Cihan University/ Sulaymaniyah

College of Health Science

Medical Laboratory Analysis

4th Stage- 1st Semester

Clinical Immunology

Lecture- 6: Failures of Host Defense Mechanisms

Immunodeficiencies

2023- 2024

Lecturer: Mohammed T. Salih

IMMUNODEFICIENCY

- Immunodeficiency – system fails to protect the body from:

1. Primary immunodeficiency
   - ✓Genetic or developmental defect
2. Secondary immunodeficiency – acquired which due to the loss or reduction of:
   - ✓Cell type
   - ✓Cell numbers
   - ✓Cell function

TYPES OF IMMUNODEFICIENCIES

Defective immunity

Primary

i.e. intrinsic defect

- missing enzyme
- missing cell type
- nonfunctioning component

Congenital / late onset

Secondary

i.e. underlying disease

- lymphoid malignancy
- infection e.g. HIV
- malnutrition
- immunosuppressive drugs

Always acquired

Types of Immunodeficiencies

1. Deficient **humoral immunity** usually results in increased susceptibility to infection by encapsulated, pus-forming bacteria and some viruses,
2. Where as defects in **cell-mediated immunity** leads to infection by viruses and other intracellular microbes.
3. **Combined deficiencies** in both **humoral** and **cell mediated immunity** make patients susceptible to infection by all classes of microorganisms.

Primary Immunodeficiencies

Lymphoid Immunodeficiencies:

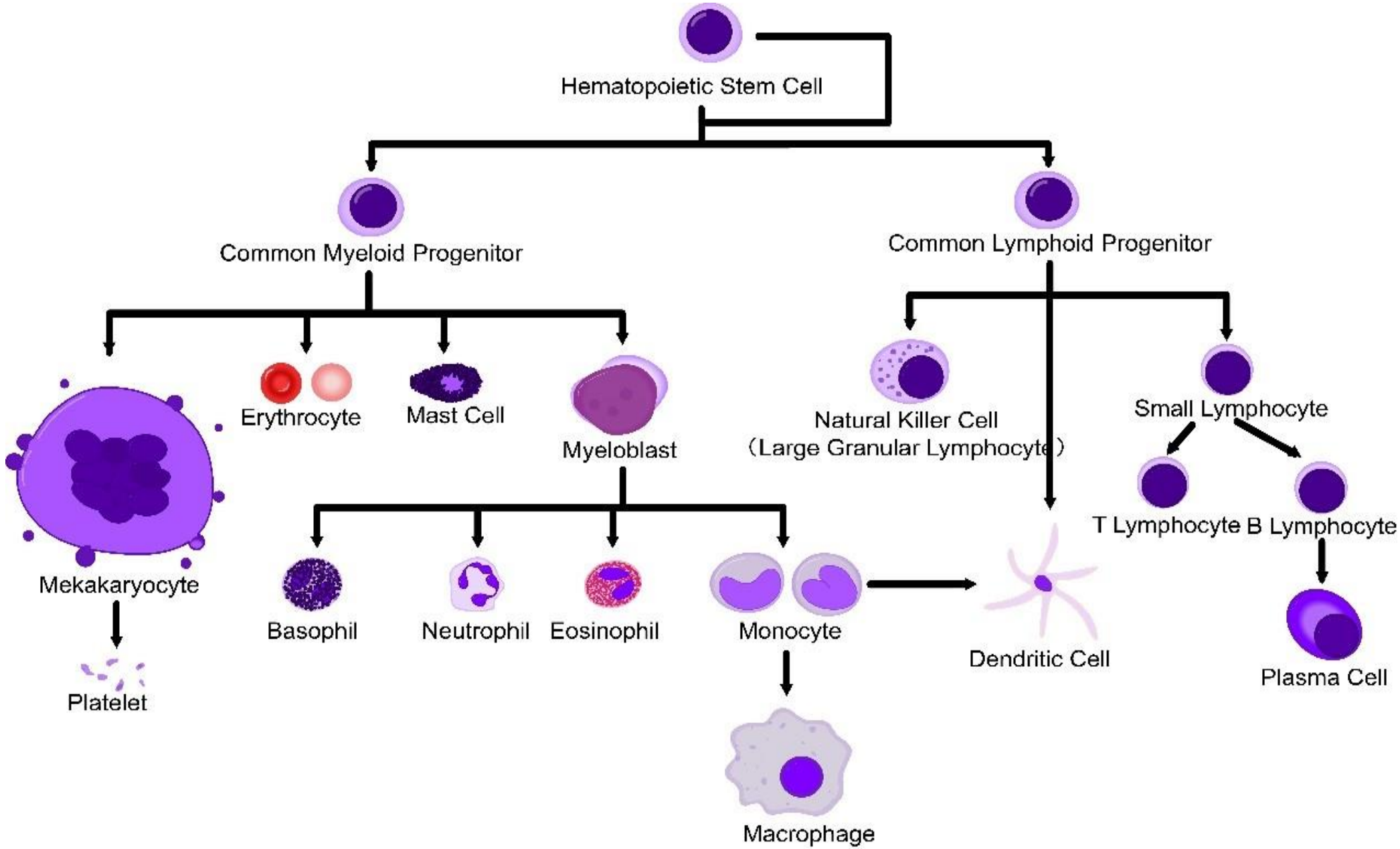
A. Combined – effects both B and T cells

B. B-cell Immunodeficiency; Range from absence of B cells, plasma cells, immunoglobulins to absence of only certain classes of Antibodies.

   - Subject to bacterial infections but do well against viral since T-cell branch is available.

C. T-cell Immunodeficiency

   - Can affect both humoral and cell-mediated.


Hematopoietic Stem Cell
Common Myeloid Progenitor
Common Lymphoid Progenitor
Erythrocyte
Mast Cell
Myeloblast
Natural Killer Cell
(Large Granular Lymphocyte)
Small Lymphocyte
Mekakaryocyte
T Lymphocyte
B Lymphocyte
Basophil
Neutrophil
Eosinophil
Monocyte
Dendritic Cell
Plasma Cell
Platelet
Macrophage

Defects in the Cell Mediated System

Defects in the cell mediated system are associated with:

- Increased susceptibility to viral, protozoan, and fungal infections.
- Intracellular pathogens such as Candida albicans, Mycobacteria are often implicated, reflecting the importance of T cells in eliminating intracellular pathogens.
- Also affect the humoral system, because of the requirement for T-helper cells in B-cell activation, particularly in the production of specific antibody

B and T-cell Deficiency

A. Selective T-cell deficiency:

Disease	Defect	Clinical Manifestation
Digeorge Syndrome	Thymic aplasia	Depression of T cell number with absence of responses.
MHC Class I Deficiency	Failure of TAP-1 molecule to transport peptide to endoplasmic reticulum	1. CD8+ T cell def. 2. CD4+ T cell normal. 3. Recurrent viral infection. 4. Normal Ab formation.
MHC Class II Deficiency (bare Lymphocyte Syndrome)	Defects in transcription factors.	1. Deficiency of CD4+ T cell. 2. Hypogammagloulinemia. 3. Clinically as SCID.

B. Combined; Partial B and T-cell Deficiency:

Disease	Defect	Clinical Manifestation
Ataxia telangiectasia	▪ Defect in kinase involved in the cell cycle.	▪ Patients experience upper and lower respiratory tract bacterial infections, multiple autoimmune phenomena, ▪ Telangectasia (capillary distortion in the eye). ▪ Deficiency of IgA & IgE production.

C. Complete Functional B and T Cell Deficiency:

Disease	Defect	Clinical Manifestation
Sever combined ID(SCID).	Defects in common γ chain of IL-2 receptor.	1. Opportunistic (fungal) infection. 2. Low level of circulating lymphocyte.

Primary Immunodeficiencies

A- Selective T-cell deficiency:

Thymus:

❖**DiGeorge Syndrome** – decreased or absent thymus

- Results from deletion of region on chromosome 22 in developing embryo, developmental anomaly.
- Third and fourth pharyngeal pouches during fetal life.
- Lowered T cell numbers, results in B cells not producing sufficient Abs.
- As in other severe T cell deficiencies, patients are susceptible to mycobacterial, viral, and fungal infections.

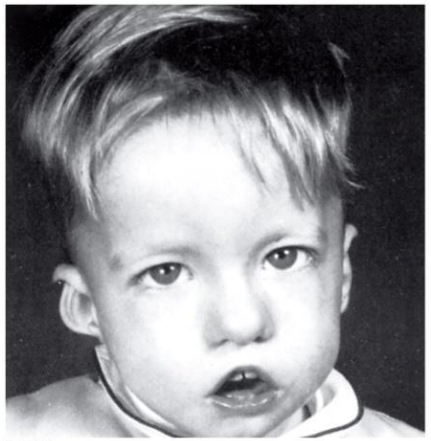


Figure 20-5
Kuby IMMUNOLOGY, Sixth Edition

Primary Immunodeficiencies

A- Selective T-cell deficiency:

❖ MHC class I deficiency (Bare lymphocytes syndrome I or TAP- 1 or 2 deficiency):

- 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 , but CD4+ is normal.
- Recurrent viral infection , normal DTH, normal Ab production.

❖ MHC class II deficiency (Bare lymphocytes syndrome II):

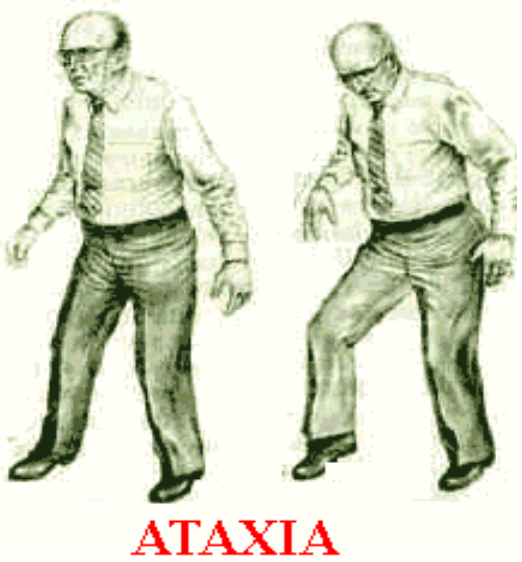
- Due to defect in the MHC class II trans-activator protein gene, which results in a lack of class-II MHC molecule on APC.
- Patients have fewer CD4 cells, immunoglobulin levels.

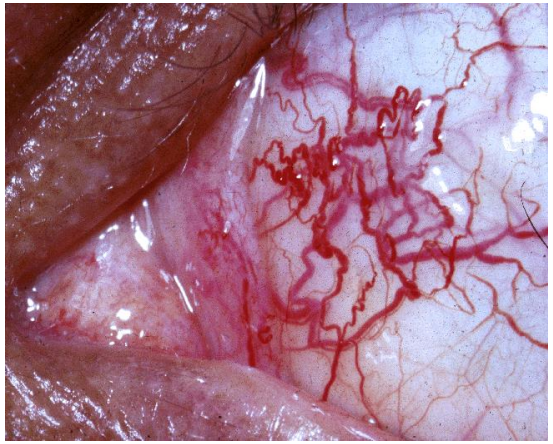
Primary Immunodeficiencies

B- Combined partial B- and T-cell deficiency

❖ Ataxia-telangiectasia

- Defect in kinase involved in cell cycle.
- 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.





Primary Immunodeficiencies

C- Complete Functional B and T Cell Deficiency:

❖Severe Combined Immunodeficiency (SCID):

- Low of circulating lymphocytes
- Non-proliferating T cells
- Thymus doesn't develop
- Usually fatal early years of life
  - Infant will have viral and fungal infections
  - Bacterial don't show up until later because of placental transfer of Abs from mother
  - Chronic diarrhea, pneumonia, lesions
- Many genetic defects can contribute to SCID.

Types of Primary Antibody Deficiencies

1. Common variable immunodeficiency disorders
2. X-linked agammaglobulinemia
3. Hyper IgM syndromes (e.g. CD40 ligand deficiency)
4. IgA and IgG subclass deficiencies
5. Selective IgA deficiency
6. Specific antibody deficiencies
7. Transient hypogammaglobulinemia of infancy

Major Causes of Primary Antibody Deficiencies in Children and Adults

Age (years)	Children	Adults
<4	Transient hypogammaglobulinaemia of infancy	
	X-linked agammaglobulinaemia (XLA)	XLA (late presentation is unusual but does occur)
	Hyper-IgM syndromes	
4–15	Common variable immunodeficiency disorders	
	Hyper-IgM syndromes	
	Selective IgA deficiency	
	Selective/partial antibody deficiencies	
16–60		Common variable immunodeficiency disorders
		Selective/partial antibody deficiencies
		Selective IgA deficiency
		Antibody deficiency with thymoma

Examples for Humoral Immunity Defects

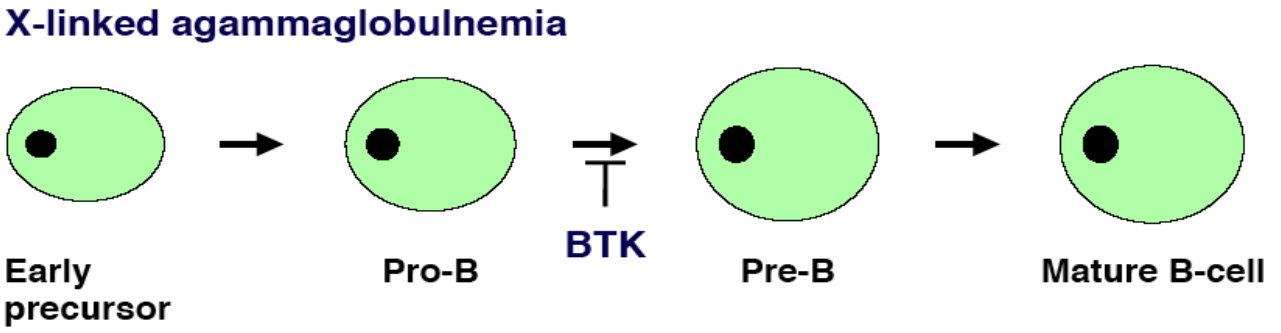
Disease	Molecular defect	Symptoms/signs	Treatment
Bruton X-linked hypogammagloulinemia	Deficiency of tyrosine kinase so blocks B-cell maturation	**1.** Low Ig of all classes. **2.** No circulating B cell. **3.** B-cell maturation stopped at pre-B stage. **4.** Normal CMI.	**1.**Monthly gammaglobulin replacement. **2.**Antibiotic.
X-linked hyper-IgM syndrome	Def of CD40L on activated T cell	**1.**Higher serum titer of IgM only. **2.** Normal B & T cell number. **3.** Susceptibility to EC bacteria & opportunists.	Antibiotic & gammaglobulin.
Selective IgA deficiency	Deficiency of IgA	Repeated sinopulmonary & GIT infections.	Antibiotic, not Ig.
Common variable immunodef	Unknown	**1.** Onset in late teens. **2.** B cell present in peripheral blood. **3.**Ig level decrease with time. **4.**increase autoimmunity & atopy	Antibiotics

Primary Immunodeficiencies

B cell Immunodeficiencies

1- X-linked Agammaglobulinemia:

- B cell defect
- Defect in kinase that keeps B cells in pre-B stage
- Low levels of IgG and absence of other classes
- Recurrent bacterial infections

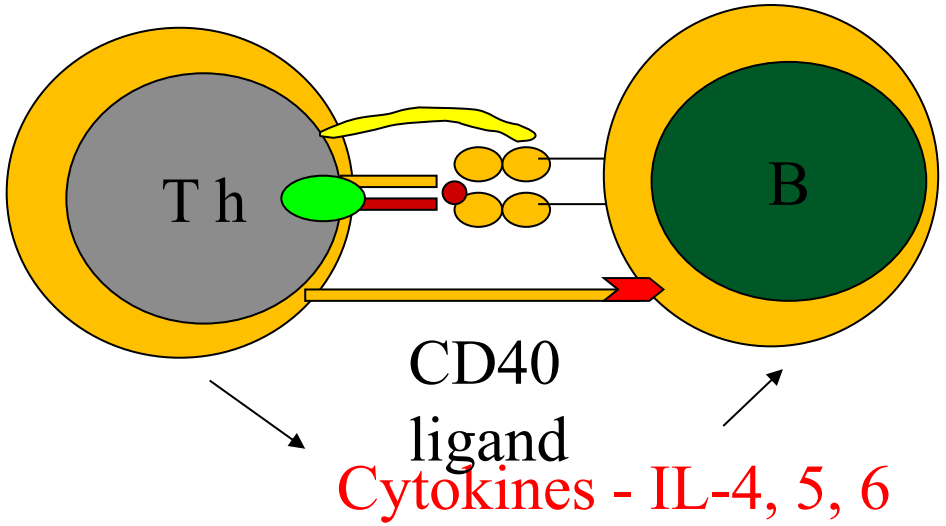


Primary Immunodeficiencies

B cell Immunodeficiencies

2- X-linked Hyper-IgM Syndrome:

- Deficiency of IgG, IgE, IgA but elevated levels of IgM
- Defect in T cell surface marker CD40L
  - This is needed for interaction between TH and B cell for class switching for T-dependent antigens
  - T independent antigens are not affected therefore there is production of IgM.

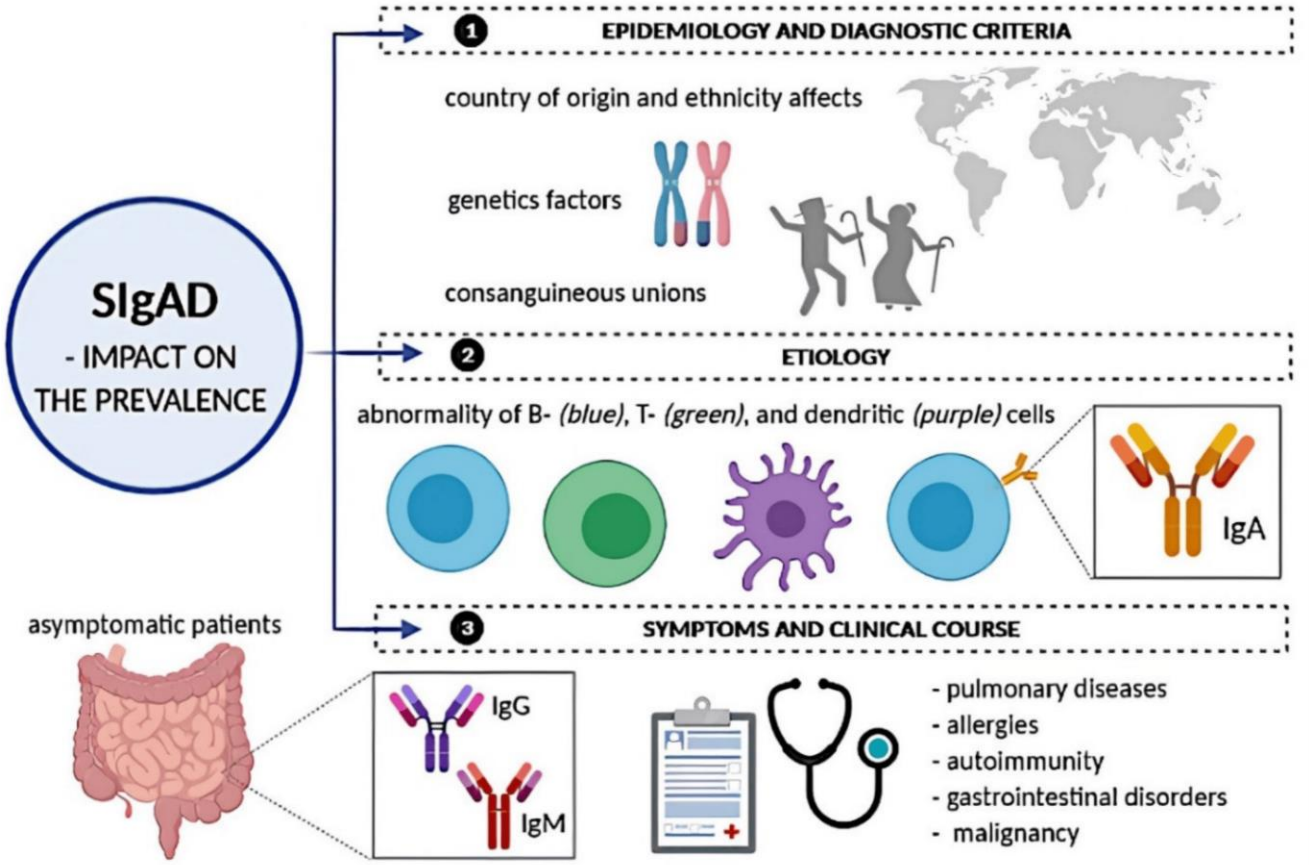


Primary Immunodeficiencies

B cell Immunodeficiencies

3- Selective Deficiencies of Immunoglobulin

- IgA deficiency is most common
  - Recurrent respiratory and urinary tract infections, intestinal problems
- IgG deficiencies are rare
  - ✓ Can often be treated by administering immunoglobulin

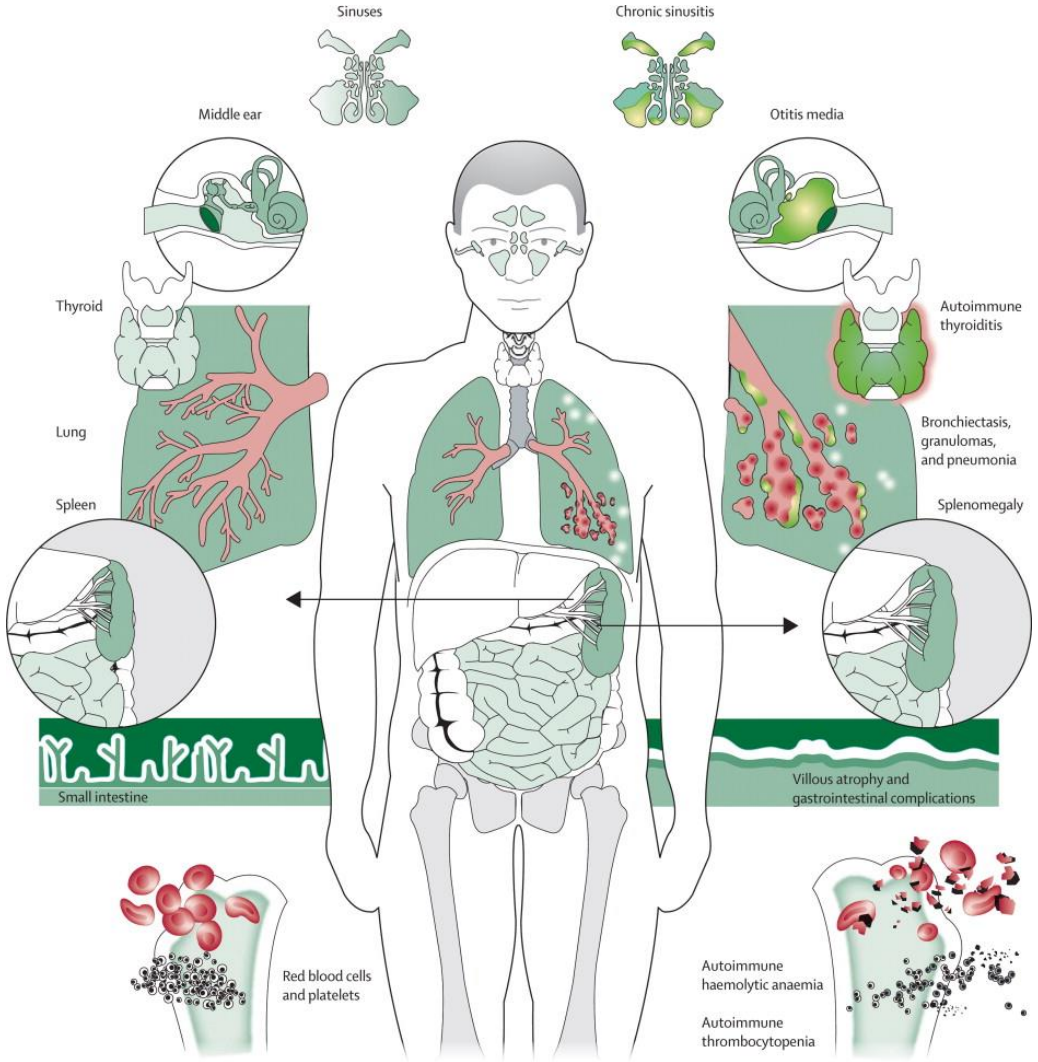


Primary Immunodeficiencies

B cell Immunodeficiencies

4- Common Variable Immunodeficiency (CVID)

- There are defect in T cell signaling to B cells
- Acquired a gammaglobulinemia in the 2nd or 3rd decade of life
- May follow viral infection
- Pyogenic infection
- 80% of patients have B cells that are not functioning
- B cells are not defective. They fail to receive signaling from T lymphocytes
- Unknown

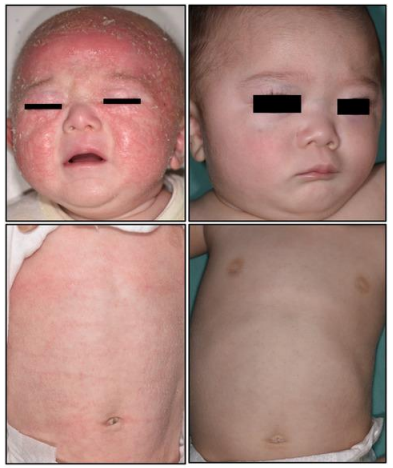


Primary Immunodeficiencies

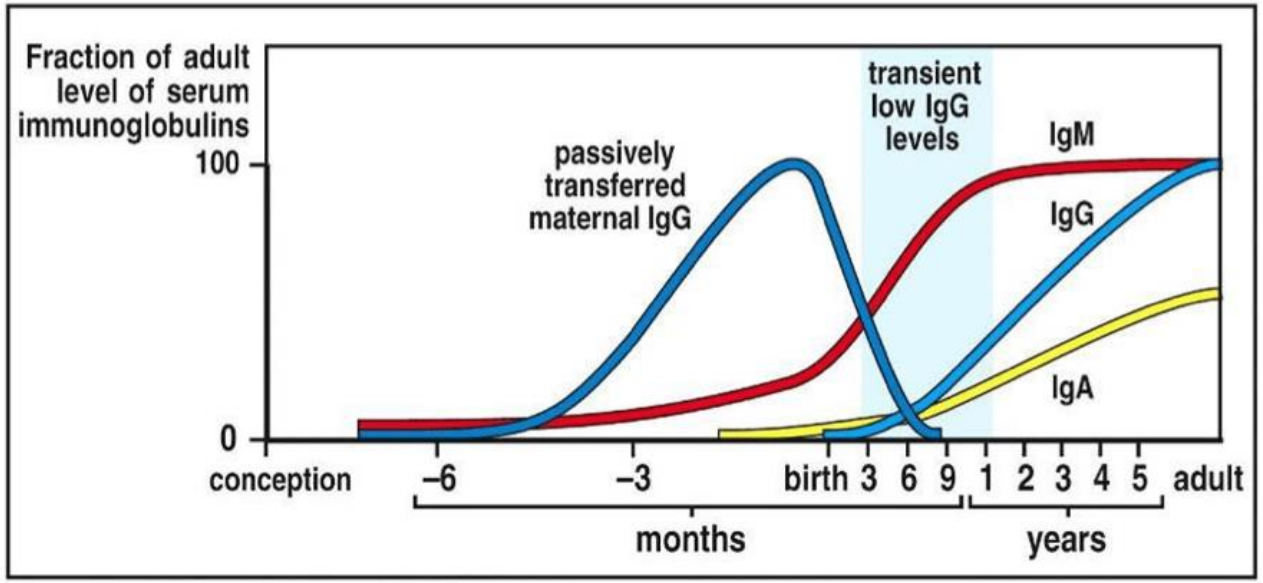
B cell Immunodeficiencies

5- Transient hypogammaglobulinemia of infancy

- Due to delay in in IgG synthesis approximately up to 36 months
- In normal infants synthesis begins at 3 months
- Normal B lymphocytes
- Probably lack help of T lymphocytes.



4 months of age 10 months of age



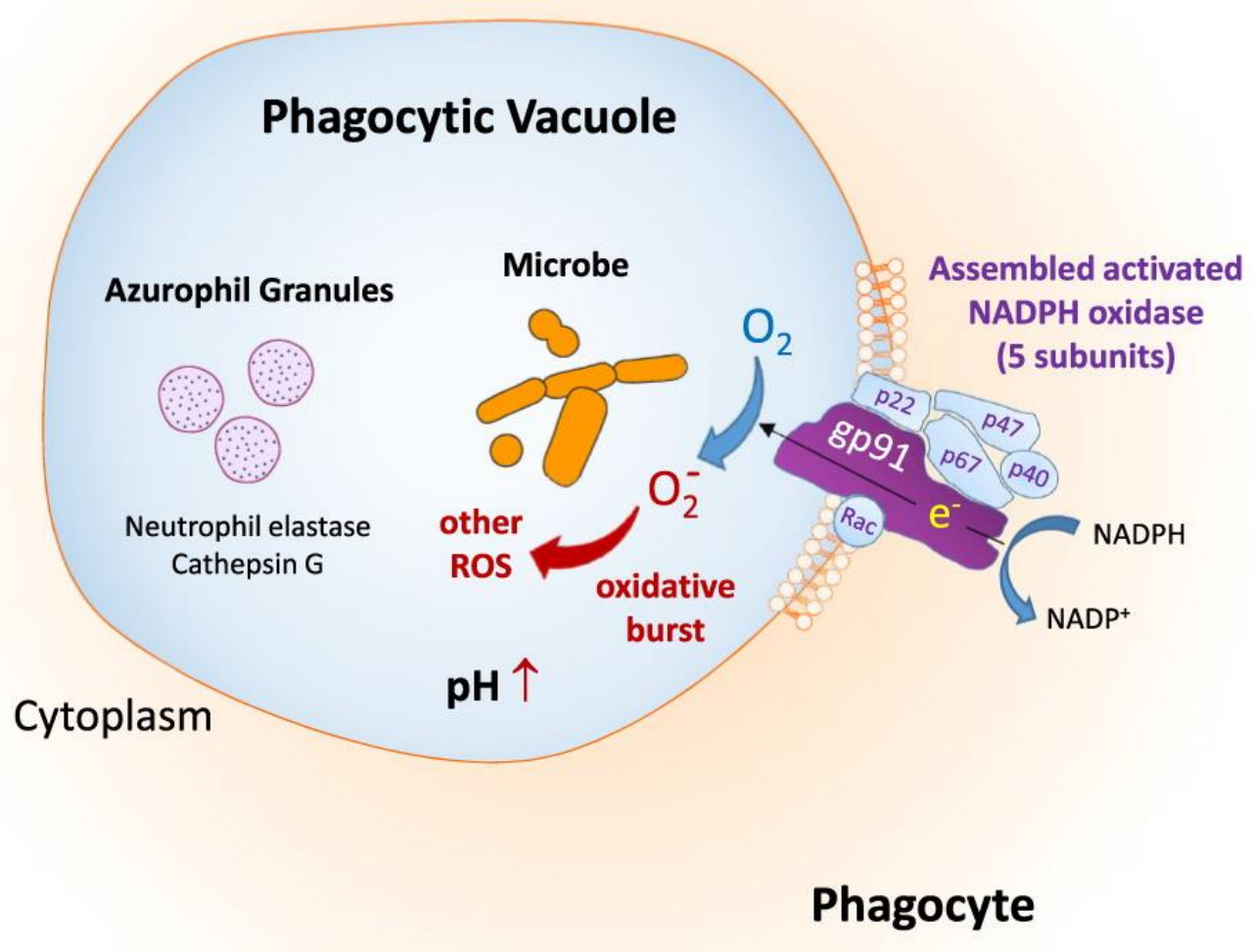
Defect in Phagocytic Cells (Myeloid)

- (Phagocytes, Neutrophils,)
- Defects are significant because of their key role in innate and adaptive I.R.

Disease	Molecular defect(s)	Symptoms
Chronic granulomatous disease(CGD).	Def of NADPH oxidase; failure to generate superoxide anion & other O2 radicals, so the microorganisms will be ingested but not killed.	Recurrent infections with catalase-positive bacteria & fungi.
Leukocyte adhesion deficiency(LAD	Absence of CD18(LFA-1) (leukocyte integrins).	Recurrent & chronic infections, fail to form pus.
Chediak-Higashi Syndrome	Defect in organelle membrane which inhibits normal fusion of lysosomes Fail to destroy ingested microbes	Recurrent infection with bacteria (chemotactic and degranulation defects, absent NK activity

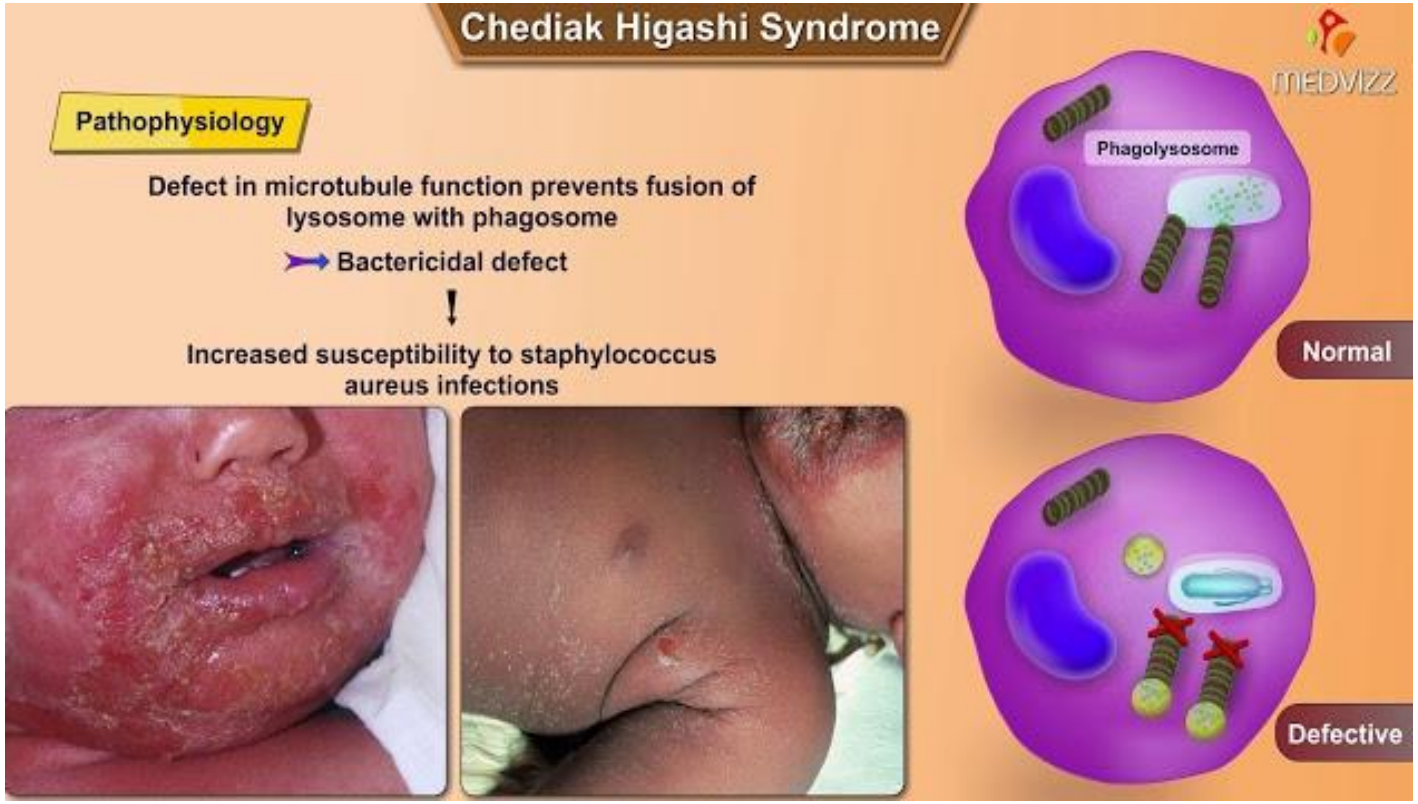
Chronic Granulomatous Disease (CGD)

- Defect in enzymes and microcidal molecules (NADPH oxidase; failure to generate superoxide anion & other O2 radicals).
- So the microorganisms will be ingested but not killed.
- Symptoms: recurrent infections with catalase-positive bacteria and fungi specially *Staphylococcus aureus*.



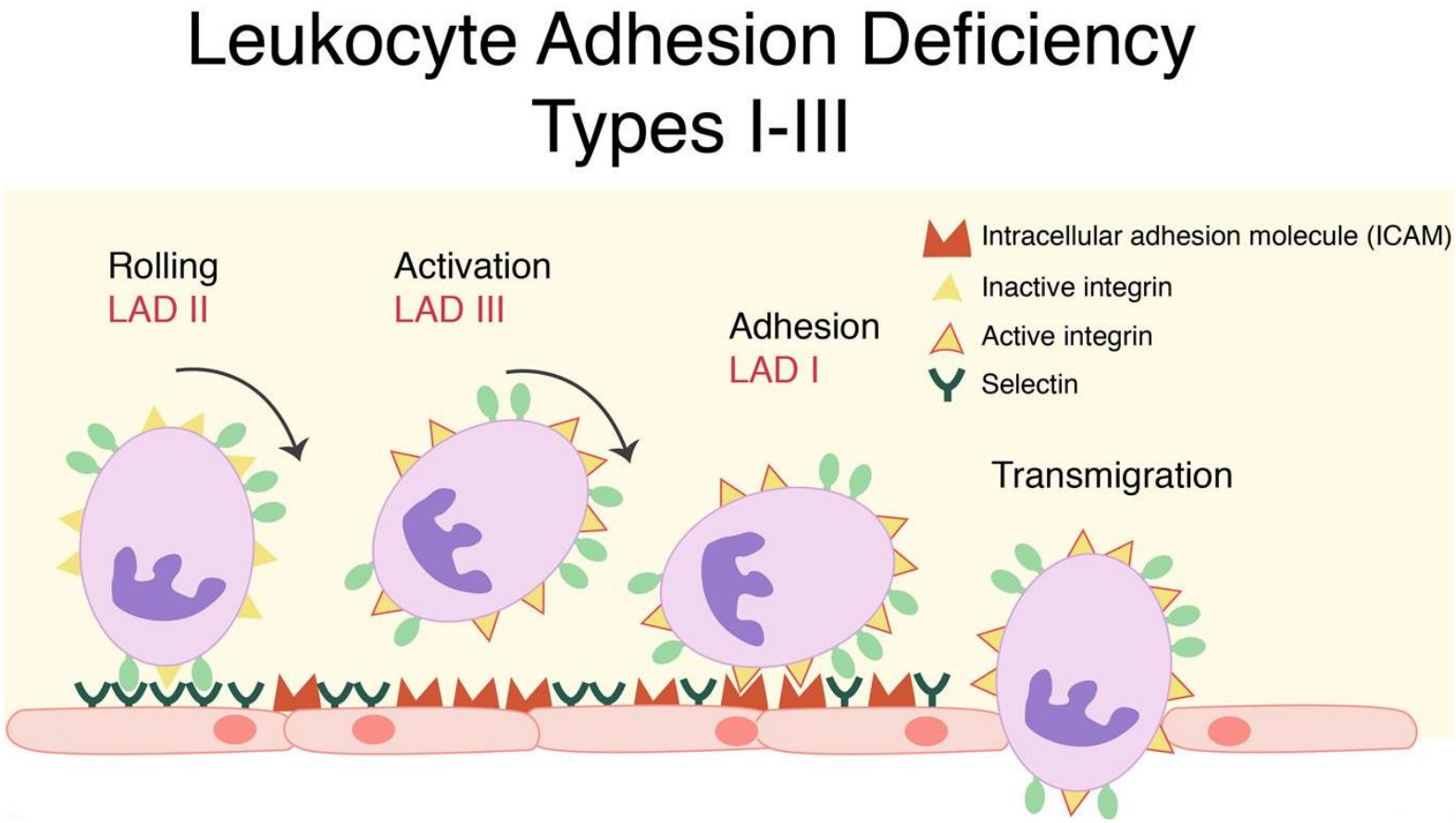
Chediak- Higashi Syndrome

- Normal levels of enzymes (digestive)
- Defect in organelle membrane which inhibits normal fusion of lysosomes.
- Fail to destroy ingested microbes,
- Symptoms : Recurrent infection with bacteria (chemotactic and degranulation defects, absent NK activity)



Leukocyte Adhesion Defect 1 (LAD-1)

- Absence of CD 18 – common β chain of leukocyte integrin, and become unable to migrate.
- Symptoms: Recurrent and chronic infection , fail to form pus

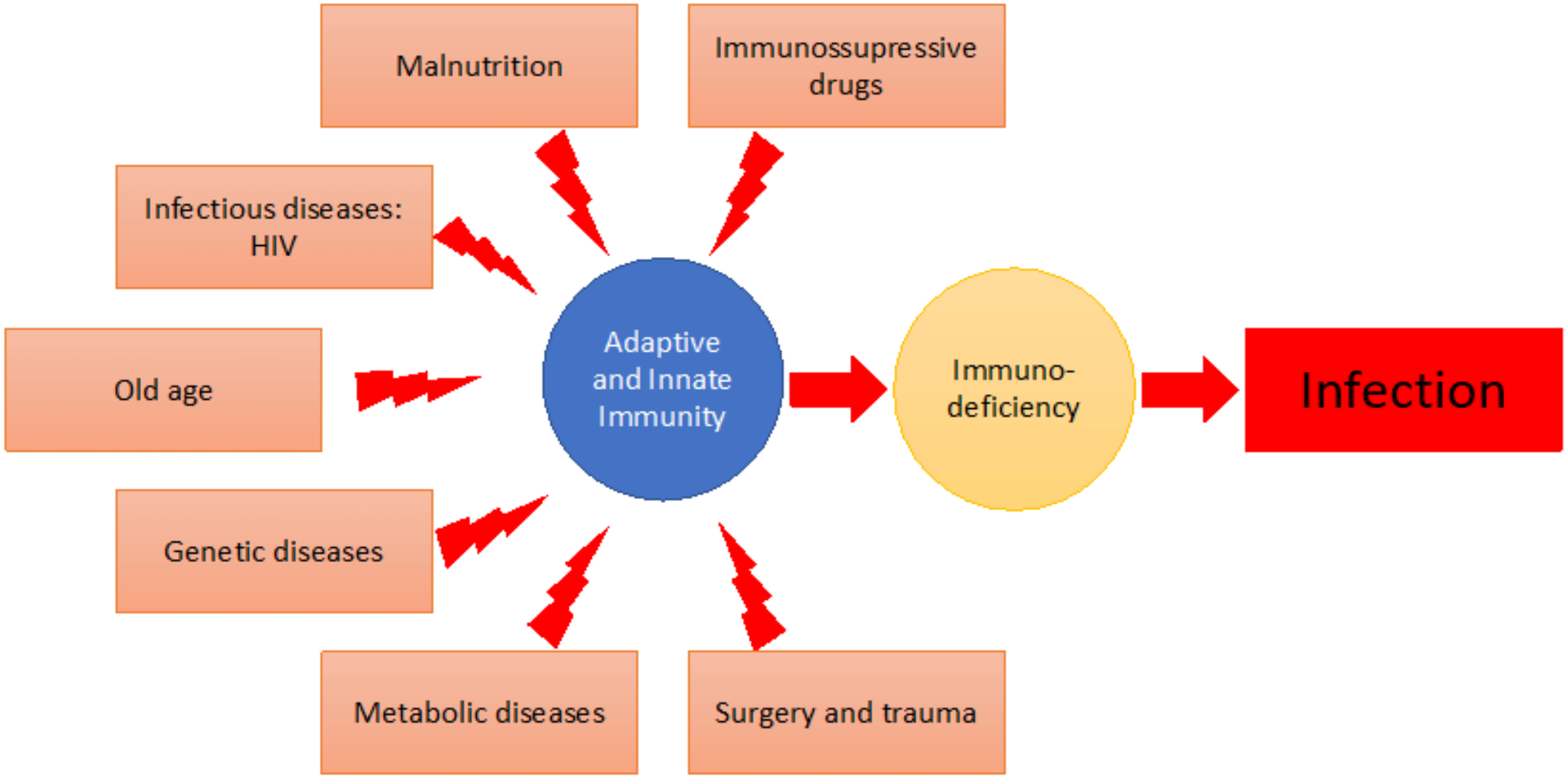


Defects of Complement System

Components	Deficiency	Signs/diagnosis
Classic pathway	C1q,C1r,C1s,C4,C2	**1.** Marked increase in immune complex disease. **2.** Increased infection with pyogenic bacteria.
Both pathways	C3	**1.** Recurrent bacterial infection. **2.** Immune complex disease.
	C5,C6,C7,C8	Recurrent meningococcal & gonococcal infections.
Deficiency of regulatory proteins.	C1-INH (hereditary angioedema)	**1.** Overuse of C1,C4 or C2. **2.** Edema at mucosal surfaces.

Secondary or Acquired Immunodeficiencies

- Agent-induced immunodeficiency



References

- ✓ Immunology , Kuby, seventh edition.
- ✓ Medical microbiology, Jawetz, 26th edition.
- ✓ Cellular and Molecular Immunology, Abul K. Abbas, 8th edition.
- ✓ Malesza, I.J.; Malesza, M.; Krela-Kaźmierczak, I.; Zielińska, A.; Souto, E.B.; Dobrowolska, A.; Eder, P. Primary Humoral Immune Deficiencies: Overlooked Mimickers of Chronic Immune-Mediated Gastrointestinal Diseases in Adults. Int. J. Mol. Sci. 2020, 21, 5223. https://doi.org/10.3390/ijms21155223
- ✓ Cunningham-Rundles, C. (2001). Common variable immunodeficiency. Current allergy and asthma reports, 1(5), 421-429.
- ✓ Reinhard A.Seger. 2019. Chronic granulomatous disease 2018: advances in pathophysiology and clinical management. LymphoSign Journal. 6(1): 1-16. https://doi.org/10.14785/lymphosign-2018-0012.
- ✓ Ni, J., & Zhang, L. (2020). Cancer Cachexia: Definition, Staging, and Emerging Treatments. Cancer management and research, 12, 5597–5605. https://doi.org/10.2147/CMAR.S261585.