Foundation block

Immune deficiency disorders

5th lecture

Objectives:

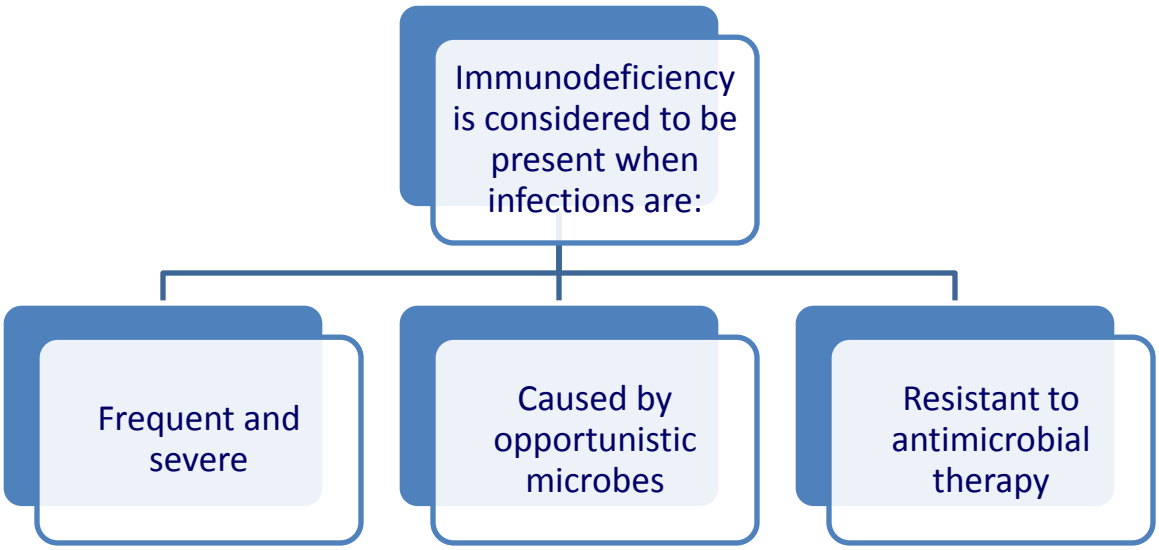
- Identify that Immunodeficiency is due to a defect in the immune function.
- Describe the classification of Immunodeficiency.
- Explain the presentations of different types of Immuno-deficiencies (e.g. recurrent infections).
- Understand the varieties of immune system deficiencies involving defects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

Note:
Black: Slides
Orange: Explanation
Purple: Extra
Red: Important

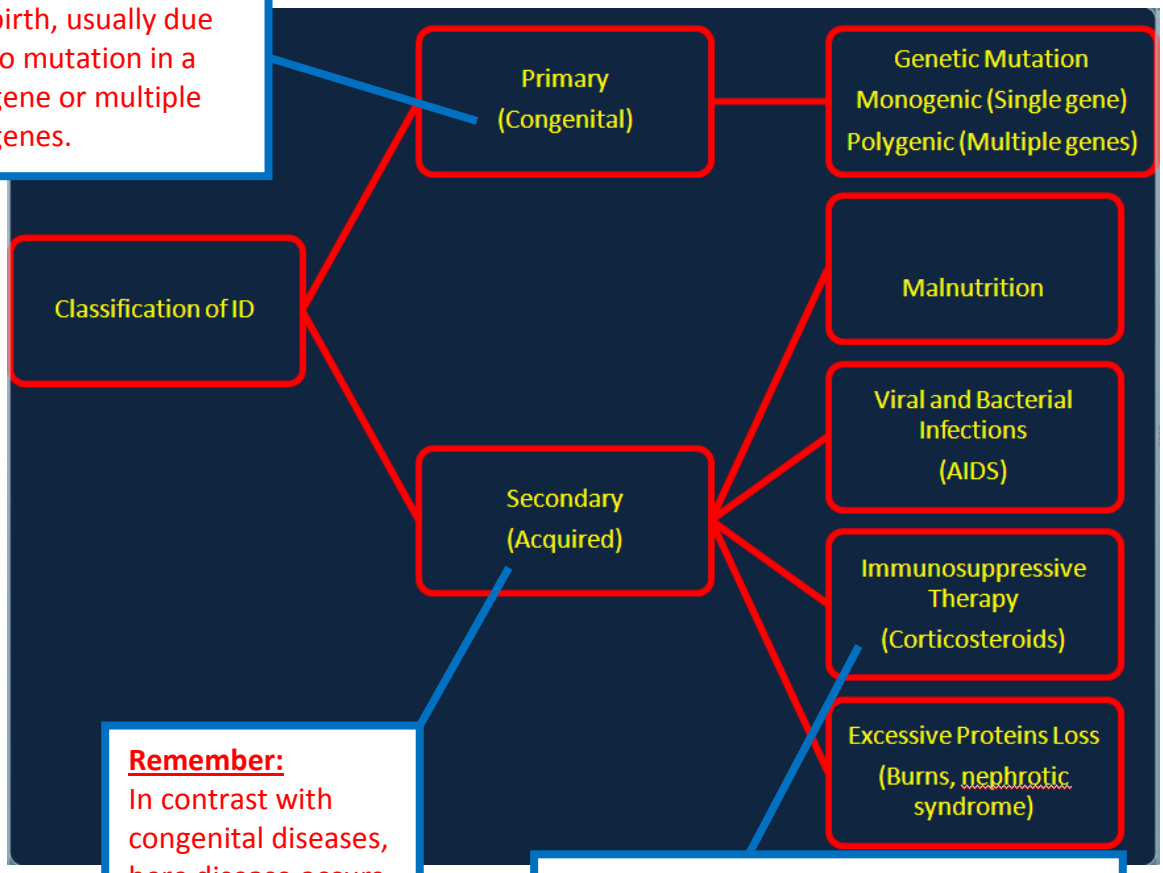
Definition:

-A state in which the ability of the immune system to fight infectious disease is compromised (part of the immune system) or entirely absent (The immune system as a whole).

-A person who has an immunodeficiency is said to be immuno-compromised.

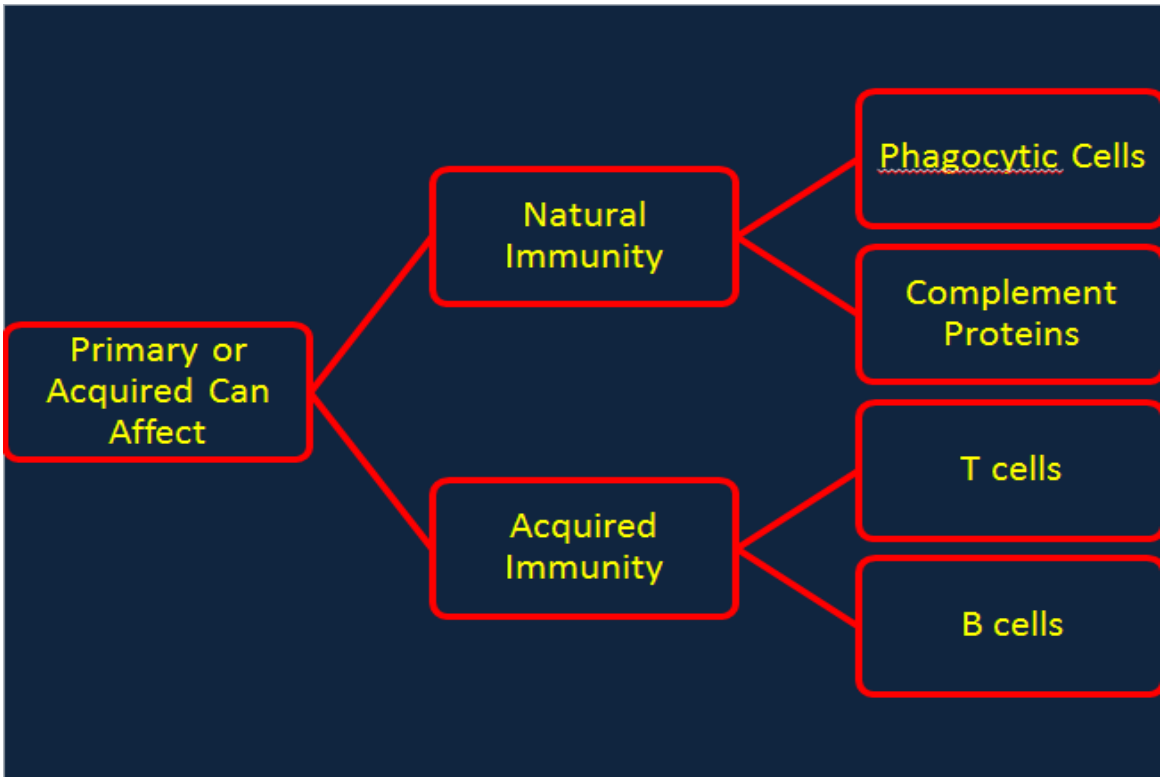


Remember:
Disease existing at birth, usually due to mutation in a gene or multiple genes.



Remember:
In contrast with congenital diseases, here disease occurs after birth due to different factors.

In some cases of immune diseases they use immunosuppression drugs (e.g. in transplantation doctors use corticosteroids to accommodate the grafted organ.



T-cells defects:

DiGeorge Syndrome (Congenital Thymic Aplasia)

A congenital defect that is marked by:

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

Usually hypoplasia of thymus gland is associated with hypoparathyroidism.

Features of DiGeorge syndrome

- Children may present with tetany
- Extreme susceptibility to viral protozoal, and fungal infections
- Profound depression of T-cell numbers
- Absence of T-cell responses

Tetany is associated with hypocalcaemia (low calcium level in blood because of hypoparathyroidism) that causes difficulties in movement due to muscle spasm.

Because there is deficiency in T-cells due to hypoplasia of thymus (**Remember** that thymus produce mature T-cells).

Remember:
Anti-bodies can be either T-dependent or T-independent. In this case T-dependent antibodies are going to be switched off, therefore only T-independent antibodies will work against foreign bodies by secreting antibodies (they have weak immune response compared to T-dependent).

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 normal immunity to most viral and fungal infections

because:

T-cells are unaffected

Because bacteria are extracellular pathogen so it deals with humeral immunity (**Remember** that acquired immunity is divided into cell mediated immunity and humeral immunity)

Diverse spectrum ranging from:

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

-X-linked disease:

Females : carriers (normal)

Males : manifest the disease

Remember that B-cells differentiate giving plasma cells that secret immunoglobulin (Antibodies), so the first 3 points are connected.

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

The most common type, 80 to 90 percent

Defect in Bruton Tyrosine Kinase (BTK)

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

BTK helps B-cells in getting mature in bone marrow (Premature B-cells BTK → mature B-cells).

Features of XLA

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

Pyogenic: bacteria that causes the formation of pus.

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

The deficiency is particular in respiratory tract and gastrointestinal tract because IgA is the master immunoglobulin in mucosal surfaces (For secretion).

X- linked hyper-IgM Syndrome (Congenital disease)

Characterized by:

- Markedly elevated IgM
- Low IgG, IgA & IgE

Management of immunoglobulin deficiencies:

*Periodic intravenous immunoglobulin (IVIG) reduces infectious complications

Severe Combine Immunodeficiency (SCID) (Congenital disease)

Causes of SCID:

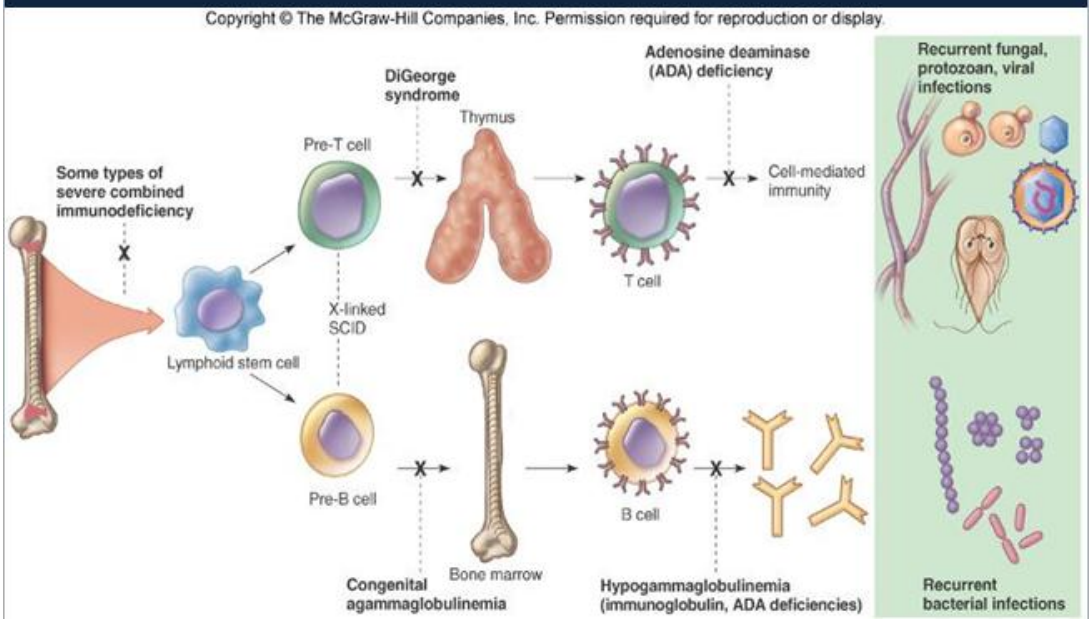
Enzyme deficiencies:

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

Accumulation of toxic metabolites will lead to cell death.

Features of SCID

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

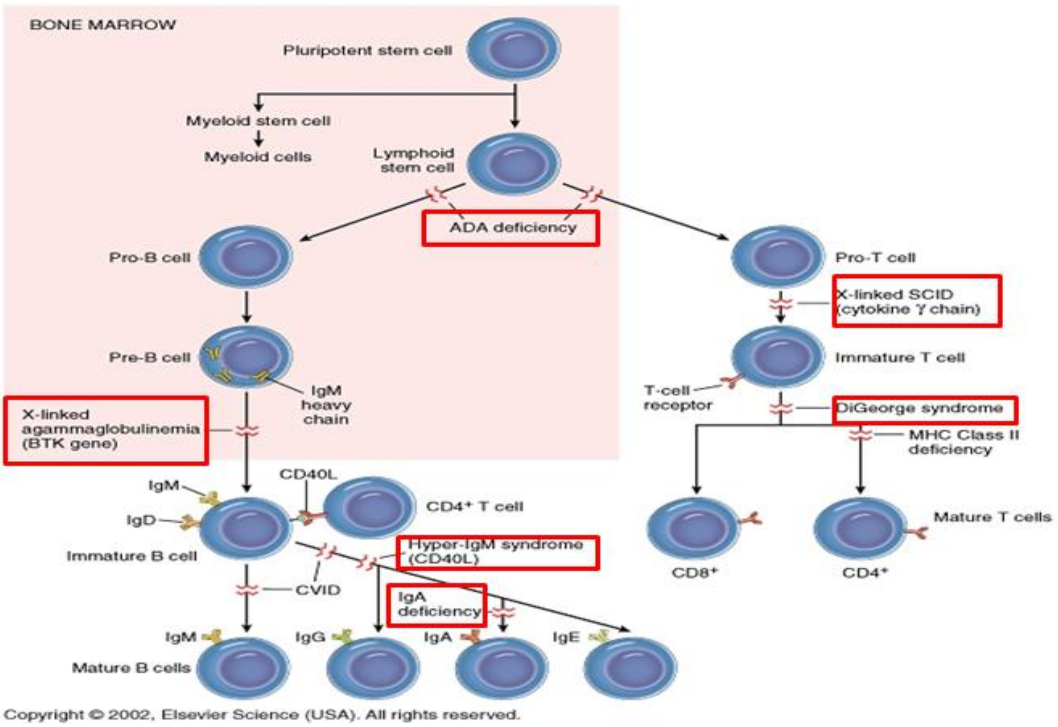


Management of SCID

1. Infusion of purified enzymes
2. Gene therapy

ADA and PNP enzyme are connected in gene therapy (Fixing the enzymes levels causing SICD).

Third way is through bone marrow transplantation from a good candidate.


BONE MARROW
Pluripotent stem cell
Myeloid stem cell
Myeloid cells
Lymphoid stem cell
ADA deficiency
Pro-B cell
Pre-B cell
IgM heavy chain
X-linked agammaglobulinemia (BTK gene)
Pro-T cell
X-linked SCID (cytokine γ chain)
Immature T cell
T-cell receptor
DiGeorge syndrome
MHC Class II deficiency
CD8+
CD4+
Mature T cells
IgM
IgD
CD40L
CD4+ T cell
Immature B cell
Hyper-IgM syndrome (CD40L)
CVID
IgA deficiency
IgM
IgG
IgA
IgE
Mature B cells
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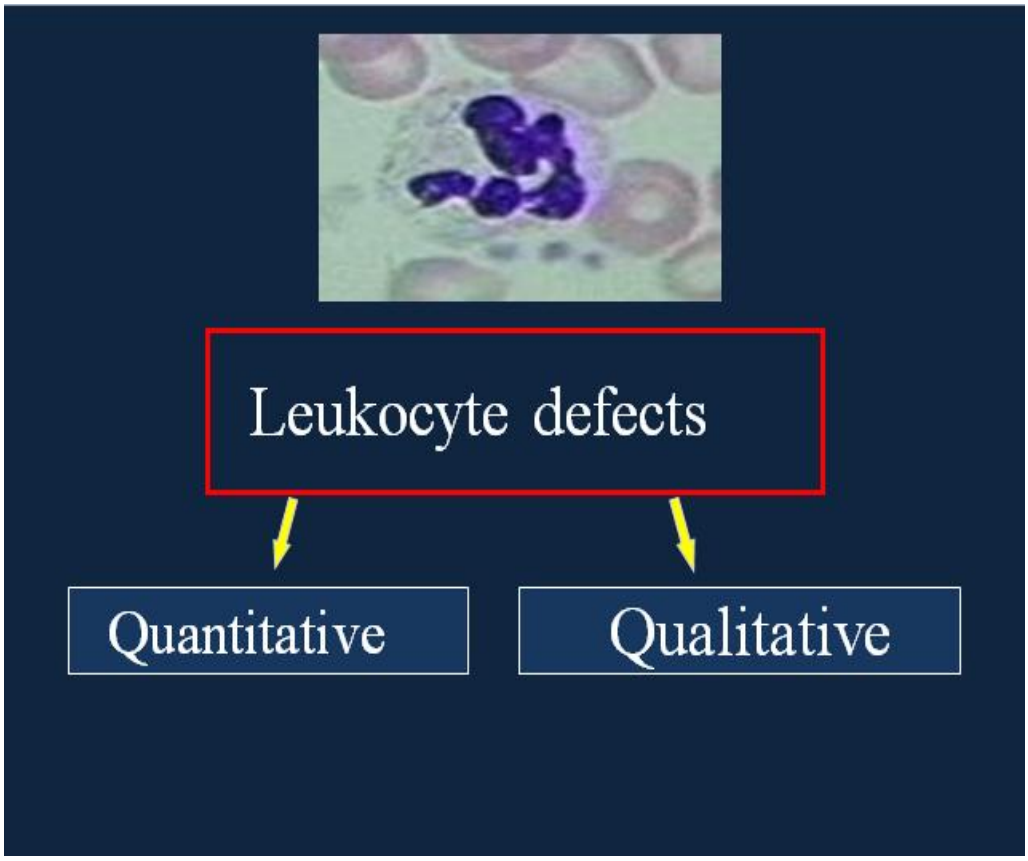

Leukocyte defects
Quantitative
Qualitative

Quantitative Defects

Congenital agranulocytosis:

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

Features:

Pneumonia, otitis media, abscesses

G-CSF is a cytokine that will lead to deficiency in granulocytes, therefore bacterial infections will increase causing different diseases like pneumonia …etc.

Qualitative Defects (Congenital disease)

A. Defect in chemotaxis

Leukocyte adhesion deficiency (LAD)

The movement of leukocytes to place of inflammation will decrease.

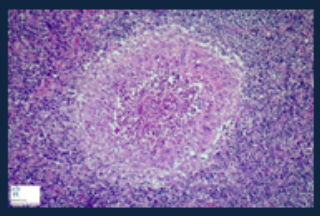
B. Defect in intracellular Killing

Chronic granulomatous disease:

Defect: in the oxidative complex responsible for producing superoxide radicals

The problem here is in the enzymes deficiency responsible for the formation of superoxide radicles.

Chronic granulomatous disease (CGD) (Congenital disease)



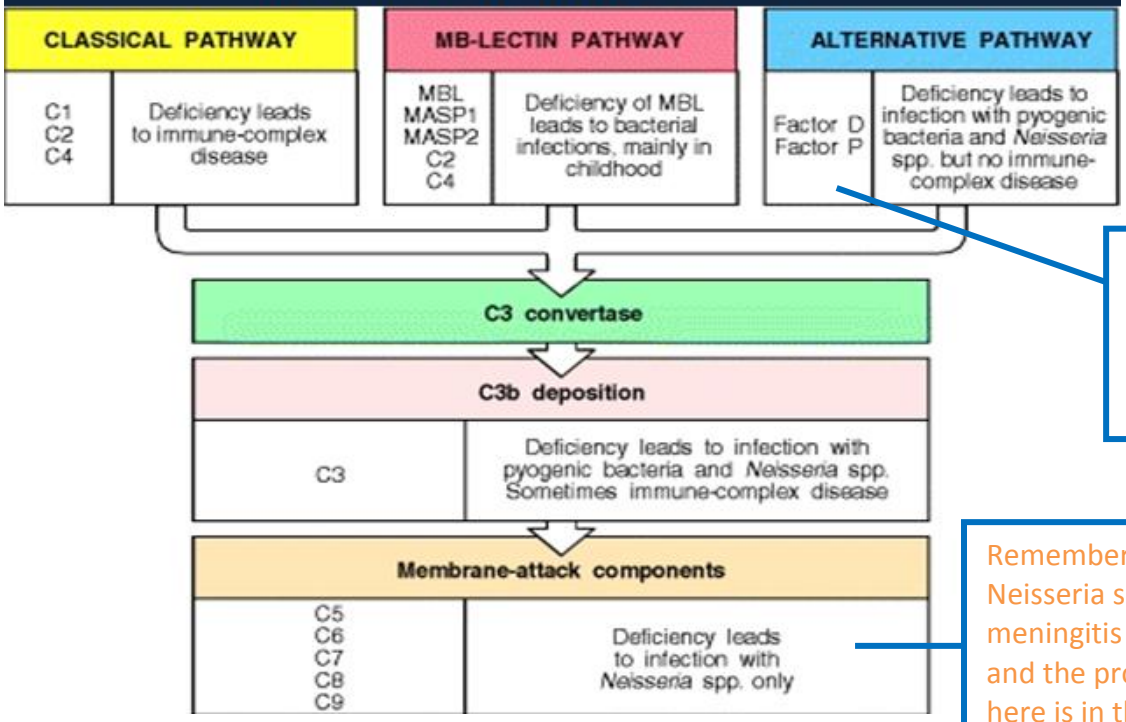
Neutrophils lack the "respiratory burst" upon phagocytosis

- Characterized by recurrent life-threatening bacterial and fungal infections and granuloma formation

It is a mechanism in which a decrease in intracellular killing occur (after phagocytosis which will be normal and unaffected) due to deficiency in the enzymes responsible for the formation of free radicals.

Complement Deficiency

Deficiency of all complement components have been described C1-C9



Factors are involved in alternative pathway.

Remember that Neisseria spp. Cause meningitis and STD, and the problem here is in the killing of bacteria.

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)

Can also be measured by Flowcytometry.