Immunodeficiency: from suspicion to diagnosis…

Dr. Nadisha Badanasinghe

Senior Lecturer

Department of Medical Microbiology

Objectives

- Classification of Immunodeficiency
    - Know the major primary immunodeficiencies and their features
    - Understand the relationship between type of infection and resulting immunodeficiency
- When to suspect
- How to investigate

Overview of immune system

Innate immunity

Components

Macrophages
Granulocytes
Natural killer cells
Complement
Other chemicals: HCL, lysozyme

Characteristics

* Action is immediate
* Response is non-specific
* Response is not enhanced on repeated exposure to pathogen (no memory)

Adaptive immunity

Humoral

Components

B cells
Antibodies

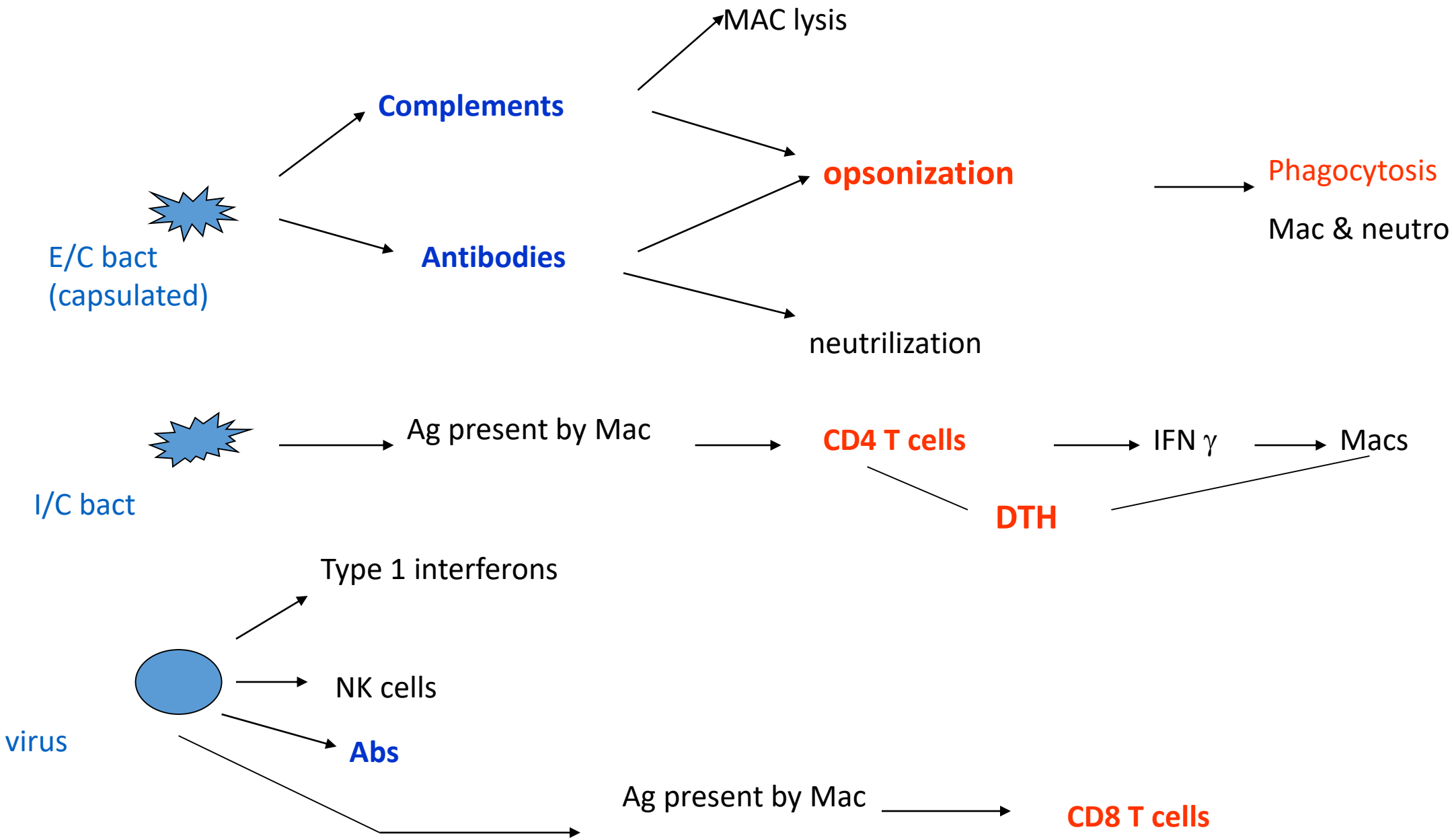
Cell-mediated

Components

T cells
CD4
CD8

Characteristics

* Action is delayed
* Response is specific
* Response is enhanced on repeated exposure to pathogen (has memory)


MAC lysis
Complements
opsonization
Phagocytosis
Mac & neutro
E/C bact
(capsulated)
Antibodies
neutrilization
Ag present by Mac
CD4 T cells
IFN γ
Macs
I/C bact
DTH
Type 1 interferons
NK cells
virus
Abs
Ag present by Mac
CD8 T cells

Classification

- Primary - inherited defects of the immune system
    - These defects may be in the adaptive or innate immune mechanisms.
    - They are classified on the basis of the site of lesion or pathway of the immune system.

- Secondary (Acquired)- consequence of other diseases and their treatments (iatrogenic)
    - Eg. Infections, AIDS, malnutrition, malignancies, transplantation

Primary immunodeficiency

- Incidence from 1/10 000 to 1/2000 live births.
- Can be classified according to the site of deficiency/ type of cells involved **(working classification)**

1. Complements defect - **Opsonic defect -** ~2%
2. Neutrophil defect –**Phagocytic defect -** ~ 18%.
3. Ab defect - **Opsonic defect -** >50%
4. T cell defect –**Cellular defect -** ~ 20-30%.

When to suspect

- Severe, Persistent, Unresponsive or Recurrent Infections.

  (SPUR)
- Unusual or opportunistic infections
- Infants with
  - Family history of ID
  - Syndromes known to be associated with ID
  - Failure to thrive
  - Lymphopaenia
- Patients with persistent infection with low virulent org., persistent diarrhoea, poor response to antibiotics
- Opportunistic cancers

10 Warning Signs Of Primary Immunodeficiency

- Ten or more otitis media infections within 1 year
- Recurrent, deep skin or organ abscesses.
- Two or more serious sinus infections within 1 year
- Persistent thrush in mouth or elsewhere on skin, after age 1
- Unusual organisms. Unusual response to organism
- Dysmorphic features with recurrent infection
- Two or more pneumonias within 1 year
- Two or more deep-seated infections
- Failure of an infant to gain weight or grow normally
- A family history of Primary Immunodeficiency

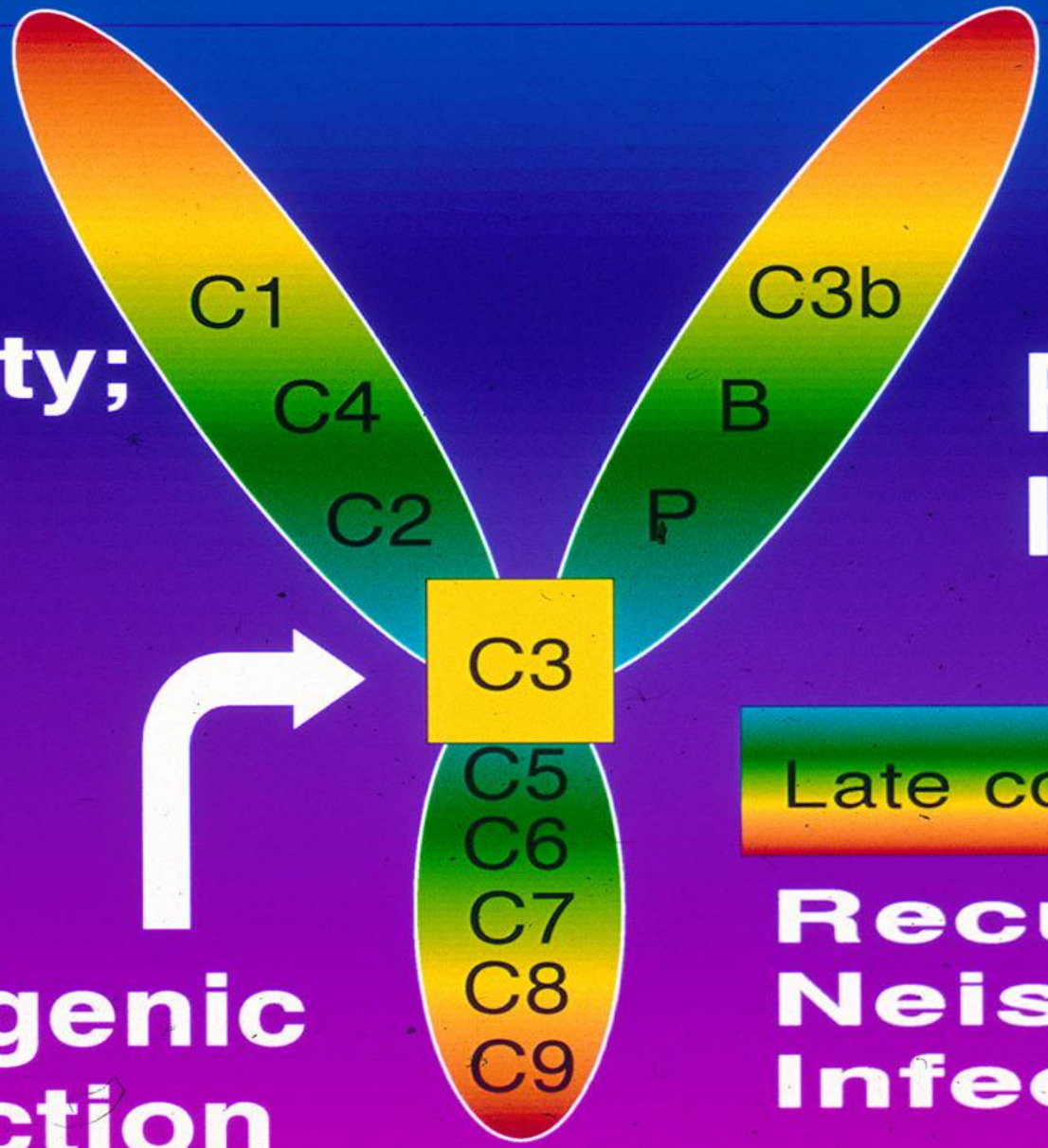
Complement deficiency

- Deficiencies in Alternative PW and Classical PW - C**3b,Factor B, C**1, C4, C2
    - Pyogenic infections with capsulated bacteria – Pneumococcus, H. influenza, gram neg
- Deficiencies in terminal PW (Membrane Attack Complex/ MAC components) C5,6,7,8,9
    - Disseminated Neisseria infections
- Deficiencies in MBL PW
    - Invasive pyogenic infections with meningococci and pneumococci in neonates
- Deficiency in early components C1,C2,C4 → autoimmune diseases

Complement and Infection

Classical Pathway

Autoimmunity; Occasional Infections



Alternative Pathway

Pyogenic Infections

Late components

Recurrent Neisserial Infections

Pyogenic Infection

Assessment of Compliments

- Screening test(functional assay)
  - Classical PW – CH50
    - Detect absence/ inactivity of classical PW
    - Tests the functional capability of complement components of classical PW to lyse sheep RBC pre-coated with anti-RBC Ab
  - Alternative PW – AP50
    - Test absence/functional abnormalities in the alternative PW

    Normal CH50 with absent AP 50 → Alternative PW deficiency
    Normal AP50 with absent CH 50 → Classical PW deficiency

- Quantitative estimation of individual complement components

Phagocytic Defects (neutrophils)

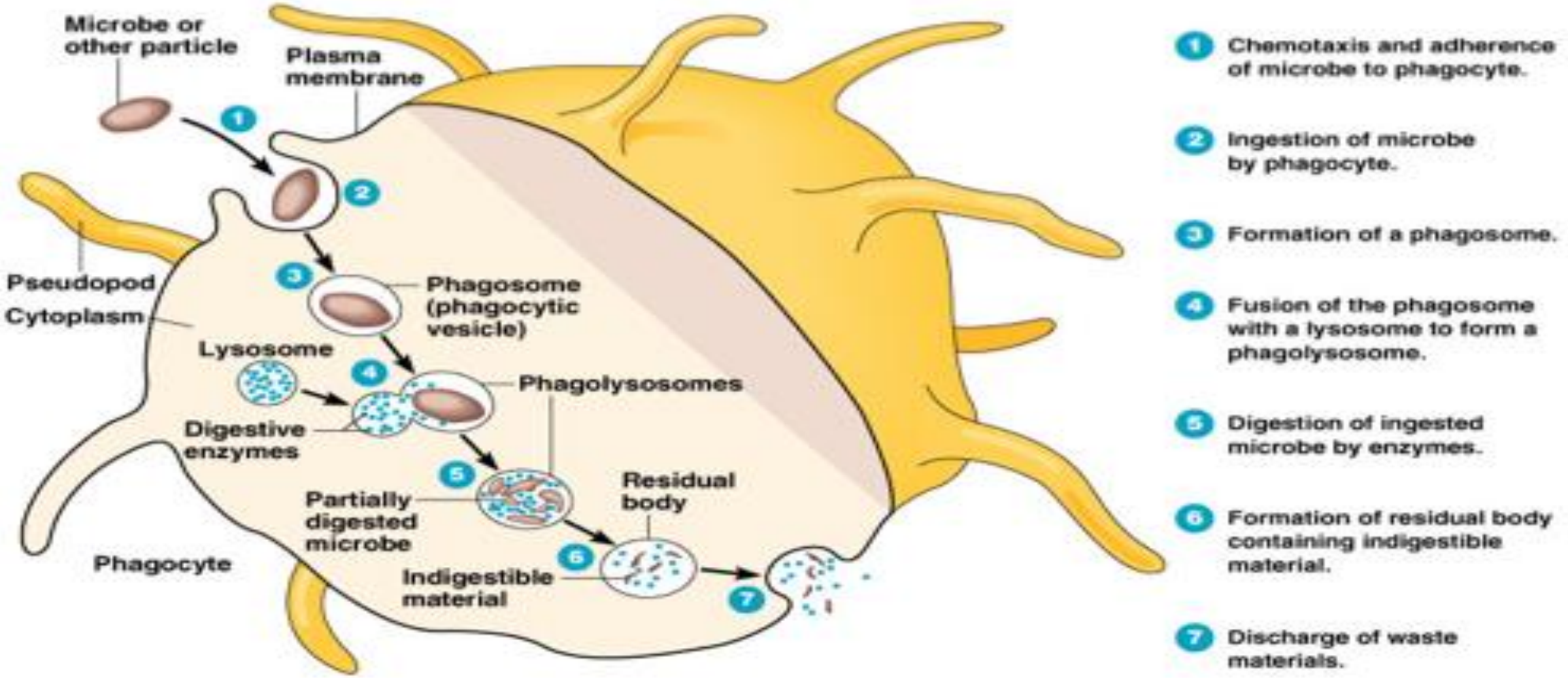
- Neutropaenia - Reduced number

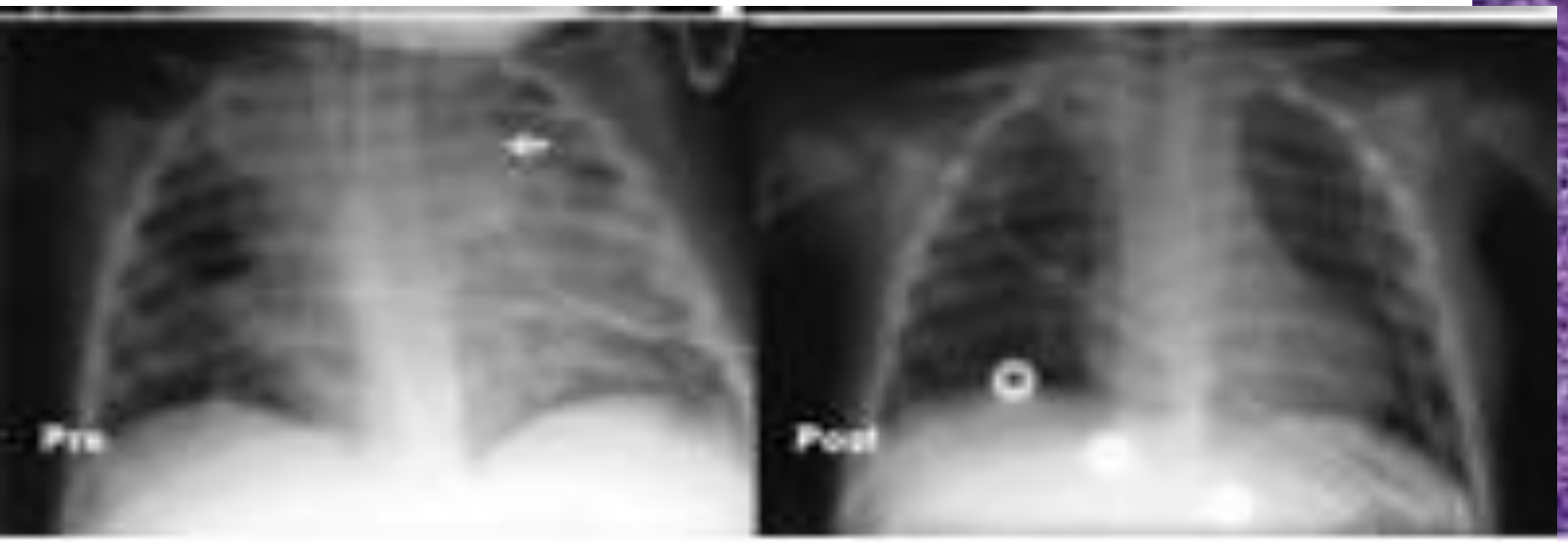
- Neutrophil dysfunction
    - Chronic granulomatous disease (CGD) – defect in the NADPH oxidase
        - Chronic suppurative granulamatous infections
        - Skin abscesses, granuloma in organs, disseminated Candida infections , cellulitis, pneumonia, otitis, arthritis, osteomyelitis

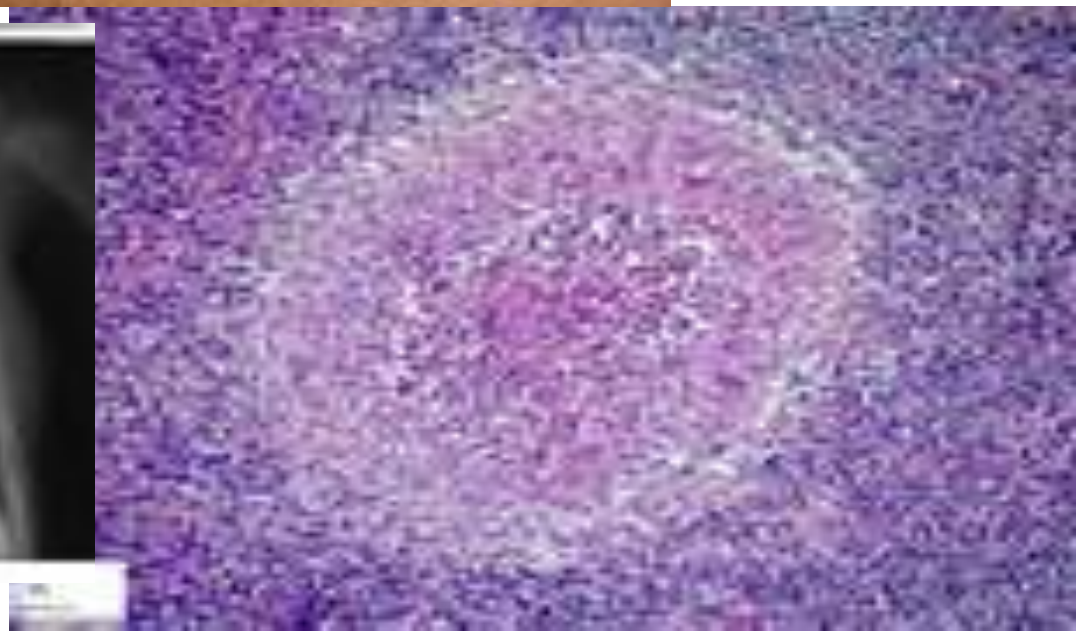
- Suseptible to infections with- Staphylococci, Coliforms, disseminated Candida, Aspergillus

- Early onset, delayed separation of cord (>8 weeks), poor wound healing

Phagocytosis




Pre
Post



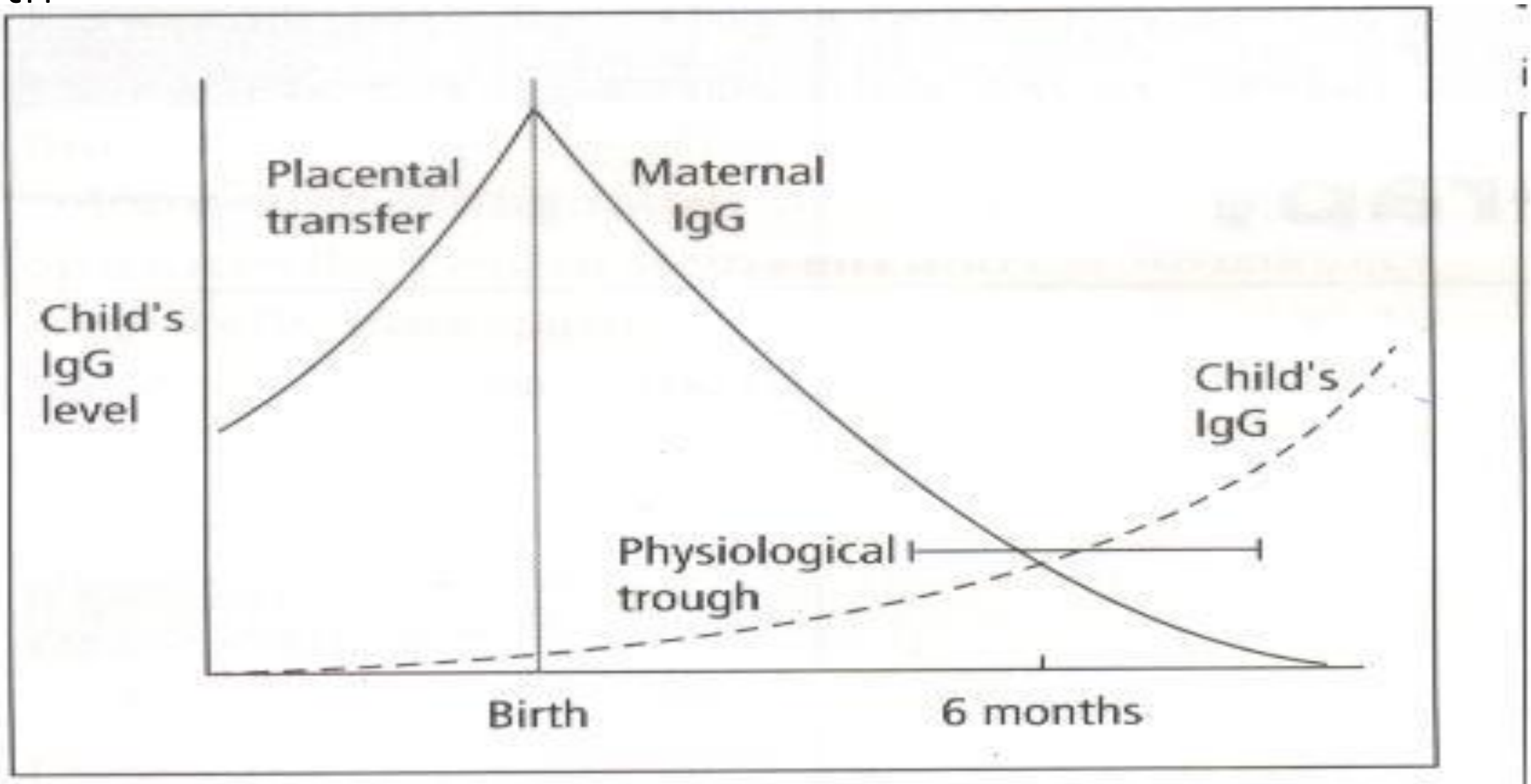
Assessment of Neutrophils

- Neutrophil count
- Blood picture
- Functional assay –
    - Chemotaxis
    - Adhesion
    - Phagocytosis
    - **I/C killing – NBT (Nitroblue tetrazolium test)** – for NADPH oxidase
        - **Done in CGD**

Ab deficiency

- Results from abnormal development of B cell system.
- T cell numbers and functions are normal: B cell numbers may be low or normal but immunoglobulin levels are low.
- Patients suffer from recurrent bacterial infections, predominantly by *Pneumococcus, Streptococcus & Haemophilus (capsulated bac) & Giardia (parasitic)*
- *Viral infections are clearly normal (except for enteroviruses)*
- *Growth – usually normal unless patients have recurrent infections*
- Onset - after 6 months of age

Changes in maternal and neonatal IgG levels before and after birth



Ab deficiencies

- Transient hypogammaglobulinemia
    - at birth IgG levels are comparable to that of the mother.
    - levels gradually decline, but by three months normal infants begin to synthesize their own IgG
    - In some infants IgG synthesis may not begin until they are 2-3 years old
    - This results in a transient deficiency of IgG which can be treated with gamma-globulin treatment.
- X-linked hypogammaglobulinemia -Bruton's hypoglobulinemia or agammaglobulinemia
    - most severe hypogammaglobulinemia
    - B cell numbers and immunoglobulin levels are very low
    - The patients have failure of B-cell maturation associated with a defective **B cell tyrosine kinase** gene

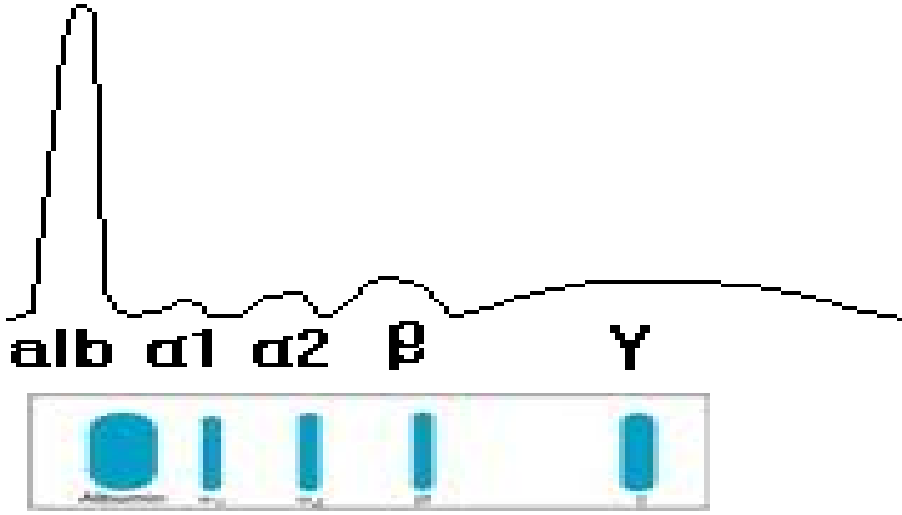
Ab deficiencies

- Common variable hypogammaglobulinemia
    - deficiencies of IgG and IgA in the 2nd or 3rd decade of the life
    - Normal B cell count but low Abs
    - Low functional Abs
    - Recurrent lung infections--> bronchiectasis

- IgA deficiency
    - commonest of all primary immunodeficiencies, but mostly asymptomatic
    - susceptible to gastrointestinal, eye and nasopharyngeal infections
    - high incidence of autoimmune diseases and lymphoid malignancies
    - Anti-IgA antibodies are detected in 30 to 40 percent of patients who should not be treated with IV immunoglobulins.

Assessment of Ab deficiencies

- Serum electrophoresis



- Quantitative estimation of immunoglobulins
  - IgA, IgG, IgM
- Natural Abs – Isohaemagglutinins
- B cell count
- Response to protein/ polysacc Ag
  - Ex. Diphtheria/ Tetanus
    Pneumococcal / Typhoid

Case - 1

- Baby S, female, 6 years
- H/o – recurrent attacks of LRTI since I year of age
- Frequent hospital admissions – once/month
- CT scan chest – collapse consolidation with bronchiolitis obliterans
- Clinically -? TB – started ATT at 1yr 4/12 (mantoux – neg)
- Paraplegia at 5 years after 5th dose of OPV(investigated as AFP)
- Dx- Enceplalo-myelopathy
- Stool for enteroviruses - + for Sabin like polio virus

Case – 1 ctd…..

- Consanguinity +
- No significant FH
- Immunization
- BCG scar +
- Wasted

Case – 1 ctd.....

- WBC/DC – NL
- Ab levels
  - IgG- 249 (419-1274)
  - IgA- 12.4 (19-235)
  - IgM- 40 (28-113)

Low IgG, IgA

- Flowcytometry
  - CD3 - 4194 μl (900-4500)
  - CD4 – 2832 μl (500-2400)
  - CD8 – 1362 μl (300-1600)
  - CD19 – 1646 μl (250-1600)

Normal T cells, B cells

- T cell function – NL

Dx - ? CVID

Stool for polio - + > 4/12 - chronic excretor

T cell deficiencies

- Recurrent opportunistic infections
- Viral infections with HSV, CMV etc.,
- Intracellular bacteria/fungi / parasites- Leigonella, TB, Salmonella infections, mucocutaneous candidiasis, Toxoplasmosis

- Onset – 4-5 months of birth

- Failure to thrive

- Live vaccines ⟶ severe infections

Severe Combined Immunodeficiency
SCID

- Functional impairment of both B and T lymphocyte limbs of the immune response.
- Inheritance is either X-linked or autosomal recessive
- Die within 2 years of life

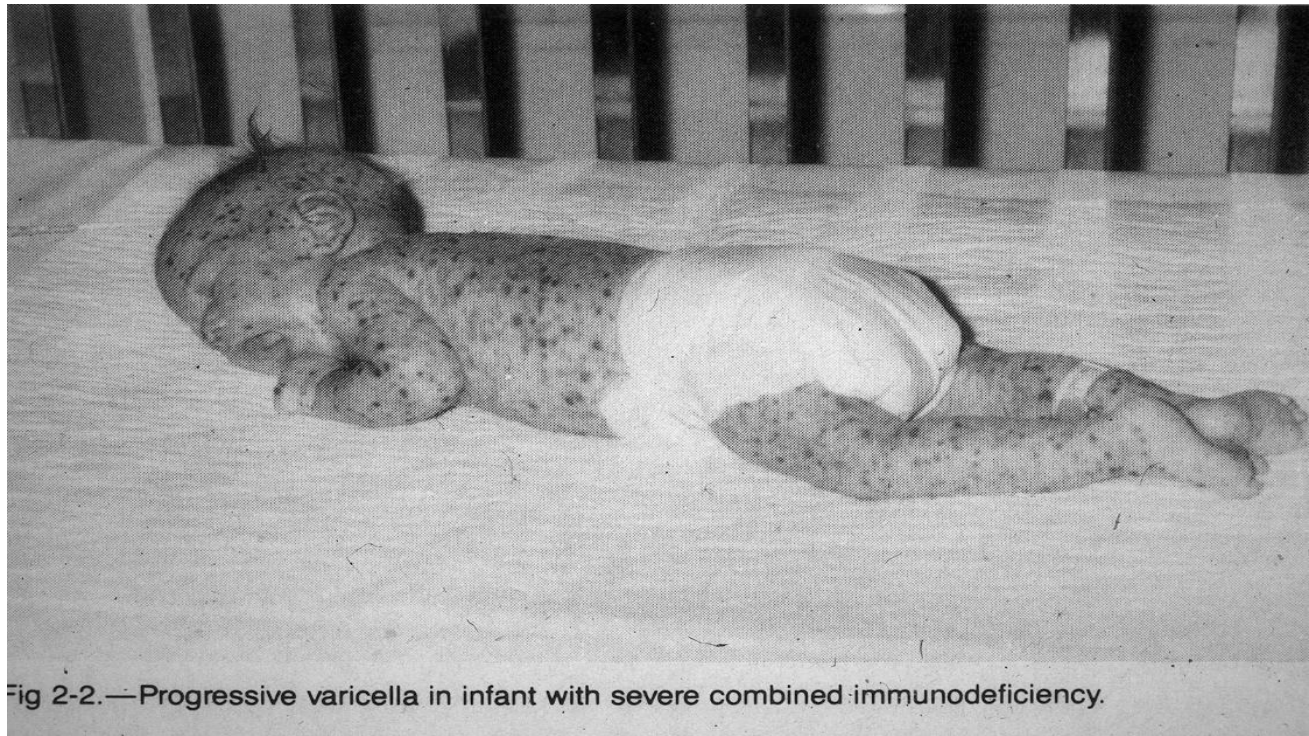


Fig 2-2.—Progressive varicella in infant with severe combined immunodeficiency.

T cell deficiencies

- **DiGeorge syndrome** (congenital thymic aplasia/hypoplasia, or immunodeficiency with hypoparathyroidism)
    - ↓ T cells, low Ig
    - Recurrent viral, bacterial and fungal infections

Partial Combined Immune Deficiency

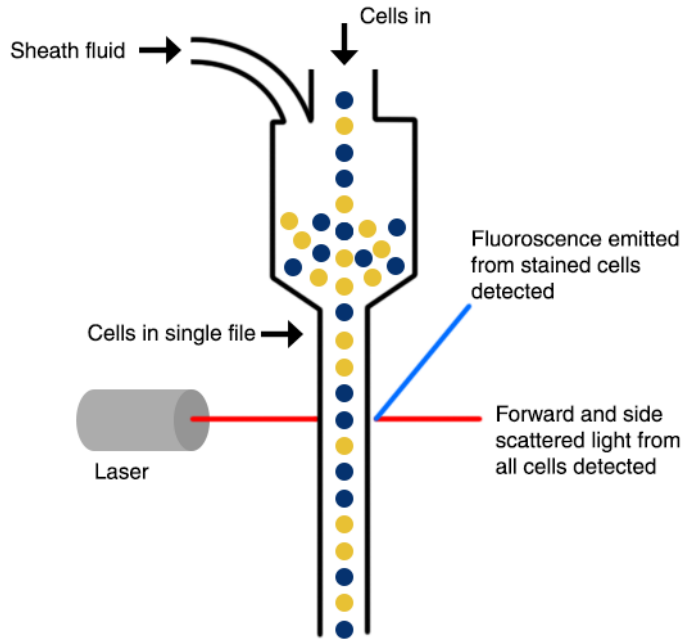
- Wiskott-Aldrich Syndrome
  - X-linked recessive disorder
  - Low CMI, low IgG

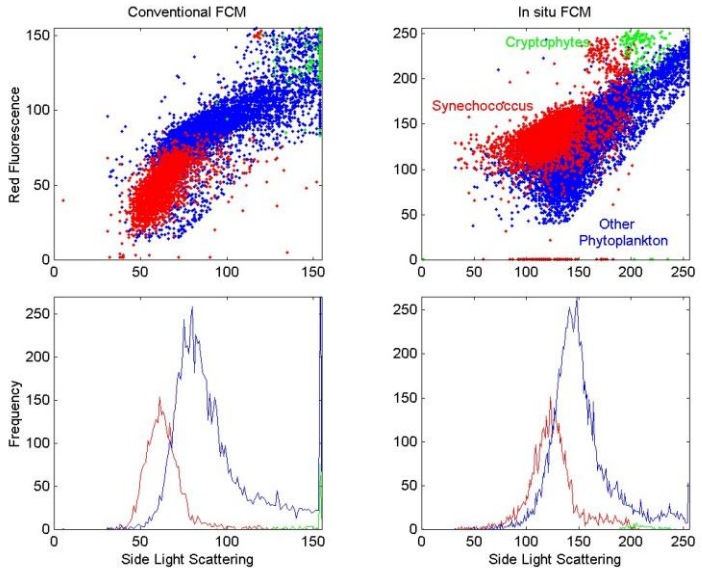
- Ataxia-Telangiectasia
  - Autosomal recessive disorder
  - Low CMI, low IgG

Assessment of T cells

- WBC/DC – lymphocyte count
- T cell count - CD4 & CD8 by Flowcytometer
- Skin test - PPD, Candida (DTH response to common Ags)
- In vitro T cell proliferation test


ACEA
NovoCyte


Cells in
Sheath fluid
Fluoroscence emitted from stained cells detected
Cells in single file
Forward and side scattered light from all cells detected
Laser


Conventional FCM
In situ FCM
Red Fluorescence
Cryptophytes
Synechococcus
Other Phytoplankton
Frequency
Side Light Scattering
Side Light Scattering

Case - 2

- Baby F,13 days, female, NVD
- H/o – fever since D3 , oral thrush
- FHx – 3 siblings died at D4 due to sepsis

  (not proven microbiologically)

  P_{1-}-> NVD 2006, male, died in D4 at home

  P_2--> NVD 2008, male, developed fever, died inD4 at home

  P_3--> NVD 2009, male, fever at D3, admitted to hospital, died in D4 due to sepsis
- Father & mother – distant relatives
- Mother's FHx – 2/3 still births
- Immunization – BCG given

Case-2 ctd…

WBC – 4300

N 50%

L 48%

E 2%

Platelet -100,000

Echo – small ASD

Case-2 ctd…

Flowcytometry

CD3 – 1704 μl (71%) (2300-7000)

CD4 – 1080 μl (45%) (1700-5300)

CD8 - 744 μl (31%) (400-1700)

CD19 – 288 μl (12%) (600-1900)

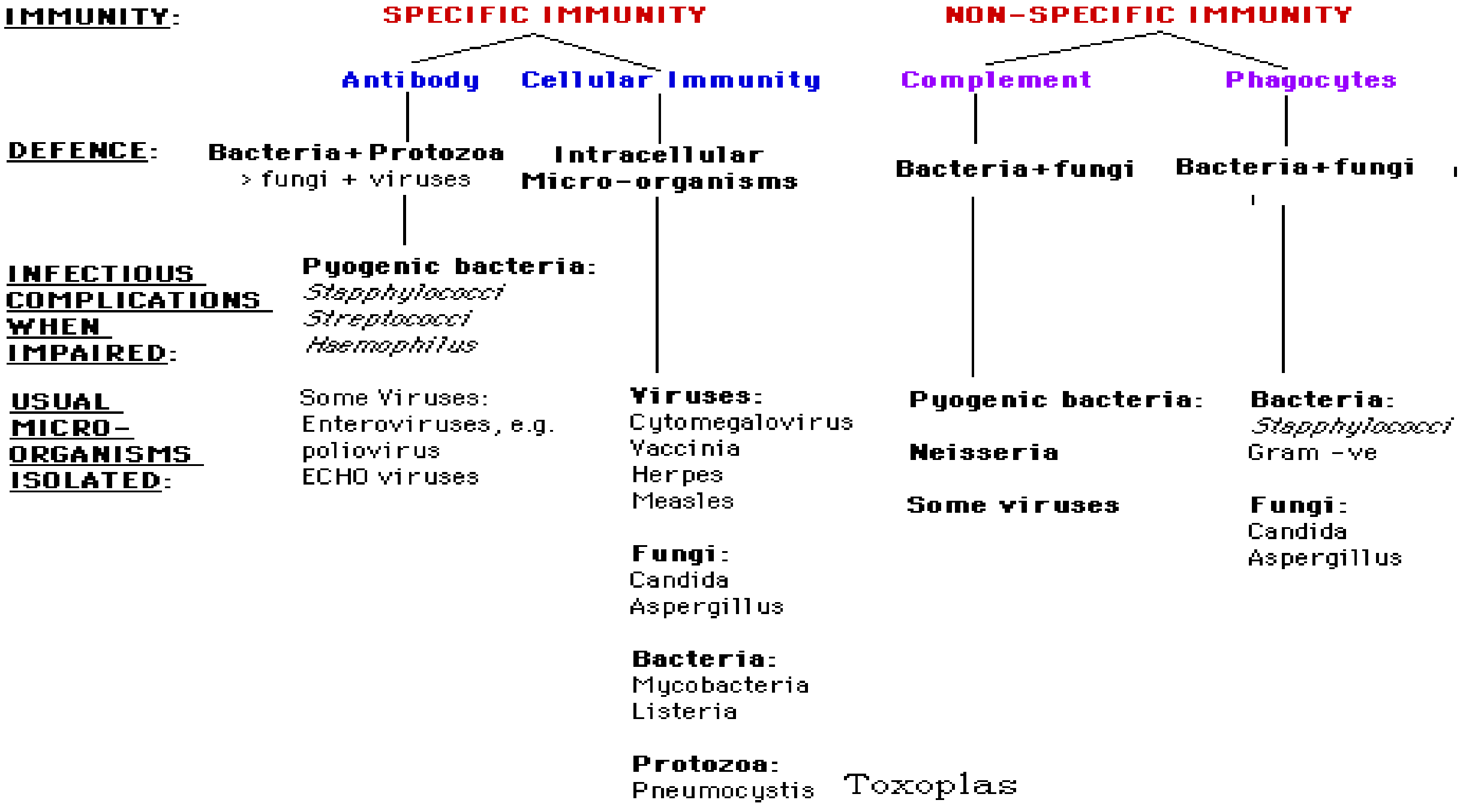
Low T cell + low B cell

A/w T cell function assay and Ab levels

? SCID

Risk of disseminated TB due to BCG

Common Infections Associated with Immunodeficiency



Diagnosis

High index of clinical suspicion

- Severe, Persistent, Unresponsive or Recurrent Infections.

  (SPUR)
- Unusual or opportunistic infections
- Infants with
  - Family history of ID
  - Syndromes known to be associated with ID
  - Failure to thrive
  - Lymphopaenia
- Patients with persistent infection with low virulent org., persistent diarrhoea, poor response to antibiotics
- Opportunistic cancers

History

- Age and sex
- Family history
- Consanguinity
- Immunization history
- Type and site of infection
- organism isolated

- **Always rule out HIV**

Physical examination

- A benign physical exam does not rule out immunodeficiency.

- Look for:
  - General appearance, weight, overall health
  - Dysmorphic features
  - Other features suggestive of an immune def
    - Tonsillar tissue, adenopathy, splenomegaly
    - Arthritis, ataxia, neuro deficits
    - Skin maniestations - eczema, petechiae, telangiectasia

Investigations

- General –FBC, CRP, ESR, BP
- Microbiological –all cultures, Ag detection, PCR
- Radiological –X-rays, CT scan
- Specific investigations – depending on the defective component

Treatment

Two goals

1. Avoid and treat infections
    - Monitor pts
    - Antibiotic – prophylaxis / treatment
    - **Immunization**
        - live vaccines should not be given
        - Killed vaccines are recommended – Pneumo, HIB, Meningo, Influenza
2. Replace the defective component
    - Intravenous Immunoglobulin
    - G- CSF – in neutropenia
    - Stem cell transplantation
    - Gene therapy

- **Investigations can not be performed after a recent blood transfusion**

Secondary (acquired) immunodeficiency

- Commonest immunodeficiency
- Contributes a significant proportion to hospital admissions
- Mainly affects the phagocytic and lymphocytic functions
- Results from infection (HIV), malnutrition, aging, cytotoxic therapy, diabetes mellitus, tumors
- Immunosuppressive microbes – malaria, measles and HIV.
- Other - burns, alcoholic cirrhosis, rheumatoid arthritis, renal malfunction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Summary

- Types of immune deficiency
  - Different types of infections in each type of ID
  - When to suspect
  - Diagnostic tests


Thank You