

T cells

- Critical for anti-viral responses, and production of class-switched antibodies (IgG, IgA, IgE)
- T cell deficiency often presents with recurrent viral or fungal infection that may be atypical or severe e.g. Candida, rotavirus.
- Investigate with **full blood count** and **lymphocyte subsets** (identifies lymphocytes by cell surface markers (CD molecules) i.e. **T cells (CD3, CD4 vs CD8)**
B cells (CD19, CD20)
NK cells (CD16, CD56)

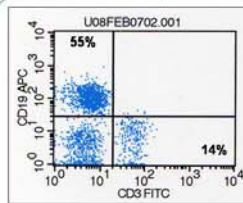
SCID

Severe combine immunodeficiency

- Lack of T cells.
- Different types depending on affected gene.
- Genetic defect blocks T cell development.
- Typically present in first few months of life.
- **Full blood count** shows low lymphocyte count.
- **Lymphocyte subsets** show low/absent T cells.
- May also have low **immunoglobulins**.
- **MEDICAL EMERGENCY**. Phone results.
- Patient urgently isolated and referred to Immunologist.

Symptoms of SCID:

- Failure to thrive
- Recurrent infections (severe/atypical)
- Diarrhea.



Low T cells
Flow cytometry plot showing lymphocyte populations. B cells=CD19+; T cells=CD3+ (CD3+ ref ~60%)

B cells

- Source of antibodies.
- B cell deficiency often presents with recurrent infections of the respiratory tract, including the middle ear (otitis media).
- Investigate with **full blood count** and **immunoglobulin concentrations**.

XLA

X linked agammaglobulinaemia

- Boys with mutations in the Btk gene on the X chromosome lack B cells and make no immunoglobulins.
- Present in infancy/early childhood.
- Treat with replacement immunoglobulin – only replaces IgG, not IgM, IgE or IgA, so monitor respiratory function.

Neutrophils

- Critical component of innate immune system. Vital for life.
- Neutropaenia can present with bacterial and fungal infections, including abscesses e.g. skin, lungs.
- Investigate with **full blood count**. May need specialist functional tests.

CGD

Chronic granulomatous disease

- Neutrophils present but respiratory burst (killing mechanism) doesn't work.
- Present in childhood with abscesses due to bacteria e.g. S. aureus or fungi e.g. aspergillus.
- Specialist functional assay shows lack of respiratory burst in patient neutrophils.
- May have raised **CRP** and **immunoglobulins**, due to infections.

NBT test

Neutrophils are incubated with a dye called nitroblue tetrazolium (NBT) and stimulated. Neutrophils undergo respiratory burst and die when activated, leaving a black precipitate where the cells were. This reaction is absent in patients with CGD. For images, refer to *Ott et al., 2006. Nature 12:401.*

CVID

Common variable immunodeficiency

- B cell function defective
- Can present in adulthood.
- May see low B cells on lymphocyte subsets (1% of patients), abnormal immunoglobulins, or may need to refer for specialist investigations.

Symptoms:

- Respiratory infections
- Autoimmune disease
- Granulomatous disease
- Lymphoma

Primary vs secondary

Primary Immunodeficiency

- Mostly rare
- Notable exception is IgA deficiency (1/700 of Caucasians)*
- Onset usually in infancy/childhood
- Notable exception is CVID - can present in adulthood.*
- Consider urgent referral of a baby with unusual infections (recurrent / severe / atypical) for investigation of primary immunodeficiency.

Secondary immunodeficiency

- Most common cause of immune deficiency in adults.
- Consider:
- Chemotherapy
 - Radiotherapy
 - Asplenia (surgery, trauma)
 - Protein loss – gut/kidney/skin
 - Infection e.g. HIV
 - Malignancy e.g. B cell malignancy
 - Malnutrition
- Other e.g.
- Diabetes (impaired neutrophil function)
 - Extremes of age

IMMUNE DEFICIENCY

When investigating the immune system, consider:
"Is it there?" "Does it work?" "Is it doing the right thing?"
An abnormal immune system may result in autoimmunity or malignancy.

Components of the immune system

Cells	Soluble mediators	Tissues
Lymphocytes (T, B, NK)	Immunoglobulins	Bone marrow
Monocytes/macrophages	Complement proteins	Thymus
Neutrophils	Cytokines	Lymph nodes
Basophils	Chemokines	Spleen
Eosinophils	Leukotrienes	MALT
Mast cells	Prostaglandins	(mucosal associated
Dendritic cells	Growth factors	lymphoid tissue)
Red blood cells	Acute phase proteins e.g. CRP	

Immunoglobulins

Investigations:

- Immunoglobulins
- Lymphocyte subsets
- IgG subclasses
- Vaccine antibody responses e.g. Pneumococcus, H. influenzae, Tetanus

Immunoglobulin deficiency

1. **IgA deficiency (1/700 of Caucasians)** - frequently asymptomatic but at risk of anaphylaxis to blood products containing any IgA.
2. **IgG subclass deficiency** - variable symptoms
3. **Specific antibody deficiency** – recurrent infections with a particular pathogen.

Considerations:

- Are B cells present and functioning?
- IgG for first 6 months of life is from Mum.
- Is the patient on replacement immunoglobulin.
- Vaccine history – has the child had their vaccines?

Only some immune deficiency conditions are given here.

Asplenia

- Spleen plays a key role in immunity to:
 - Blood borne infections e.g. malaria
 - Encapsulated bacteria e.g. pneumococcus, meningococcus, H. influenzae.
- Asplenia can be congenital (rare) or due to splenectomy.
- Prone to recurrent infection with encapsulated bacteria.
- Vulnerable to sepsis, which could be fatal.
- If possible, check immune responses to encapsulated bacteria and vaccinate if necessary before splenectomy.
- May see Howell-Jolly bodies on blood film
 - Inclusions in red blood cells that contain DNA.
 - Also seen in other conditions e.g. some leukaemias, haemolytic anaemia

DiGeorge syndrome

- Due to mutations on chromosome 22q, resulting in malformation of structures derived from 3rd and 4th pharyngeal pouch
- Defects in thymus disrupt T cell development, ranging from mild phenotype to absent T cells → SCID-like phenotype.

Symptoms

- Heart defects
- Hypocalcaemia (tetany, seizures)
- Cleft palate
- Immune deficiency – lack of T cells.
- Patients vary in structures affected and severity.

Affected structures

- Heart
- Thymus
- Parathyroid gland
- Facial structures

Classical pathway (C1, C4, C2) activated by immune complexes

Lectin pathway (MBL, C4, C2) activated by MBL binding to sugars on pathogen surfaces

Alternative pathway (Factors B, D, P) activated by bacterial surfaces

Terminal pathway (membrane attack complex – C5-9).

Tightly regulated by inhibitors e.g. C1 esterase inhibitor (C1HIB), which regulates C1 activity.

Complement

See Renal poster for reminder of Complement Cascade.

Investigations

- **C3 and C4 concentration** first
 - Low C4 = classical pathway activation
 - Low C3, normal C4 = alternative pathway activation.
- **CH50** (activity of classical pathway)
- **AP50** (activity of alternative pathway)
- **MBL** concentration
- **C1HIB concentration and function.**

Diseases of complement deficiency

1. Deficiency of classical pathway components - associated with **SLE**, especially C2.
2. Defects in C3, alternative or terminal pathways - associated with **bacterial meningitis** due to meningococcus.
3. **MBL deficiency** - associated with recurrent **respiratory infections**.
4. C1 esterase inhibitor (C1HIB) deficiency – **Hereditary/Acquired angioedema**.

Hereditary angioedema

- Episodes of painless swelling of face, limbs or trunk.
- Most dangerous when near airways e.g. mouth, face, neck.
- Due to genetic defect in C1HIB, causing impaired expression or function.
- Symptoms caused mainly by excessive bradykinin activity.
- **Low C4 concentration** due to lack of inhibition of classical pathway.
- Low **C1HIB expression**, or normal/raised C1HIB expression but low **C1HIB function**.
- **Acquired angioedema** due to autoantibodies to C1HIB e.g. in B cell malignancy.