
  - Without aggressive treatment children die in early, infancy
- Deficiency in cytokine signaling:
  - Defects in the gene encoding for common gamma chain of the IL-2, IL-4, IL-7, IL-9.
  - IL-15 and IL-21 receptors.
  - This leads to widespread defects in B-cell , T-cell and NK-cell development. NK-cell (Natural Killing Cell)

Leukocyte defects

Quantitative defects (Related to numbers)

Congenital Agranulocytosis

other name : Kostmann's Syndrome

- Defect in the gene inducing G-CSF (Granulocyte Colony Stimulating Factor) note 439 : important for producing granulocytes (play a major role in bacterial infections)
- Features : pneumonia , otitis media , abscesses

****Note**

-patient with deficiency in the G-CSF , what's the defect ?
Quantitative congenital agranulocytosis defect

Qualitative defects (Related to function)

A) Defects in chemotaxis

Leukocyte Adhesion Deficiency

-Defect in the adhesion deficiency molecules responsible of leukocyte trafficking and migration to sites of infection

مسؤولة عن تحريك كريات الدم البيضاء
الى مكان العدوى لقتل البكتيريا

B) Defects in intracellular killing

Chronic Granulomatous Disease (CGD)

-congenital disease
-Defect in the oxidative complex responsible for producing superoxide radicals
-Neutrophils lack the "Respiratory burst" upon phagocytosis
-characterized by recurrent life-threatening and granuloma formation
These severe infection include : skin and bone infection + abscess in internal organs such as : lung , liver and brain

Go back to lecture 2 for a clear explanation on the pathways

Complement Deficiency

★ Thanks to Teams 439+438

Deficiency in	Components	Deficiency lead to
Classical pathway	C1 , C2 , C4	Immune-complex disease
Alternative pathway	Factor D Factor B	Infection with pyogenic bacteria and neisseria Spp. No immune-complex disease
MB-lectin pathway	MBL , MASP 1 , MASP 2 C2 , C4	Bacterial infections (Mainly in childhood)
C3b deposition	C3	Infection with pyogenic bacteria and neisseria Spp. Sometimes immune-complex disease
Membrane attack complex components	C5 , C6 , C7 C8 , C9	Infection with neisseria Spp. Only

**Note

-immune-complex disease caused of ? Deficiency in Classical pathway

-Patient came with infection with neisseria **only** , what's the deficient in this patient ?
Membrane attack complex components

Laboratory diagnosis of ID (Immunodeficiency)

- Complete blood Count : total & differential
- Evaluation of antibody levels and response to antigens
- T and B cells counts (Flow Cytometry)
- Measurement of Complement proteins and function (CH50)
- Assessment of Phagocytosis and respiratory burst (Oxygen Radicals)

Take Home Messages

1. Immunodeficiency may be congenital or acquired
2. It can involve any component of the immune system such as cells, antibodies, complement etc.
3. Most common presentation of immunodeficiency is recurrent infections that may be fatal due to delay in diagnosis and lack of appropriate therapy

MCQs

Q1: Excessive protein loss is an example of			
A- Primary ID	B- Secondary ID	C- Both A, C	D- None is correct
Q2: Which one of the following is the most common primary ID			
A- Complement defect	B- Cellular (T cells)	C- Humeral (B cells) defect	D- Phagocytic defect
Q3: Digeorge syndrome include the following except ?			
A- Absence of the Thymus gland (hypoplasia).	B- Hyperparathyroidism.	C- Cardiovascular abnormalities.	D- Facial abnormalities.
Q4: which one of the following is an example of T-cell defect ?			
A- Bruton's hypogammaglobulinaemia	B- CGD	C- Selective immunoglobulin deficiency	D- Digeorge syndrome

Q1- B , Q2- C , Q3-B Q4-D

MCQs

Q5: Which one is the common type in B-cell defects ?			
A- Selective immunoglobulin deficiency	B- Digeorge syndrome	C- XLA	D- X-linked hyper-IgM syndrome
Q6: A deficiency in which of the following may lead to bacterial infectious (mainly in childhood)?			
A- C3b deposition	B- alternative pathway	C- classical pathway	D- MB-lectin pathway
Q7: which one of the following is marked by pneumonia , otitis media and abscesses ?			
A- congenital agranulocytosis	B- leukocyte adhesion deficiency	C- chronic granulomatous disease	D- SCID
Q8: which one of the following is characterized by recurrent life-threatening & granuloma formation?			
A- congenital agranulocytosis	B- leukocyte adhesion deficiency	C- chronic granulomatous disease	D- SCID

Q5-C , Q6-D , Q7-A , Q8-C

Special thanks and gratitude to
Immunology Team (439)

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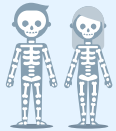

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