Module: Infection & Immunity
Semester: 5
Session: 10, **L1**
.

Immunocompromised host

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This Lecture was loaded in blackboard and you can find the material in: Lippincott's Illustrated Reviews: Microbiology. (Third Edition 2013), Harvey, RA, Cornelissen, CN, Fisher, BD.

For more detailed instructions, any question, or you have a case you need help in, please post to the group of session

Learning Objectives LO

1. Describe the main reasons for a patient to be immunocompromised
2. Understand the links between the innate and adaptive immune system in defence against infections.
3. Apply the infection model to a patient who is immunocompromised
4. To consider infections in situations and illnesses where a patient is immunocompromised

Immunosuppression: LO-1

It is a state in which the immune system is unable to respond appropriately and effectively to infectious microorganisms . The defect could be aquired or congenital, involving one or more of immune system components.

What is an "immunocompromised" host?

The individual with defective immune system.

Immunodeficiencies (IDs) LO-1

Why as doctors should you care?

– Immunodeficiency is associated with an increase in the frequency and severity of infections

– Immunodeficiency is associated with autoimmune diseases and malignancy

– Failure to recognize and diagnose leads to increased morbidity and mortality

LO-2

10 warning signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

Four or more new ear infections within one year

Two or more serious sinus infections within one year

Two or more months on antibiotics with little effect

Two or more pneumonias within one year

Failure of an infant to gain weight or grow normally

Recurrent, deep skin or organ abscesses

Persistent thrush in mouth or fungal infection on skin

Need for intravenous antibiotics to clear infections

Two or more deep-seated infections including septicemia

A family history of PI

This public service message is brought to you by
MALAYSIAN PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES (MYPOPI)
MyPOPI is a non-profit organisation and registered society caring for patients and supporting families affected by Primary Immunodeficiencies (PID)
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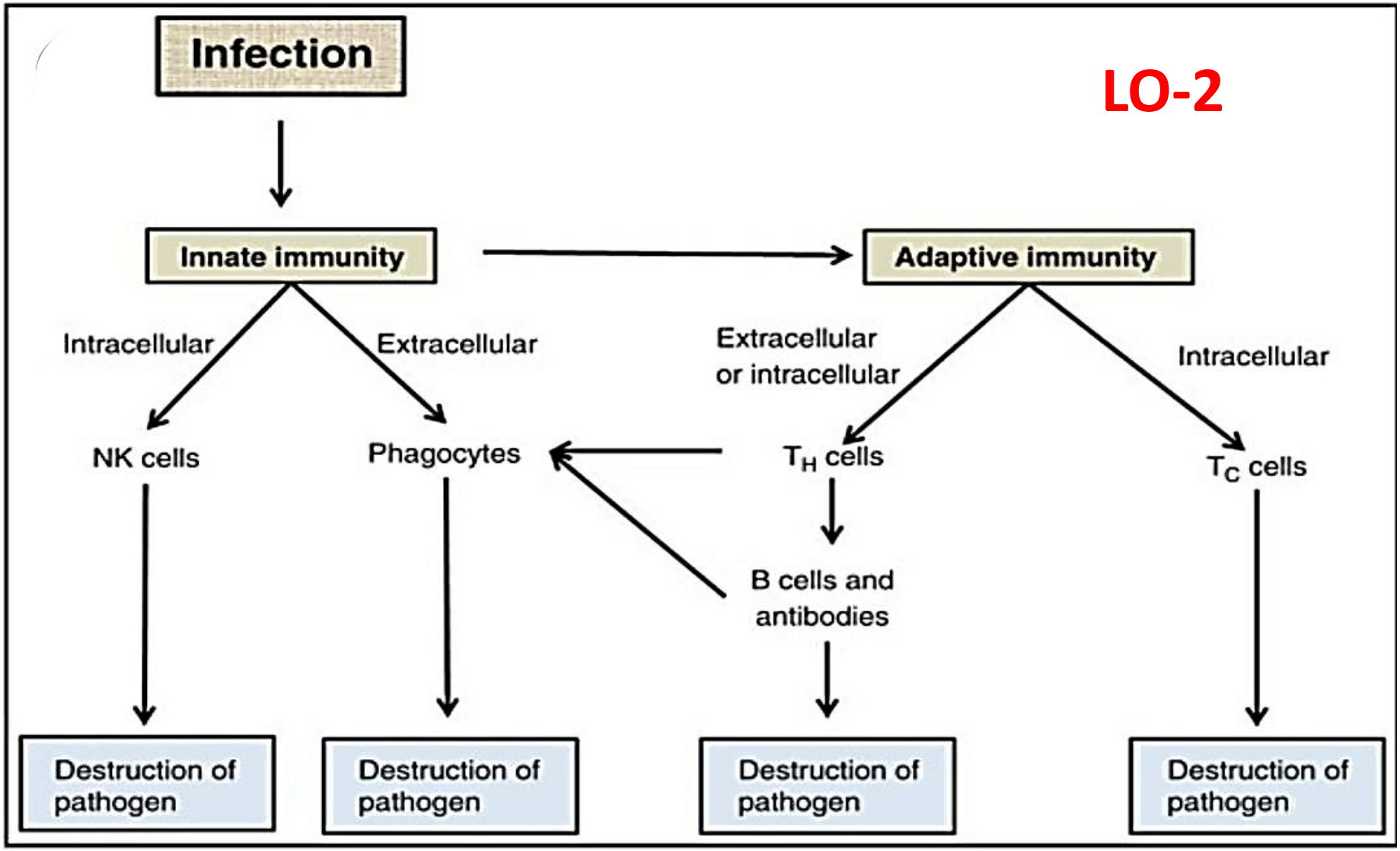
LO-2


Infection
Innate immunity
Adaptive immunity
Intracellular
Extracellular
Extracellular or intracellular
Intracellular
NK cells
Phagocytes
T_H cells
T_C cells
B cells and antibodies
Destruction of pathogen
Destruction of pathogen
Destruction of pathogen
Destruction of pathogen

LO-3

Infections suggesting underlying immune deficiency defined as "SPUR"

–**S** severe
–**P** persistent (chronic)
–**U** unusual etiologies
–**R** recurrent
(with slow recovery or poor response to treatment)

LO-3

Immunodeficiency Diseases

Primary(congenital) immunodeficiency 10%

usually starts at 1st months of life
80% patients <20 yrs.
70% male (X-linked)

The defect in innate immunity

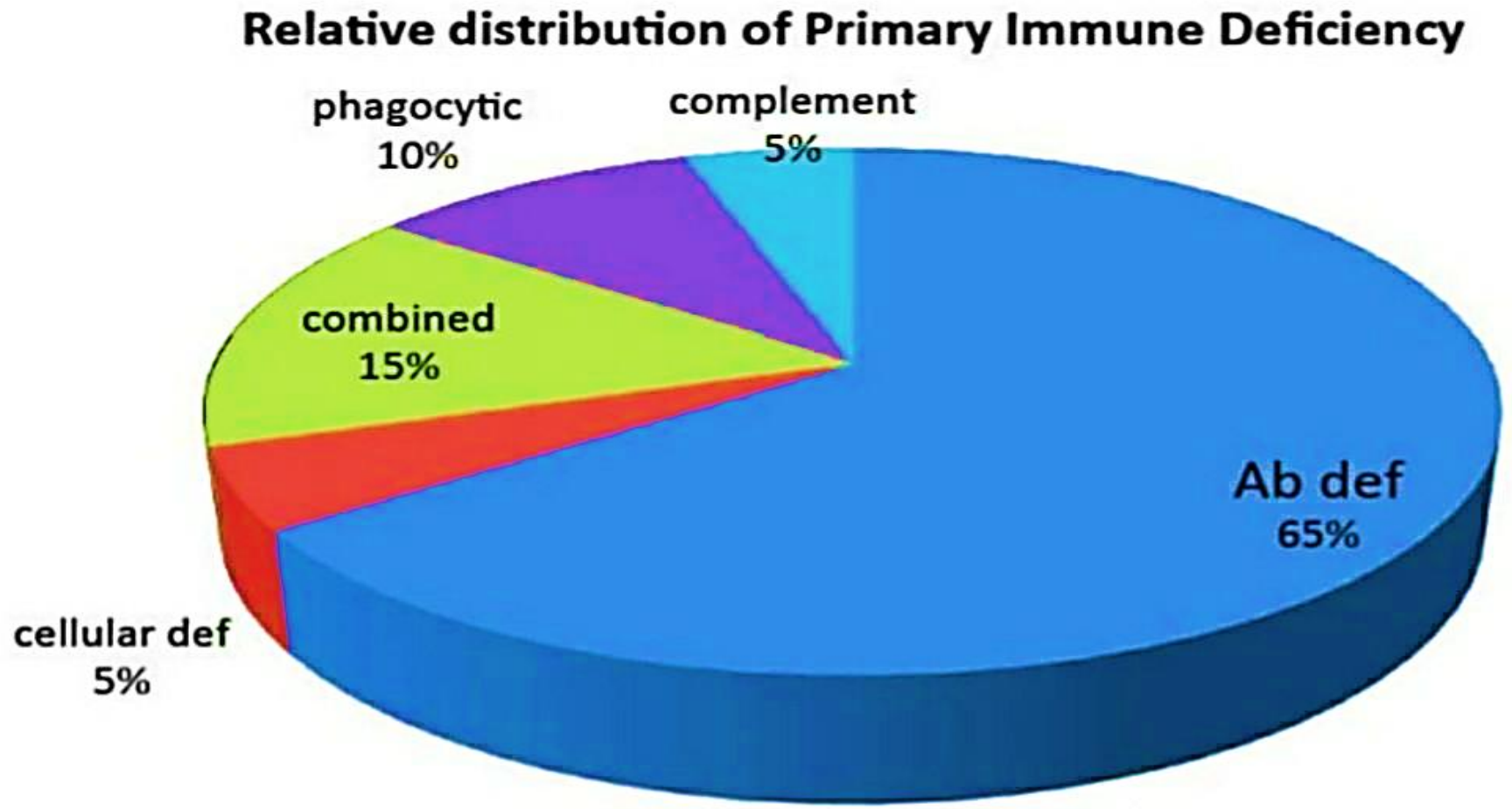
- Phagocytic cells
- complement

The defect in adaptive immunity

- T cells
- B cells

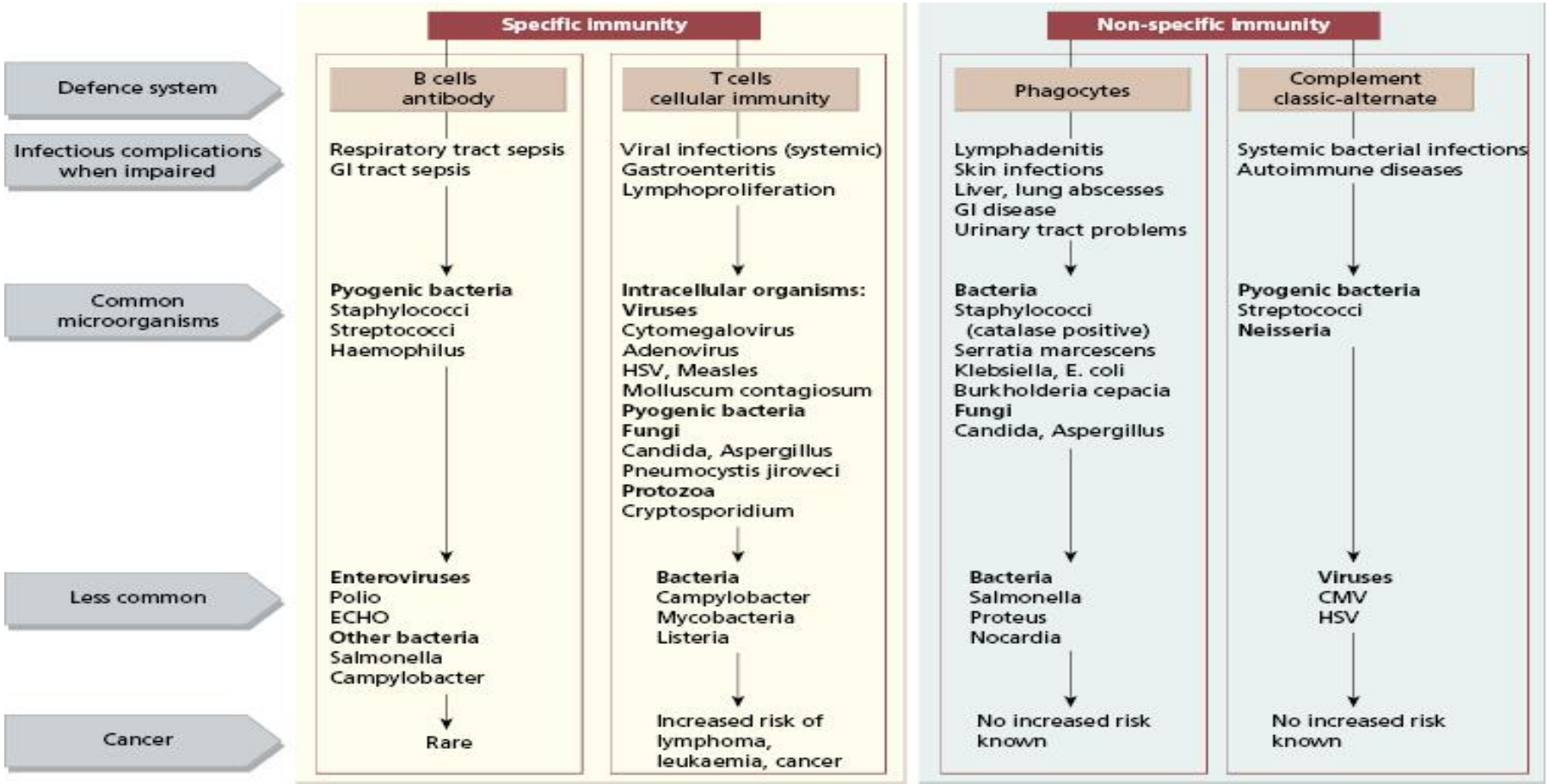
Secondary(acquired) immunodeficiency 90%

LO-1


Relative distribution of Primary Immune Deficiency
phagocytic
10%
complement
5%
combined
15%
Ab def
65%
cellular def
5%

LO-3

Defects in immunity suggested by infections with certain organisms:



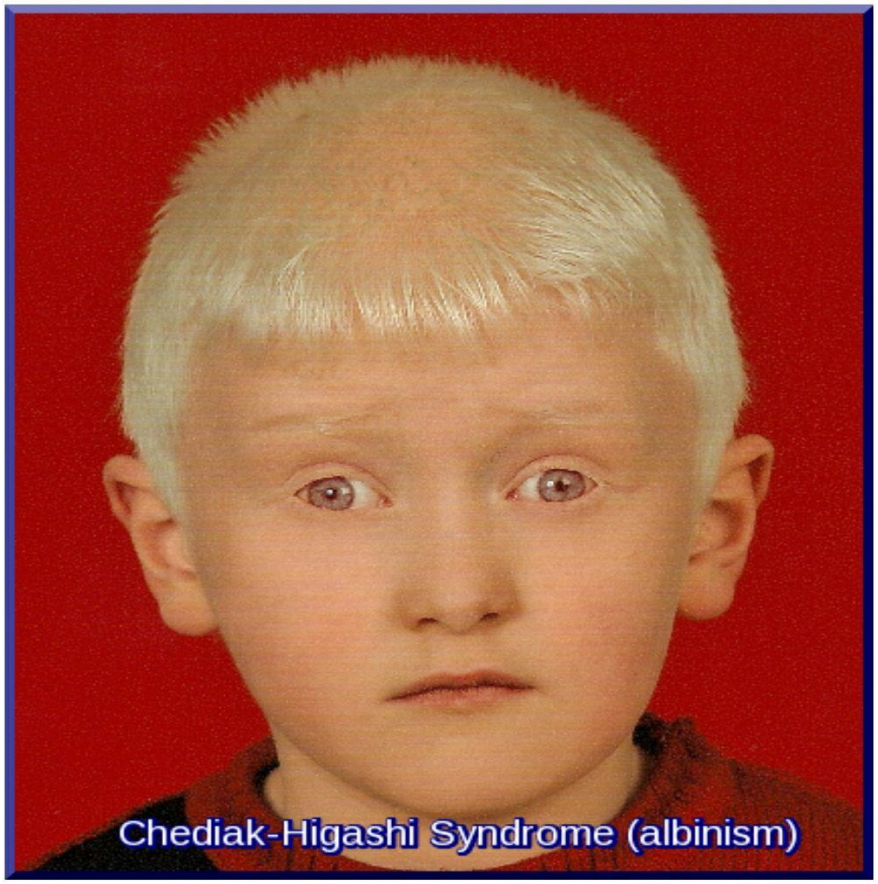
Phagocytic disorders

LO-4

Defect in phagocytic cells involves macrophages and neutrophils.

Disorder	Inheritance	Defect	Clinical findings
Chronic granulomatous disease	X- linked	defect in NADPH oxidase. Phagocytes can not produce O2 ➔ H2O2 ➔ weak oxidative burst causing defective intracellular killing	infection with catalase positive MO. Like *E. coli, Staphylococci spp., Candida and aspergillus*.
Chediak-Higashi syndrome	Autosomal recessive	Mutation in lysosomal trafficking regulator gene LYST, resulting in inability of the endosomes to fuse with the lysosomes, leading to decrease in phagocytosis	recurrent pyogenic infections (*staph. & strept*.), albinism, peripheral neuropathy
Cyclic neutropenia	Autosomal dominant Or aquired	Recurrent episodes of low level of neutrophils >200/µl, for 3-6 days each 21 days Due to irregular production of G-CSF	During the neutropenic stage patient susceptible to life threatening infections
Leukocytes adhesion deficiency	Autosomal recessive	Mutation of β chain of integrin causing failure of phagocytes adhesion to blood vessels wall lead to defective migration into infected tissues	chronic infections with out pus formation, delayed wound healing, newborn will have delay in umbilical cord sloughing

Chediak-Hiashi syndrome



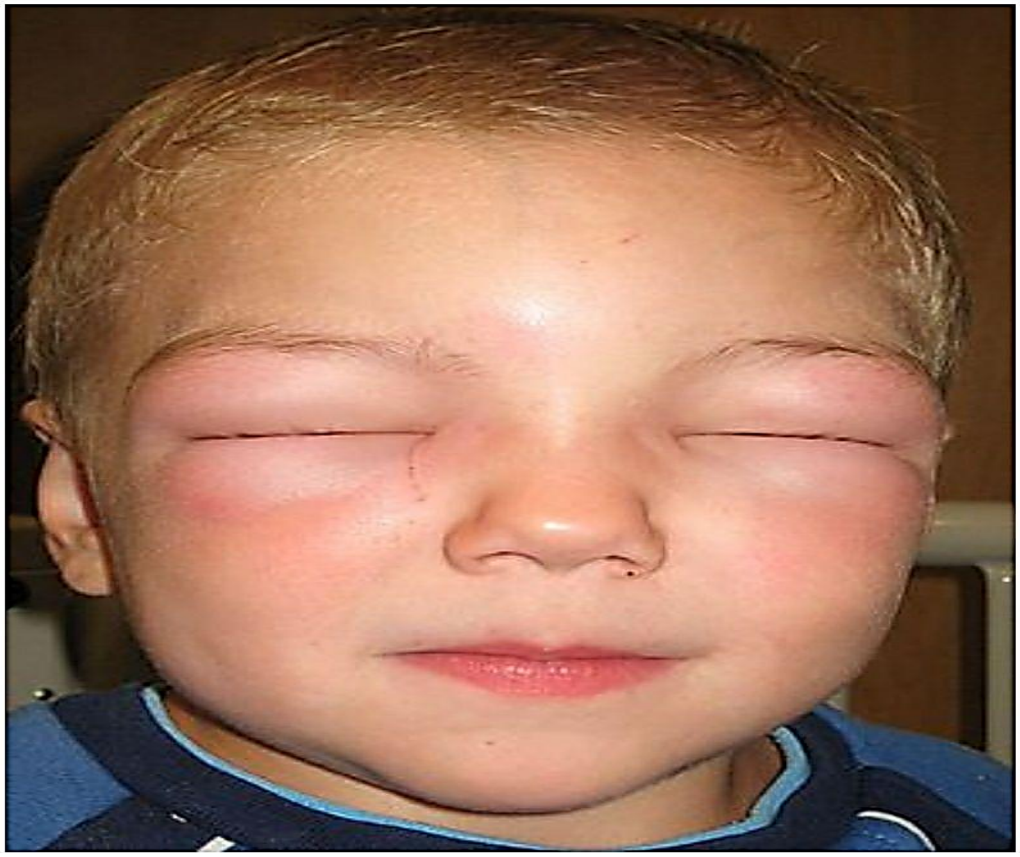
Complement deficiencies:- LO-4

A group of disorders caused by deficiency of one or more complement proteins. Acquired deficiencies are more common than inherited ones.

Component	Deficiency	Clinical findings
Classic pathway	C1q, C1r, C1s,C2,C4	1.Marked increase in immune complex disease e.g(SLE) 2.Increase infection with pyogenic bacteria
Both pathways (Classic & alternative pathway)	C3	1.Recurrent bacterial infections 2. Immune complex diseases
	C5,C6,C7,C8	Recurrent meningococcal &gonococcal infections
Regulatory proteins	C1-INH	Hereditary angioedema

LO-4

C1-inhibitor deficiency (Hereditary Angioedema)



T-cells disorders:

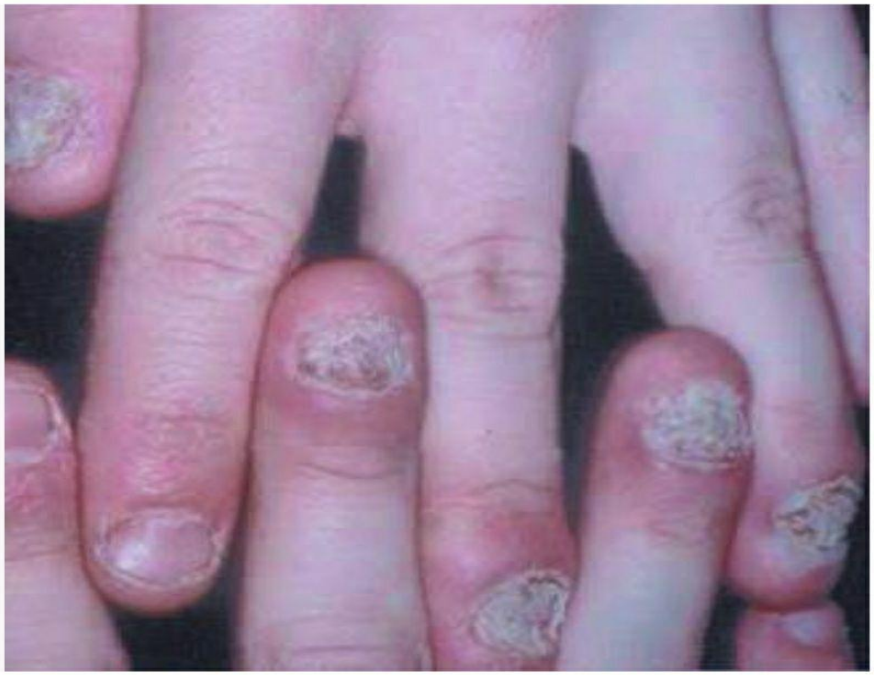
LO-4

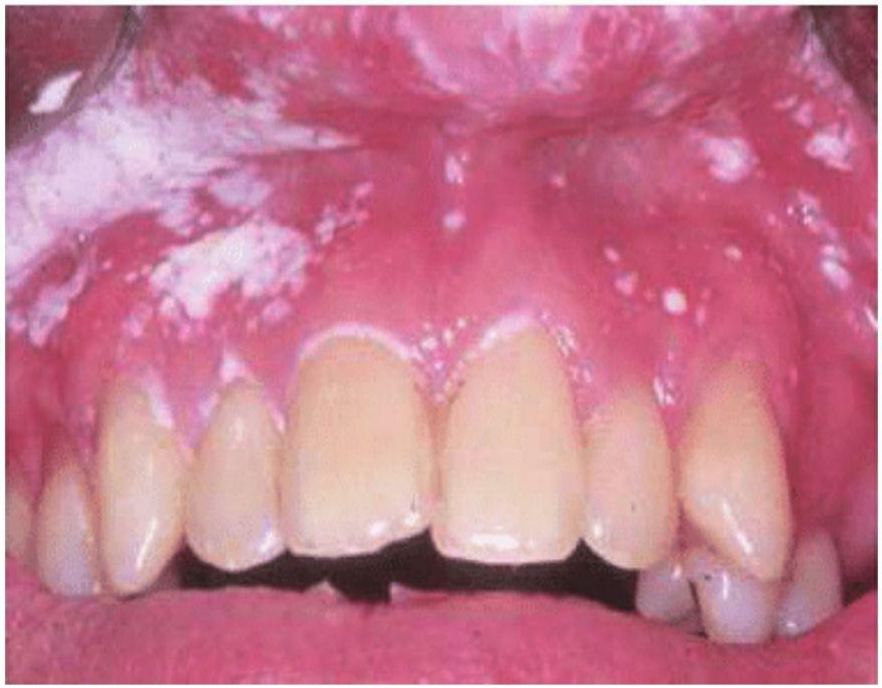
A group of disorders affect cellular immunity that results in recurrent infections with intracellular pathogens

Disorder	Defect	Clinical features
Severe combined immunodeficiency	Defect in T&B cells development	Recurrent both bacterial and viral infections Chronic diarrhea Failure to thrive
DiGeorge syndrome	Small deletion in chromosome 22 causing thymus and parathyroid aplasia or hypoplasia	Signs of hypothyroidism: hypocalcemia (tetanus), facial abnormalities, cardiovascular abnormalities Recurrent infections, may be fatal in first year
Chronic mucocutaneus candidiasis	Deficiency in IL-17or IL-17 receptor lead to defect in cell mediated immunity	chronic persistent non invasive candida infection involving skin, nails and mucous membranes
Ataxia telangiectasia	Autosomal recessive mutation in the genes that encode DNA repair enzyme	progressive neurologic impairment, ataxia , recurrent respiratory tract infections , ocular & cutaneous telangiectasia
Hyper IgE syndrome(Job's syndrome)	Autosomal dominant inheritance STAT3 mutation leads to deficiency of Th17 cells	Impaired B-cells class switching & impaired neutrophils migration, causing high IgE level in serum , recurrent staphylococcal skin infections.

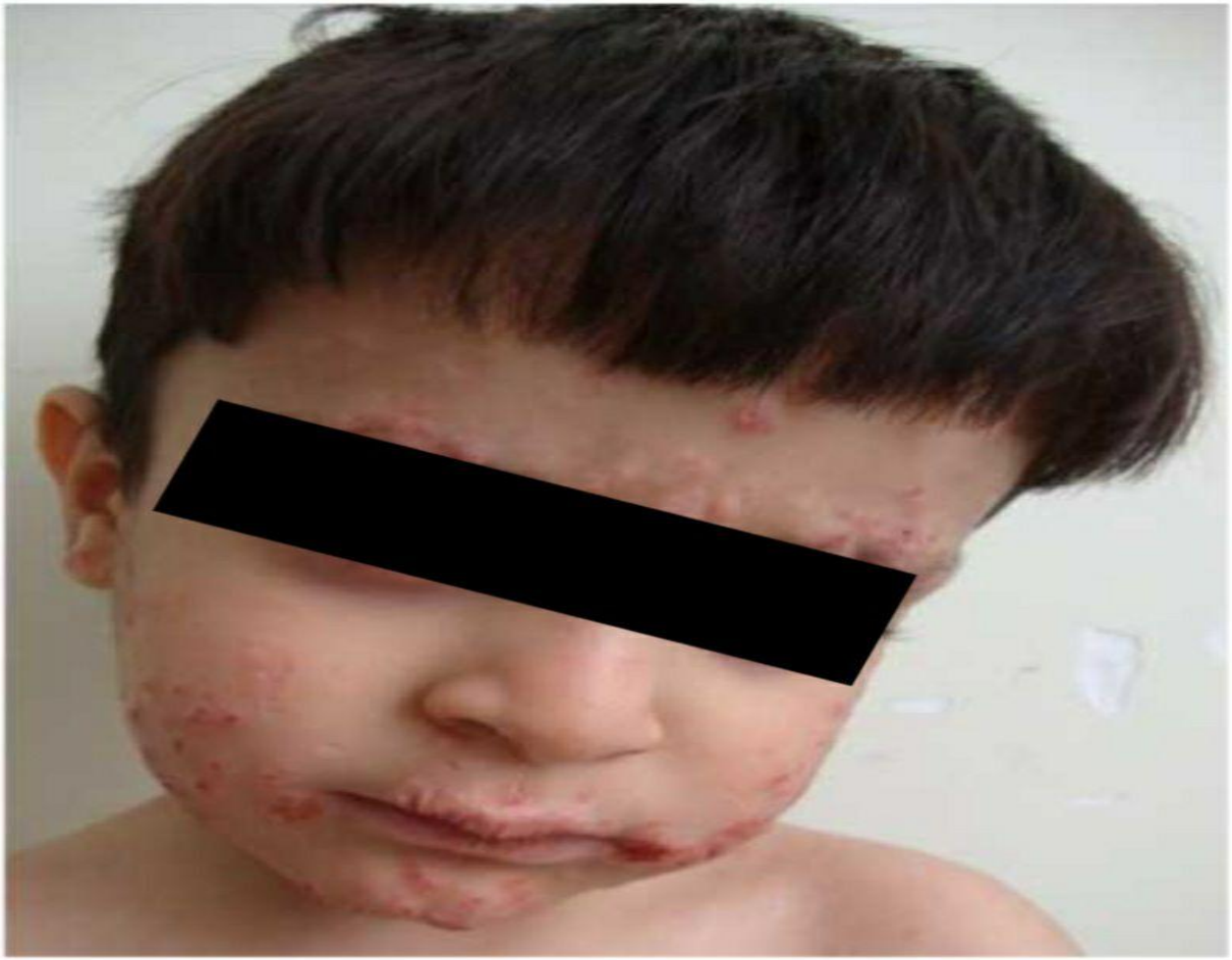
Chronic mucocutaneus candidiasis

LO-4



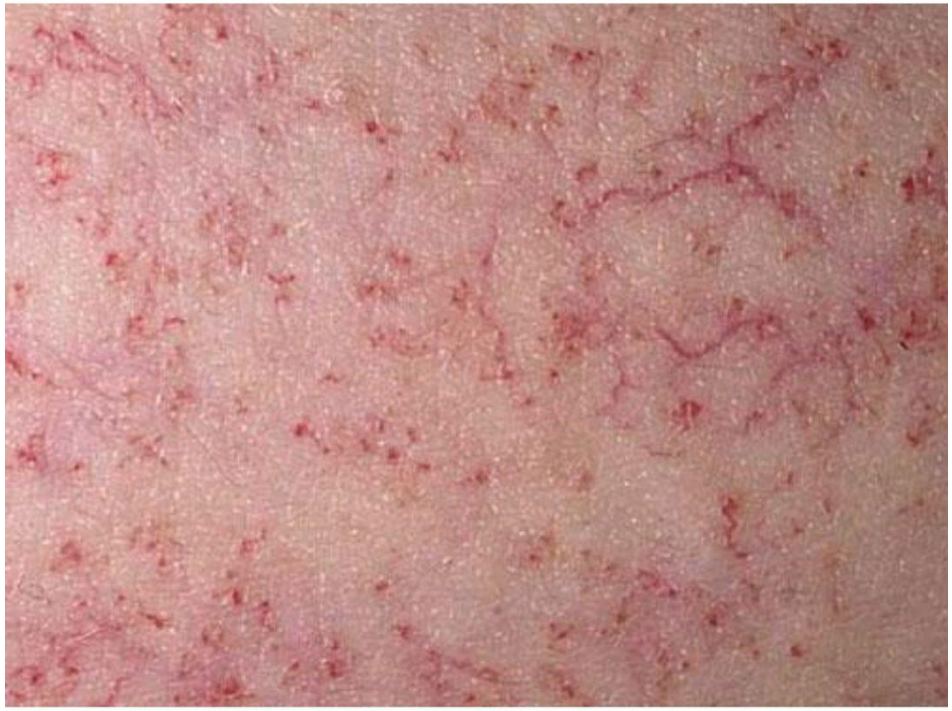


Hyper IgE syndrome



Ataxia telangiectasia

LO-4



B-cell deficiency disorders

LO-4

- The causative agent of infection in such cases are mostly extracellular organisms mainly pyogenic bacteria, because the patient is deficient in serum opsonin (Ab) which is necessary for phagocytosis.

- Site of infection include skin, sinuses, meninges, respiratory, urinary and gastrointestinal tract.

B-cell deficiency disorder

LO-4

Disorder	Defect	Clinical picture
X-linked Agammaglobulinemia (Bruton's disease)	X-linked recessive Mutation in the Bruton's tyrosine kinase (Btk) gene No mature B cells All antibody classes deficiency Intact T-cells	Manifestations starts at age of 6 months Recurrent bacterial infection with *Pneumococci, Streptococci, Meningococci, Pseudomonas and H. influenza*.(e.g., sinusitis, pneumonia, meningitis), while viral infections can be overcome due to intact T-cells
Selective immunoglobulin deficiency (IgA)	Variable (inherited or aquired)	Increase liability of skin or mucosal infections, with increase frequency of atopy, asthma or rheumatoid arthritis

Approach to a patient with PID LO-4

Diagnosis of PID is difficult and need high suspension index.

1. **history**
2. **Physical examination**
3. **Laboratory assessment**

Laboratory assessment:

Suspected cells have specific tests:

B-cell:

1. **Total Igs**
2. **Selected Ig e.x: (IgA&IgG)**
3. **Antibodies for previous vaccine**

T-cells:

1. **Lymphocyte count**
2. **Delayed hypersensitivity reaction to tuberculin test and candida**

Phagocytes:

1. **Neutrophil count** **2. NBT test**

Complements:

Total and specific complement count

Secondary immunodeficiency

LO-4

It's more common cause of immunodeficiency than PID. It may results from different underlying disorders:

1.Debilitating conditions that lead to protein loss:

- **Malnutrition**
- **Renal insufficiency**
- **Extensive burns**
- **diabetes**
- **Old age**

LO-4

2.Drug-induced :

- Immunosuppressive / cytotoxic therapy
- Side effect eg. anti-epileptics; gold/penicillamine
- Corticosteroids

3. Malignancy

- Lymphoma / leukemias
- Multiple myeloma

4. Splenectomy

LO-4

5. Infectious diseases

- Bacterial infection (TB) → IL10 & IL4 → ↓ Th1
- Parasitic infection (*Trypanosome cruzi*) ↓ CMI
- Measles & other viral infections → Transient suppression of delayed hypersensitivity.

LO-4

- Acquired immune deficiency syndrome (AIDS)

➢ Caused by human immunodeficiency virus (HIV) which interact with a large number of different cells in the body and escaping the host immune response against it.

➢ Transmit through sexual intercourse and contact with infected blood, and infected mothers can pass HIV to their infants.


THANKS