MEDICINE
KING SAUD UNIVERSITY

Foundation Block

Lecture Six

Immunodeficiency

IMMUNOLOGY

4 3 6 ' s T E A M W O R K

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

- **Important.**
- **Extra notes.**
- **Females notes**
- **Males notes.**

Definition:

- 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 said to be immuno-compromised.

Immunodeficiency is considered to be present when infections are:

1- Frequent and severe.

2- Caused by opportunistic microbes.

3- Resistant to antimicrobial therapy.

Classification of ID (Immunodeficiency) :

Primary (Congenital)

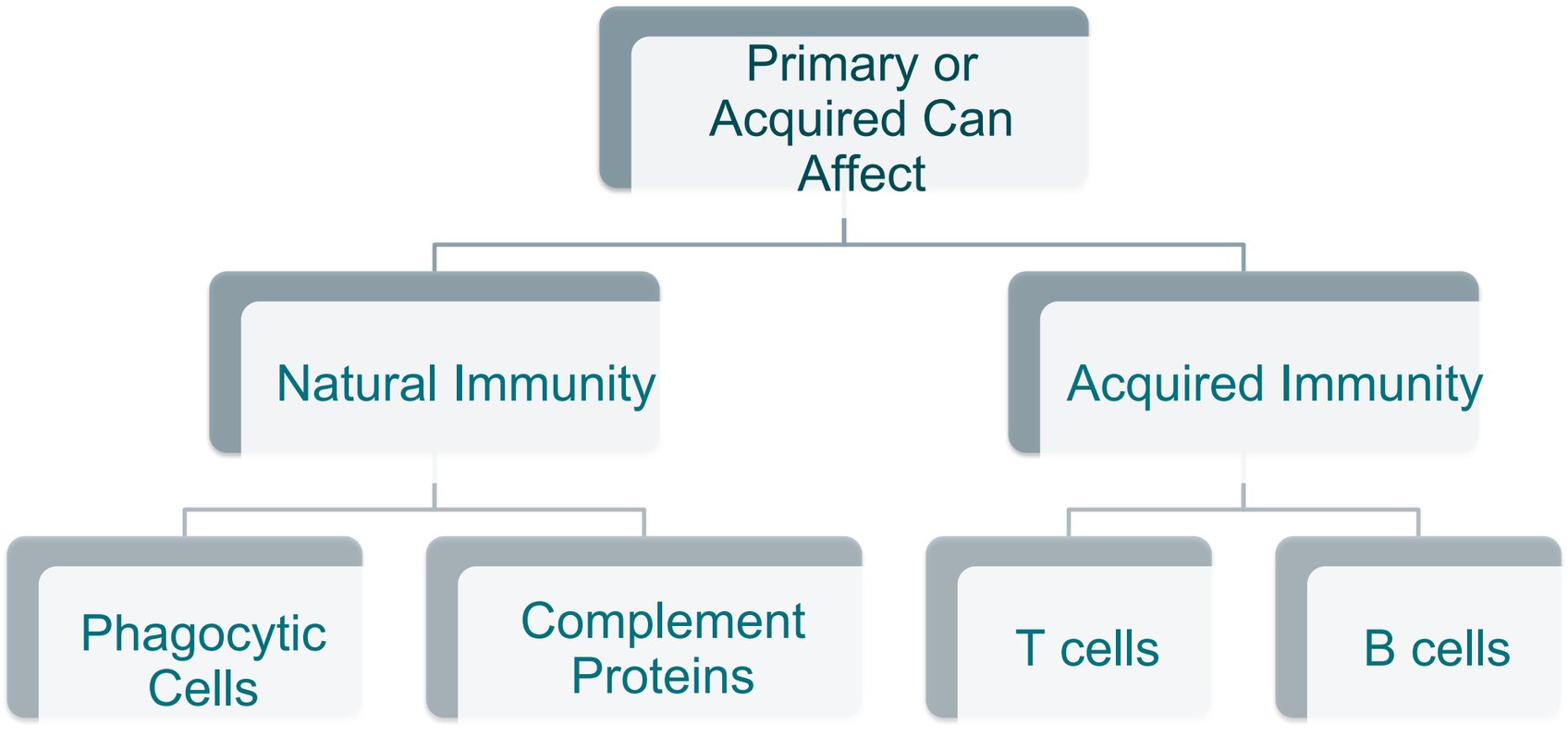
- Genetic Mutation :

  1- Monogenic (Single gene)

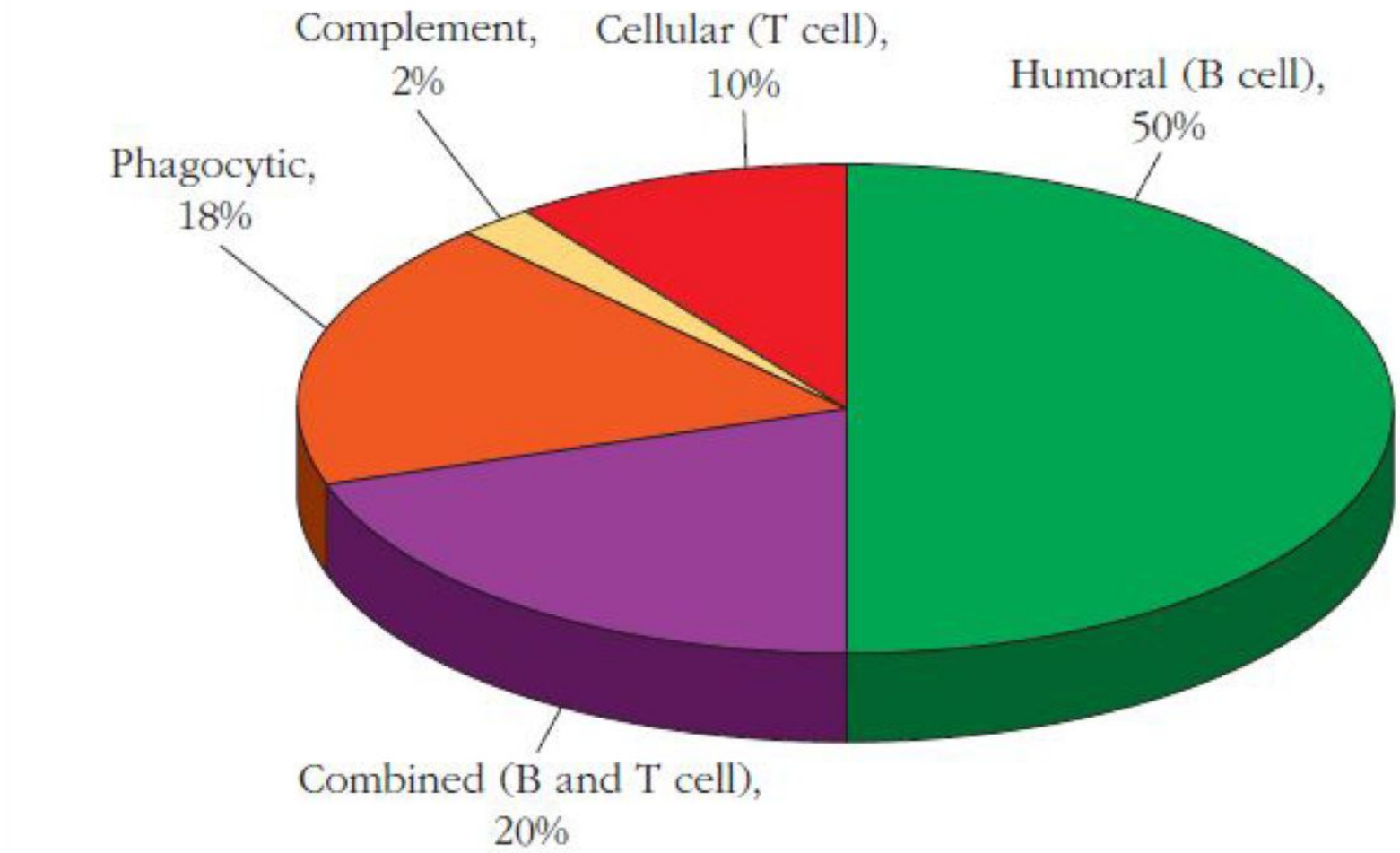
  2- Polygenic (Multiple genes)

Secondary (Acquired)

- Malnutrition
- Viral and Bacterial
- Infections (AIDS)
- Immunosuppressive Therapy (Corticosteroids)
- Excessive Proteins Loss (Burns, nephrotic syndrome)



Distribution of primary Immunodeficiencies:



Pattern of infections and symptoms associated with primary immunodeficiencies:

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

Source: Adapted from H. M. Lederman, 2000, The clinical presentation of primary immunodeficiency diseases, Clinical Focus on Primary Immune Deficiencies. *Towson, MD: Immune Deficiency Foundation* ***2****(1):1.*

T-cell defects

DiGeorge Syndrome (Congenital Thymic Aplasia)

A congenital defect that is marked by:

- - Absence or underdevelopment of the Thymus gland (hypoplasia)
- - Hypoparathyroidism
- - Facial abnormalities
- - Cardiovascular abnormalities

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

Management of DiGeorge syndrome:

Fetal thymus tissue graft (14 weeks old).

B cells defect (Gammaglobulinaemias):

Patients with B-cell defects are subject to:

Recurrent **bacterial** infections, but display the normal immunity to most **viral and fungal** infections.

Diverse spectrum ranging from:

- Complete absence of B-cells.
- Complete absence of plasma cells.
- Low or absent immunoglobulins.
- Selective absence of certain immunoglobulins.
- Genetic Transmission:
    1. Autosomal recessive.
    2. X-linked disease:
        - Females: carriers (normal)
        - Males: manifest the disease (effected) (لأن الذكر ما عنده الا اكس واحد فيتأثر بينما الأنثى لديها اثنين فتكون مجرد حاملة للمرض)

B cells defect:

Diseases:

(1) X-linked agammaglobulinaemia (XLA) or Bruton's hypogammaglobulinaemia (Congenital disease):

The most common type (80%-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.

Features of XLA:

- Reduced B-cell counts to 0.1% (normally 5%-15%).
- Absence of Immunoglobulins.
- Affected children suffer from recurrent pyogenic bacterial infections. (It appears at the age of 6-9 months in newborns)

(2) Selective immunoglobulin deficiency (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.

(3) X- linked hyper-IgM Syndrome (Congenital disease): (CD 46 ligand)

- Low **IgG, IgA & IgE**. (We use them in secondary response but in this disease they get stuck in the primary)
- Variable **IgM** levels most frequently **high**.

Management of immunoglobulin deficiencies:

Periodic intravenous immunoglobulin (IVIG) reduces infectious complications. (ننقل اميونوقلوبلنز من المتبرعين بدون تحديد ولأن الآي جي **جي** يعيش أطول مدة ٢١ يوم ننقل اميونوقلوبلنز كل ٢١يوم)

Severe Combined (T +B) Immunodeficiency (SCID) (Congenital disease):

Cause: **Enzyme deficiencies**:

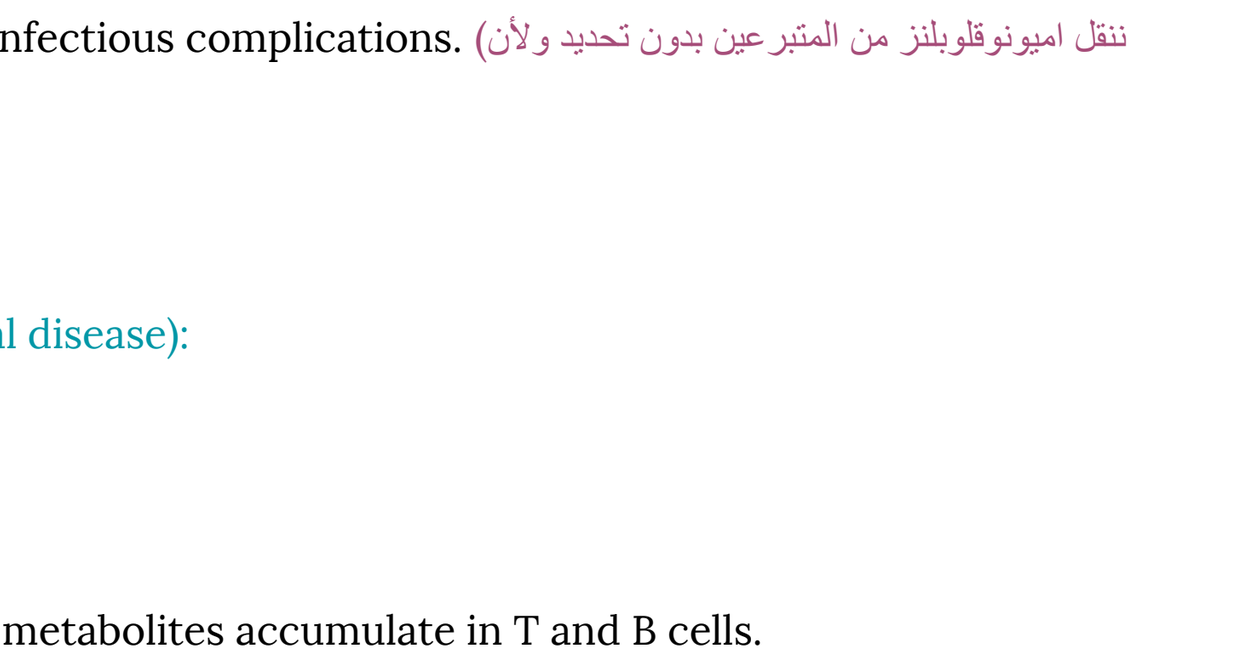
- ADA (adenosine deaminase) deficiency.
- PNP (purine phosphorylase) deficiency Toxic metabolites accumulate in T and B cells.

Features of SCID:

Increased susceptibility to: viral, fungal, bacterial protozoal infections (starting at 3 months of age)

Management of SCID:

- Infusion of purified enzymes.
- Gene therapy. (Replacing the muted gene with normal gene)



*A boy with congenital ID lived in a bubble for 12 years before he died.

Leukocyte defects:

Leukocyte defects (Innate immunity)

Quantitative
(مشكلة بالعدد)

Congenital agranulocytosis:

Defect in the gene inducing G-CSF (granulocyte colony stimulating factor).

Features:

Pneumonia, otitis media, abscesses

Qualitative
(Natural number but they're not working well)

- Defect in chemotaxis:

Leukocyte adhesion deficiency (LAD)

(These patients won't have puss because it's composed of neutrophils)

Defect:

in the adhesion molecules responsible of leukocyte trafficking and migration to sites of infection.

- Defect in intracellular Killing:

Chronic granulomatous disease

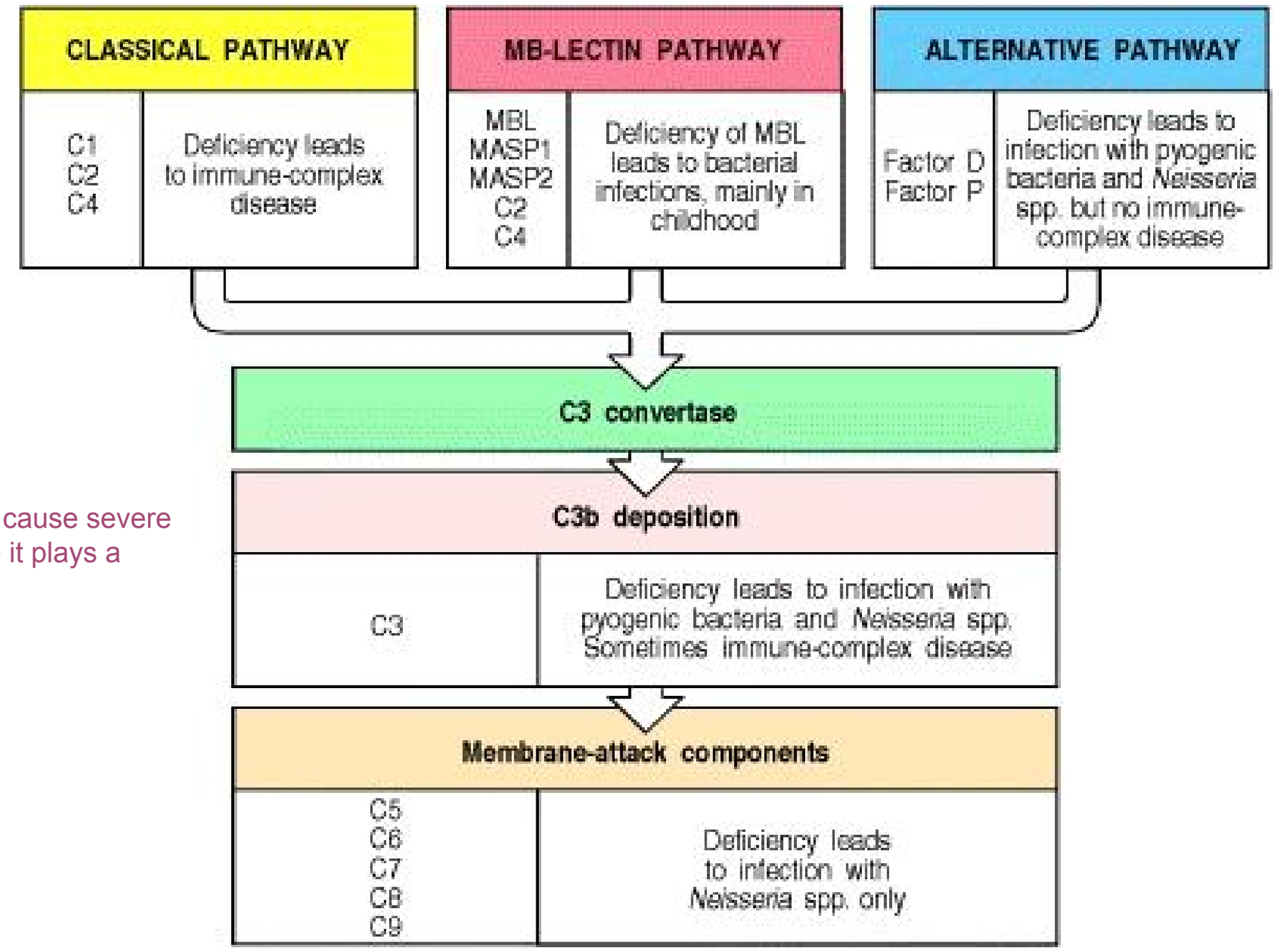
Defect:

in the oxidative complex responsible for producing superoxide radicals

Chronic granulomatous disease (CGD) (Congenital disease): is an example

- Neutrophils lack the "**respiratory burst**" upon phagocytosis
- Characterized by recurrent life-threatening bacterial and fungal infections and granuloma formation
- Granuloma is a physiologic process. It's pathological when it's chronic.

Complement Deficiency:



*Defect in C3 will cause severe infection because it plays a central role.

Classical Pathway		Lectin Pathway		Alternative Pathway	
Deficiency in: C1, C2 and C4	**Leads to immune complex disease**	**MBL MASR1 MASR2 C2, C4**	**Barcterial infection**	**Factor D Factor B**	**Bacteria and Neisseria species infections**

*from 434

Laboratory diagnosis of ID:

1. Complete blood count : total & differential
2. Evaluation of antibody levels and response to antigens
3. T and B cells counts (Flowcytometry)
4. Measurement of complement proteins and function (CH_{50})
5. Assessment of phagocytosis and respiratory burst (oxygen radicals)

Acquired Immunity

BOTH

Severe Combined Immunodeficiency (SCID) (Congenital disease):

*Causes:
• Enzyme deficiencies:
1. ADA deficiency.
2.PNP deficiency: Toxic metabolites accumulate in T and B cells.

*Features:
Increased susceptibility to :Viral, Fungal, Bacterial, Protozoal infections.

*(starting at 3 months of age)

*Management:
- Infusion of purified enzymes.
- Gene therapy.

T-cell defects

Ex. DiGeorge Syndrome (Congenital Thymic Aplasia):

(congenital defect)

*Marked by:
- Absence or underdevelopment of the Thymus gland (hypoplasia).
- Hypoparathyroidism.
- Cardiovascular abnormalities.

*Features:
- Children may present with tetany.
- Extreme susceptibility to viral, protozoal, and fungal infections.
- Profound depression of T- cell numbers.
- absence of T- cell responses.

*Management:
-Fetal thymus tissue graft (14 weeks old)

B-cell defects (Gammaglobulinaemias)

(recurrent bacterial infections)
Remember: B=Bacteria .

3) X- linked hyper-IgM Syndrome

*(Congenital disease)

*Characterized by:
-markedly elevated IgM.
- Low IgG, IgA, IgE.

*Management:
-Periodic intravenous immunoglobulin (IVIG) reduces infectious complications.

2) Selective immunoglobulin deficiency:

*(Congenital disease).

*IgA deficiency.

*(1:700) Ratio.

*Asymptomatic.

*May have increased incidence of respiratory tract infections (R.T.I)

*Management:
-Periodic intravenous immunoglobulin (IVIG) reduces infectious complications.

1) X-linked agammaglobulinaemia (XLA) or Bruton's hypogammaglobulinaemia:

*(Congenital disease)

*The most common type.

*The defect involves a block in maturation of pre- B- cells to mature B-cells in bone marrow.

*Cause:
Defect in Bruton Tyrosine Kinase (BTK).

*Features:
- Reduced B-cell counts to 0.1%
- Absence of Immunoglobulins

*affected children suffer from recurrent pyogenic bacterial infections.

Summary: (Thanks to Ghada alhadlaq)

Take Home Message

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

Useful videos:

immunodeficiency:

https://www.youtube.com/watch?v=ma4WUpJ6gvQ

T cell defects:

Digeorge syndrome: https://youtu.be/YdDs92gaWl8?t=1m45s

B cell defects:

XLA: https://www.youtube.com/watch?v=GRra7J3ahUc

MCQ's

1 - Which of the following is primary Immunodeficiency ?

a) Malnutrition b) Genetic Mutation c) AIDS d) nephrotic syndrome

2 - **DiGeorge Syndrome** is marked by which of the following ?

a) absence of B-cells b) Pneumonia c) Hypoparathyroidism d) Recurrent bacterial infections

3 -Block in maturation of pre- B- cells to mature B-cells in bone marrow is due to defect in?

a) adenosine deaminase b) Bruton Tyrosine Kinase c) purine phosphorylase

4 – which of the following is a feature of XLA ?

a) Facial abnormalities b) Cardiovascular abnormalities c) Absence of Immunoglobulins d) abscesses

5- increase incidence of respiratory tract infections is due deficiency of ?

a) IgA b) IgG c) IgE d) IgD

6 - Management of SCID by which of the following ?

a) Fetal thymus tissue graft b) gene therapy c) Periodic intravenous immunoglobulin

7 – All the following are features of agranulocytosis except ?

a) Pneumonia b) otitis media c) abscesses d) Facial abnormalities

8 - Patients with B-cell defects are subject to which type of infection ?

a) viral b) bacterial c) fungal d) protozoal

1-B
2-C
3-B
4-C
5-A
6-B
7-D
8-B

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