Children with Recurrent Infections

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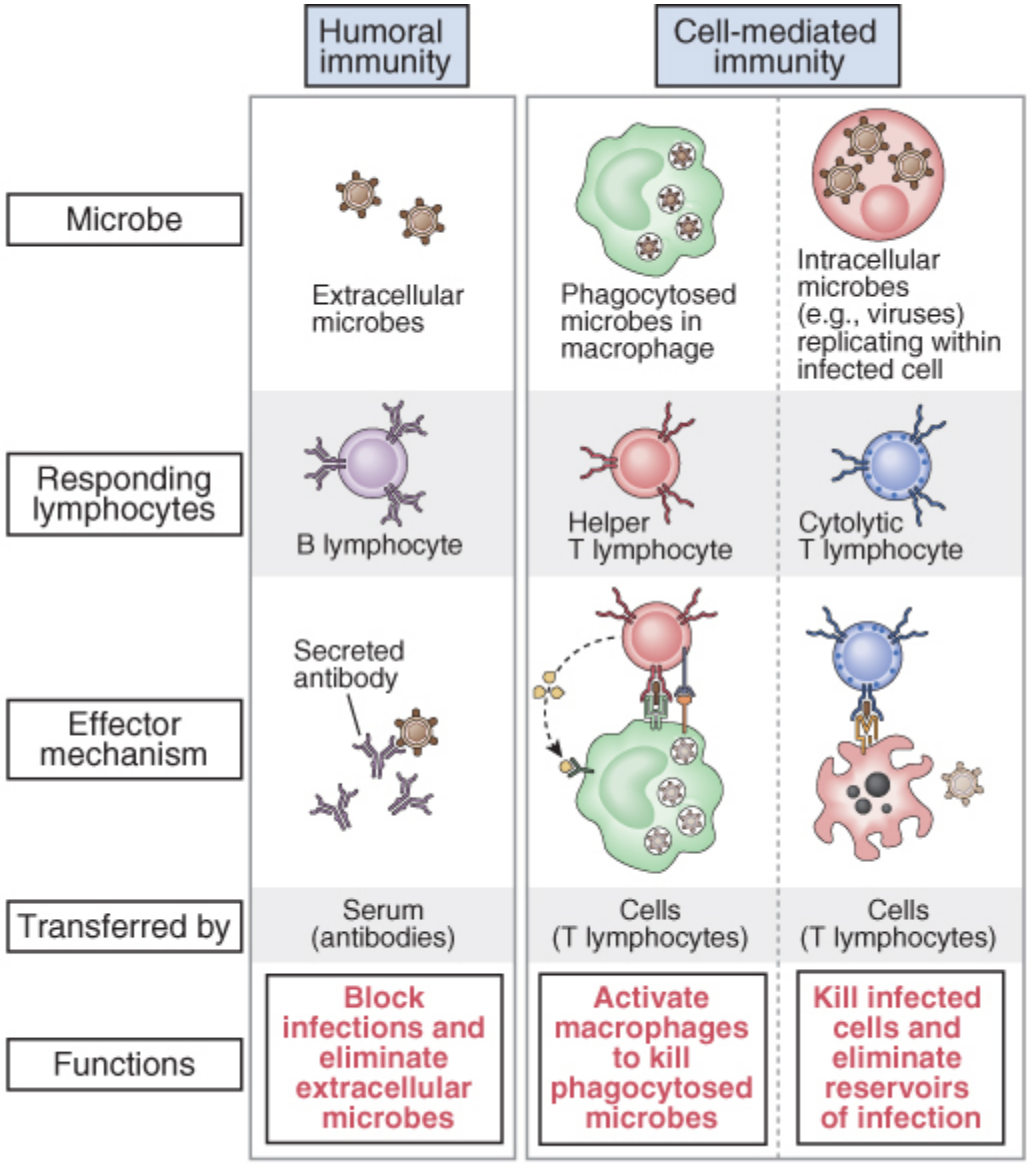
Host Immune Defense Mechanisms

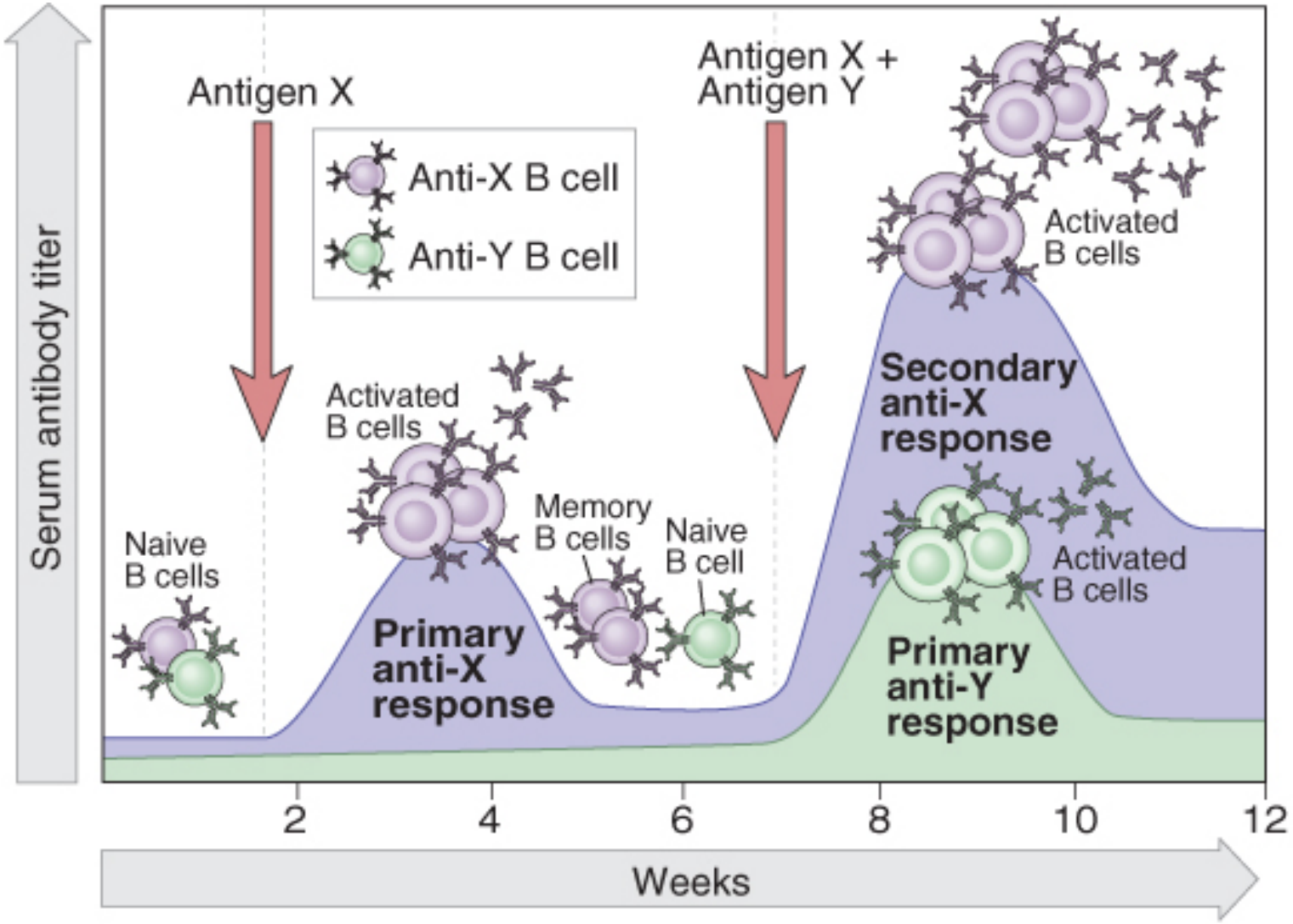
Non-specific (innate)

- Barriers
  - Skin
  - Secretions (mucous, tears, saliva)
  - Mucociliary clearance, peristalsis
- Phagocytes
  - Neutrophils
  - Macrophages
- Complement
- Cytokines

Specific (adaptive)

- Humoral (B-lymphocytes)
- Cellular (T-lymphocytes)





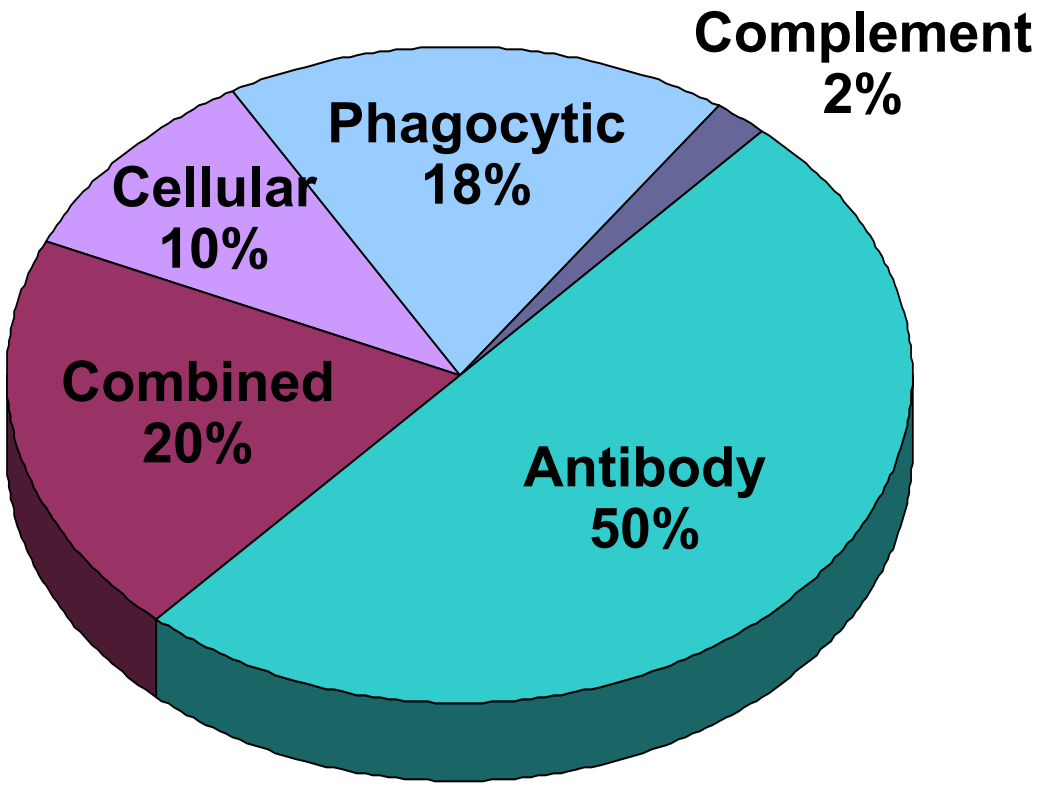
Immunodeficiency

- Definition:
  Immunodeficiency represents a diverse group of abnormalities of the immune system resulting primarily in an increased susceptibility to infection.

- Primary Immunodeficiency:
  Congenital (inherited).

- Secondary Immunodeficiency:
  Acquired. Could be transient or permanent.

Primary Immunodeficiency: Frequency



Over all prevalence of clinically significant PID is thought to be about 1 in 2000.

Primary immunodeficiency: Introduction

- Recurrent infections are generally the most common presenting feature of primary immunodeficiency diseases (PIDs).
- Certain non-immune related illnesses may present with recurrent infections. For example, CF and ciliary dyskinesia cause recurrent sinopulmonary infections, H-type TE fistula cause recurrent chest infections, and VUR cause recurrent UTI.
- Many PIDs are complicated by autoimmunity and malignancy.
- Careful history and physical examination can give the most important clues that will direct your investigations and further management.

Specific Immune Deficiencies affecting different lines of the immune system

Complement Deficiencies

- Early classical pathway components (C1, C4, C2,C3): Pyogenic infections, lupus like illness, vasculitis.

- Late complement components (C5-9): Recurrent or disseminated *Nisserial* infection.

Phagocytic Defects: Types and examples

A. Disorders of neutrophil number:
   - Cyclic neutropenia and severe congenital neutropenia.

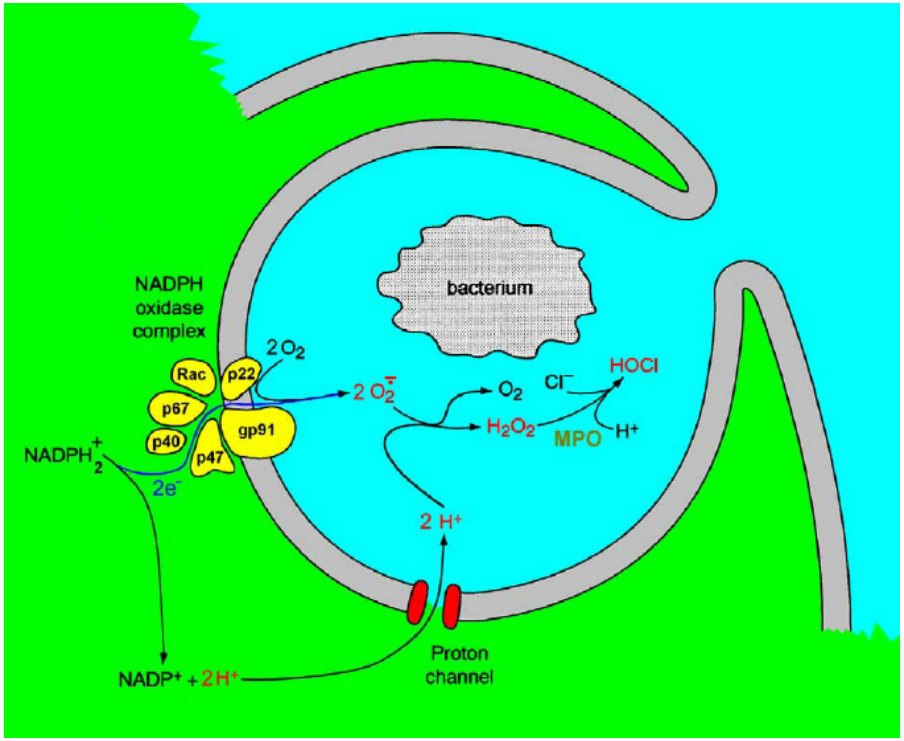
B. Disorders of adhesion:
   - Leukocyte adhesion defect.

C. Disorders of chemotaxis :
   - Chediak-Higashi syndrome. (also have abnormal intracellular killing)

D. Disorders of intracellular killing:
   - Chronic Granulomatous Disease.

Chronic Granulomatous Disease

- A defect in the NADPH oxidase enzyme system leading to failure of production of oxygen radicals and hydrogen peroxide which lead to inability of intracellular killing of mostly catalase + bacteria and fungi.
- Manifest with recurrent pneumonia or deep seated abcesses due to staph aureus, serratia, B. cepacia, aspergillus and other organisms.
- Can be inherited as X-linked or autosomal recessive.
- Diagnosis: NBT or oxidative burst assay.
- Patients are put on bactrim and itraconazol prophylaxis. BMT is recommended for some patients.



T.E. DeCoursey.FEBS Letters 555 (2003) 57-61

Deficiencies in T-cell immunity

- **Clinical Characteristics:**

- Often present before 5 months of age.
- Usually associated with recurrent infections with fungal, viral, or mycobacterial pathogens.
- Patients may develop infections with opportunistic organisms. e.g: *Pneumocystis jerovici*
- Severe failure to thrive.
- GVHD may develop secondary to blood product transfusion or in-utero from materno-fetal transfusion.
- Often associated with humeral (B-cell) defect because of lack of T-cell help.

Deficiencies in T-cell immunity - Causes

- I- Acquired:

- Severe malnutrition.
- Immunosuppressive drugs
- Radiation.
- Infections: like HIV.

Deficiencies in T-cell immunity - Causes

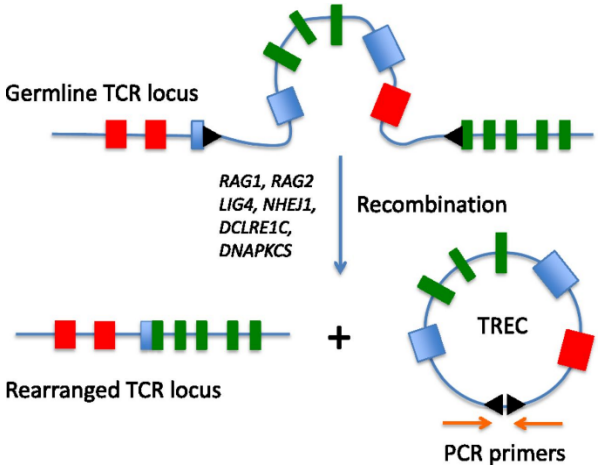
- II- Congenital:

A. Severe Combined Immunodeficiency Syndromes (SCID):

  - Usually characterized by marked lymphopenia and very early presentation in the first few months of infancy.
  - Lymphopenia (< 2000/ul) in a healthy neonate is an indication for investigation.
  - Pediatric Emergency.
  - The success rate of stem cell transplantation in the first 3.5 months of life, and before infection develops, is >95% as compared to < 80% if done later with infections.

Newborn Screening for SCID

- Since early detection and early BMT for patients with SCID is critical a newborn screening was developed.
- This screening is based on the detection of T-cell receptor excision circles (TRECs) by PCR, which indicate production of naïve T-cells from the thymus.



Deficiencies in T-cell immunity - Causes

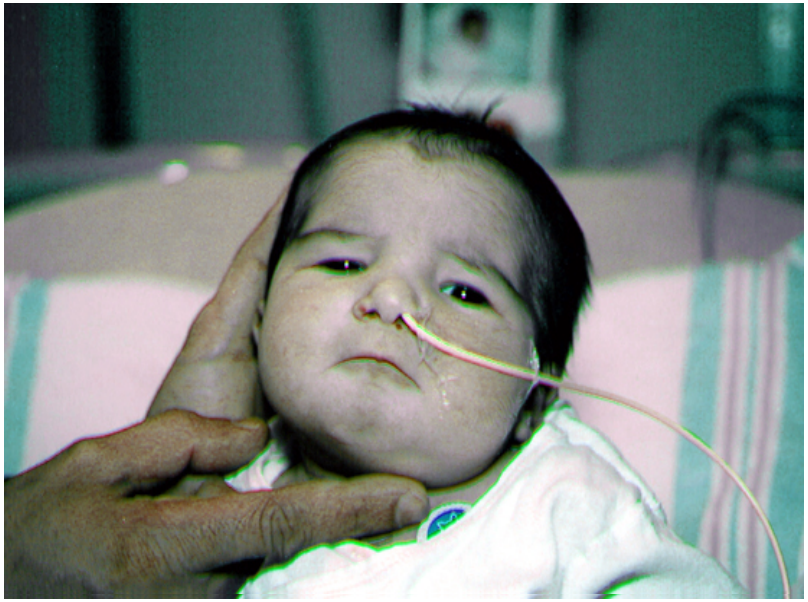
B. Combined immune deficiency (CID): T-cells are not severely deficient (> 300/ul) and presentation may be less severe. Examples:

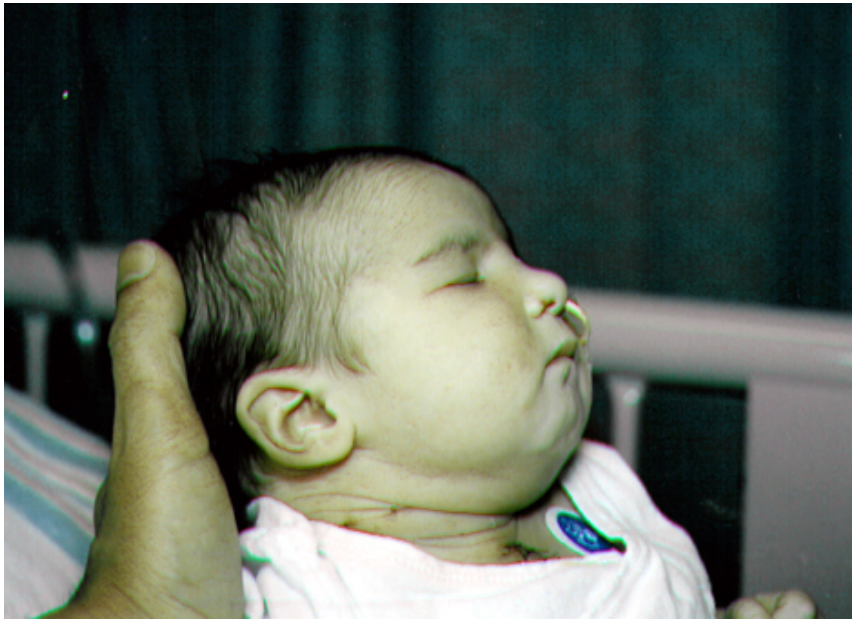
- Wiskott-Aldrich Syndrome.
- Ataxia Telangictasia.
- DiGeorge syndrome.

And many others……

Deficiencies in T-cell immunity

- **DiGeorge Syndrome:**
  - Features: congenital cardiac malformation involving large vessels, hypoplastic thymus, parathyroid deficiency, velopharyngeal insufficiency, cleft palat, and dysmorphic features.
  - Results form a defect in the embryonic development of the 3rd and 4th pharyngeal arches.
  - Most patients have microdeletions affecting 22q11.
  - Most patients have normal T cell number and functions and most of those with lymphopenia will recover by the end of their 1st year.



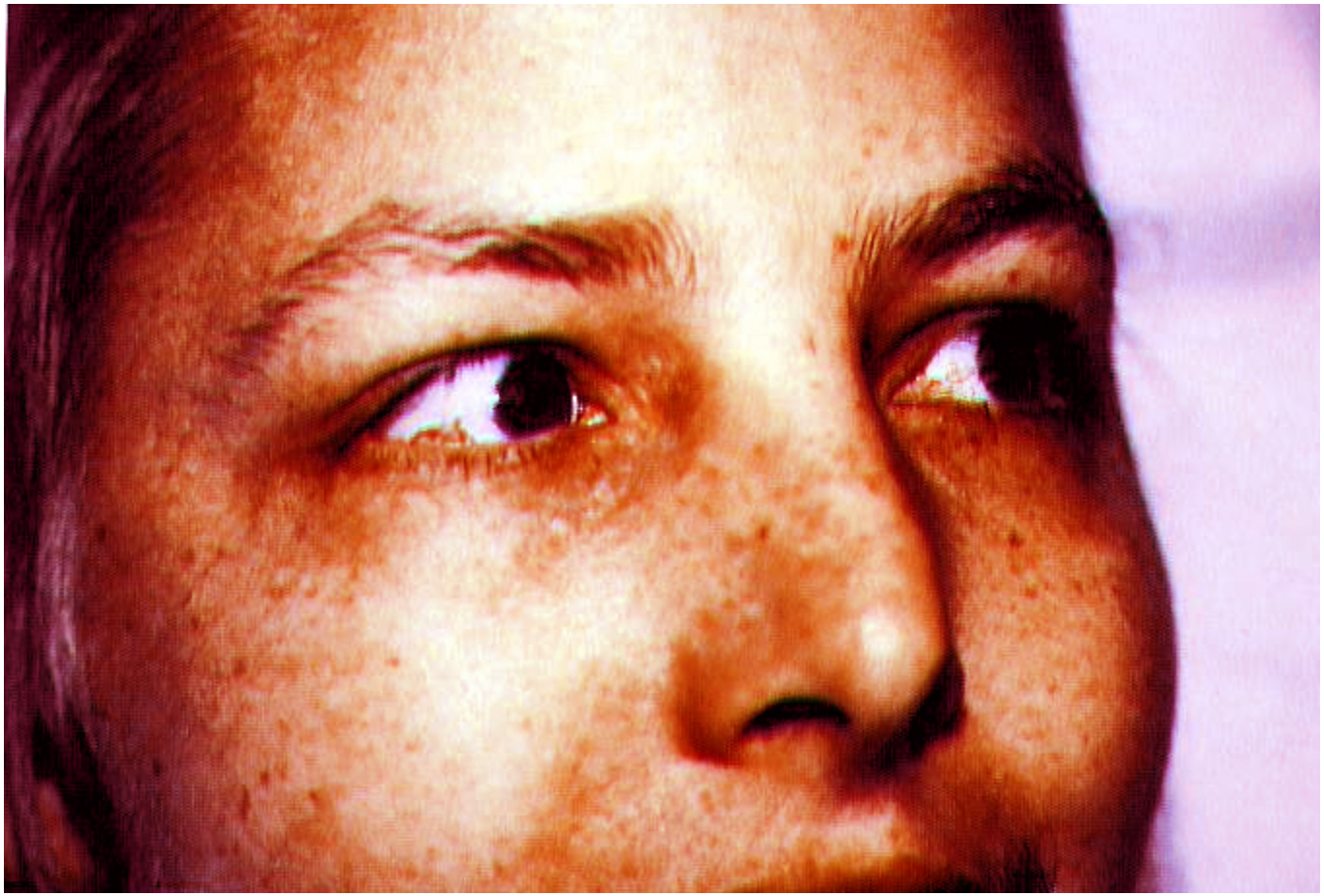


Deficiencies in T-cell immunity

- **Wiskott-Aldrich Syndrome:**
  - X-linked disease.
  - Characterized by: eczema, thrombocytopenia with small platelets, and immunodeficiency.
  - Patient's Lymphocyte proliferation is depressed. They may have variable antibody abnormalities.
  - Treatment is by BMT.

Deficiencies in T-cell immunity

- **Ataxia-Telangiectasia:**
  - Autosomal recessive disease.
  - Progressive cerebellar degeneration.
  - Cutaneous or ocular telangiectasia.
  - Immunodeficiency affecting predominantly cellular immunity (T & B cells).
  - Sensitivity to ionizing radiation.
  - High incidence of malignancies.
  - The basic problem is a defect in DNA repair.
  - Patients have elevated α-fetoprotein.



Deficiencies of B-cell immunity

- **Clinical Characteristics:**

- Onset is usually after 7-9 months.
- Recurrent infections with encapsulated organisms.
- Patients usually develop chronic or recurrent sinusitis, otitis media, pneumonia. They may also develop recurrent sepsis, meningitis, or osteomyelitis.
- Few problems with fungal or viral infections (except enteroviruses and polio)
- Little growth failure.

Deficiencies of B-cell immunity – major causes

- X-linked agammaglobulinemia.
- AR agammaglobulinemias.
- Common variable immunodeficiency (CVID): hypogammaglobulinemia with poor antibody responses to antigens.
- Hyper-IgM syndromes: High-normal IgM with low IgG and IgA.

General Approach to Patients with Suspected Immunodeficiency

History:

- Usually, the earlier the onset the more the likelihood of severe immunodeficiency.

  For example:

  * SCID (severe combined immunodeficiency) usually presents in the first 4-5 months of life.

  * Agammaglobulinemia usually presents at 7-9 months of life.

- Family history is extremely important!

History: Site of infection

- Involvement of specific sites is likely more common with specific types of immunodeficiency than others.

- Examples:
  - Recurrent Gingivitis and skin abscesses: Phagocytic defects.
  - Recurrent Sinopulmonary infections: B-cell defects.
  - Recurrent Meningitis: complement defects.

- Chronic diarrhea should always raise the possibility of immunodeficiency. The nature of the infecting organism may indicate the type of immune defect.

Type of the infecting organism

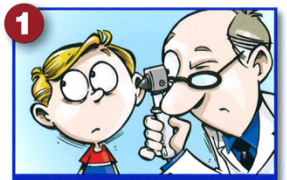
- Recurrent viral, fungal, mycobacterial, or opportunistic infections suggest T-cell defects.
- Recurrent infections with invasive encapsulated bacteria (e.g: pneumococcus) suggest B-cell defects.
- Recurrent infections with bacteria of low virulence (e.g: staph) suggest a neutrophil abnormality.
- Recurrent Nisseria infections suggest terminal complement defect.

History of Adverse Reactions to Vaccines

- Live attenuated vaccines may cause disease in immunodeficient patients. For example, OPV can cause paralysis in a patient with SCID or hypogammaglobulinemia if he receives the vaccine or exposed to it through vaccinated children who are still shedding the live attenuated virus in their stool.

10 Warning Signs of Primary Immunodeficiency

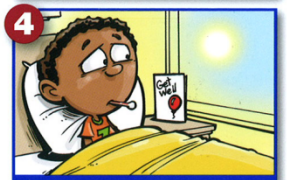
Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. **If you or someone you know is affected by two or more of the following Warning Signs, speak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

1. 
Four or more new ear infections within one year.

2. 

Two or more serious sinus infections within one year.

3. 
Two or more months on antibiotics with little effect.

4. 

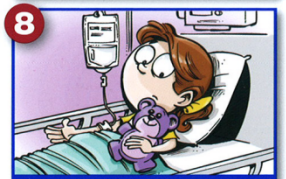
Two or more pneumonias within one year.

5. 

Failure of an infant to gain weight or grow normally.

6. 
Recurrent, deep skin or organ abscesses.

7. 
Persistent thrush in mouth or fungal infection on skin.

8. 
Need for intravenous antibiotics to clear infections.

9. 

Two or more deep-seated infections including septicemia.

10. 
A family history of PI.

Presented as a public service by:

Jeffrey Modell Foundation | Curing PI. Worldwide.
CDC Funding was made possible in part by grant 5H75DP225146-05 from the United States Centers for Disease Control and Prevention (CDC)
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For information or referrals, contact the Jeffrey Modell Foundation: 866-INFO-4-PI | info4pi.org

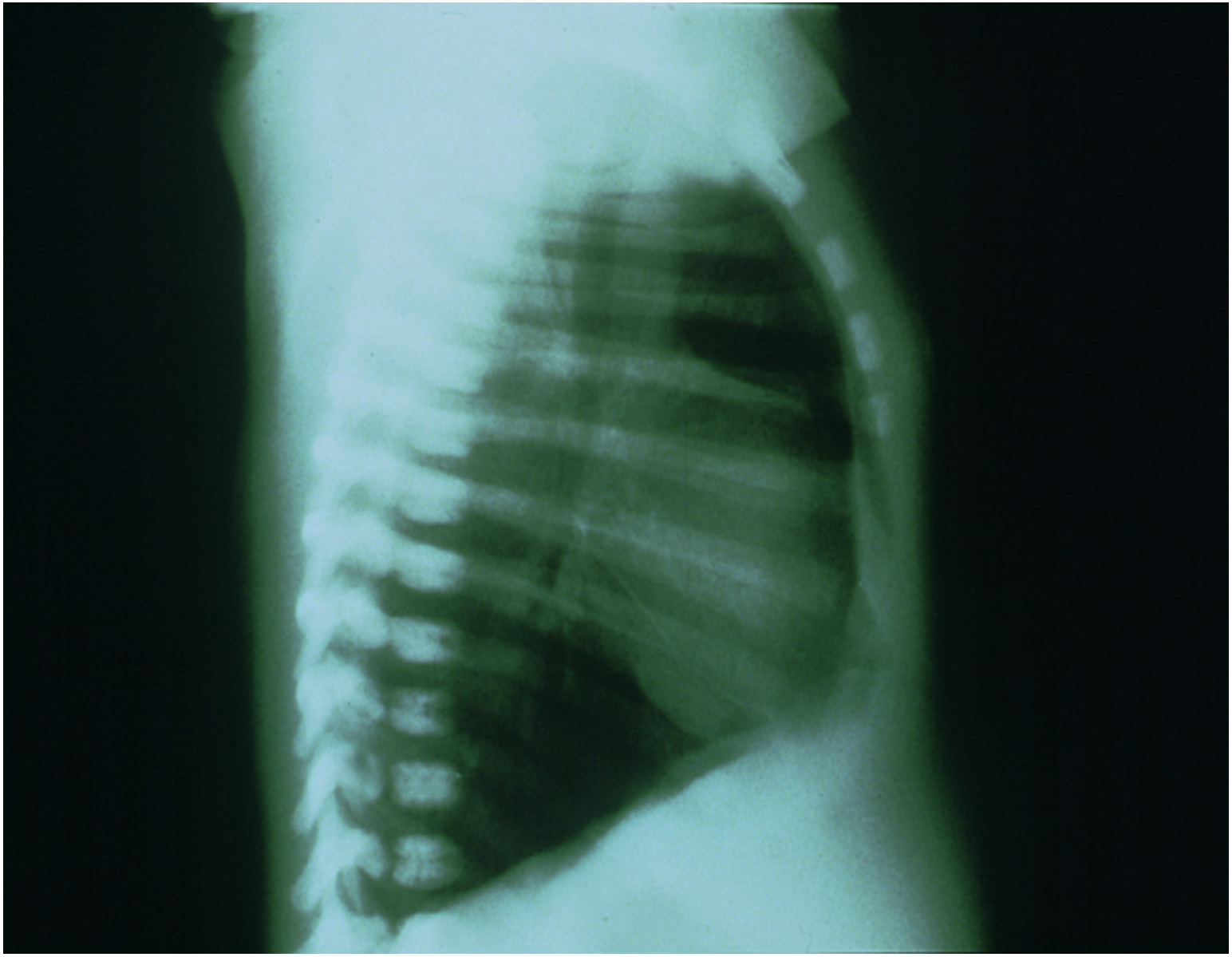
Physical Examination

- Absent tonsils ---------- B cell defect
- Absent lymphnodes --------- T/B cell defect
- Lymphnode hyperplasia ---- CVID, CGD
- Absent BCG scar ---------- T cell defect
- Delayed separation of the umbilical cord ---------- Leukocyte adhesion defect
- Others ……

Assessment of the Immune System

STAGE-I: General non-specific evaluation.

- CBC, differential and blood film.
- Quantitative immunoglobulin levels.
- In newborns, CXR for thymic shadow.



STAGE-II: Evaluation based on the suspected type of immune deficiency

A. Innate immunity:

- ✓ Phagocytic function study (NBT, or oxidative burst).
- ✓ CH50, AH50.
- ✓ Flowcytometry for adhesion molecules.
- ✓ Chemotaxis.

STAGE-II: Evaluation based on the suspected type of immune deficiency

B. **Specific immunity:**

1. Humeral component:

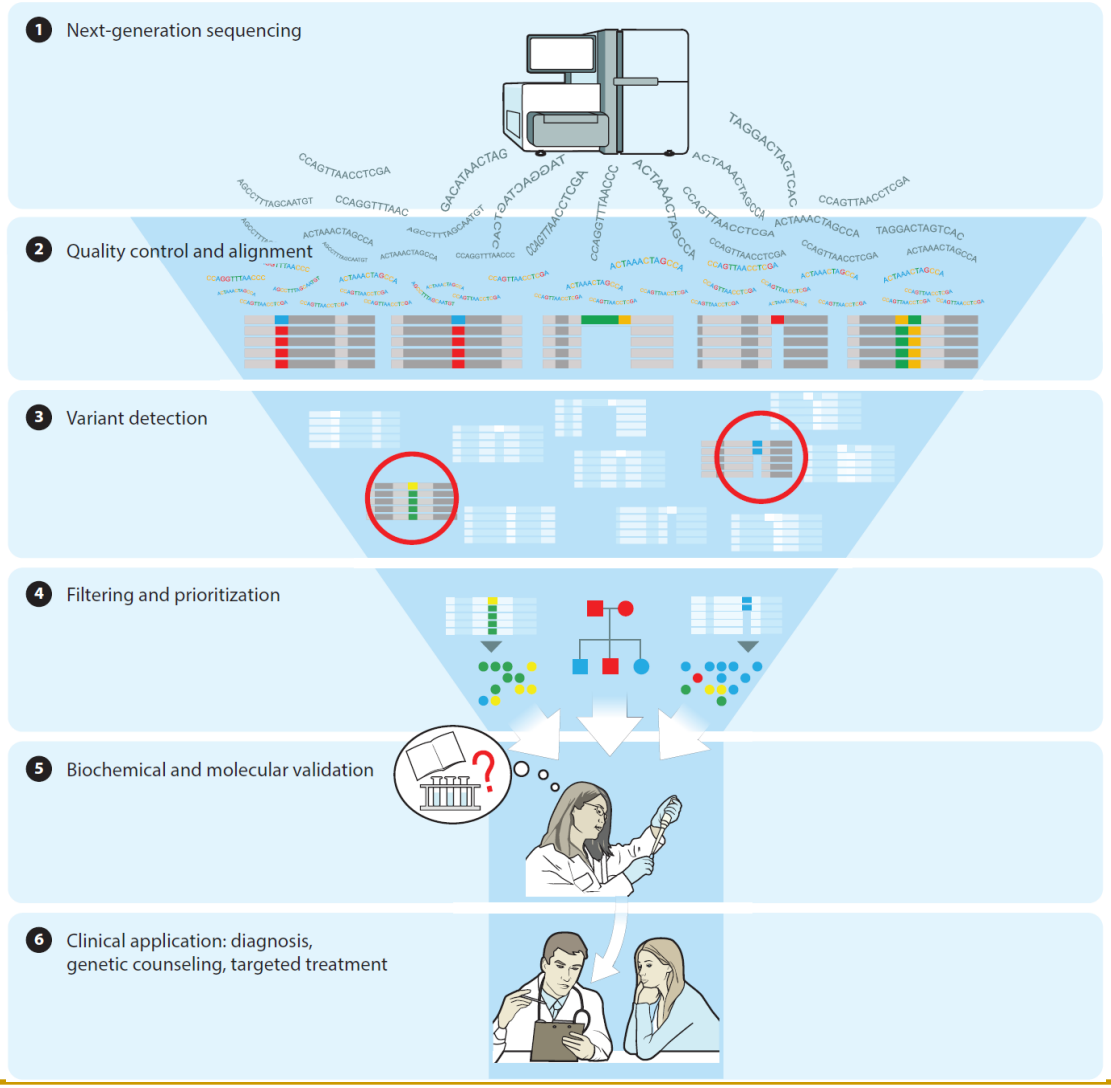
    1. Specific antibodies responses to tetanus, hemophilus influenzae, and pneumococcus.
    2. Isohemagglutinins.
    3. IgG subclasses.

STAGE-II: Evaluation based on the suspected type of immune deficiency

2. Cellular Component:

    1. Lymphocyte subsets (CD3,CD4,CD8,CD19,CD16/56)
    2. Delayed skin hypersensitivity reaction to intradermal candida or tetanus (not sensitive with limited availability).
    3. Lymphocyte proliferation assays in vitro.
    4. HIV testing.

STAGE- III: More detailed investigations



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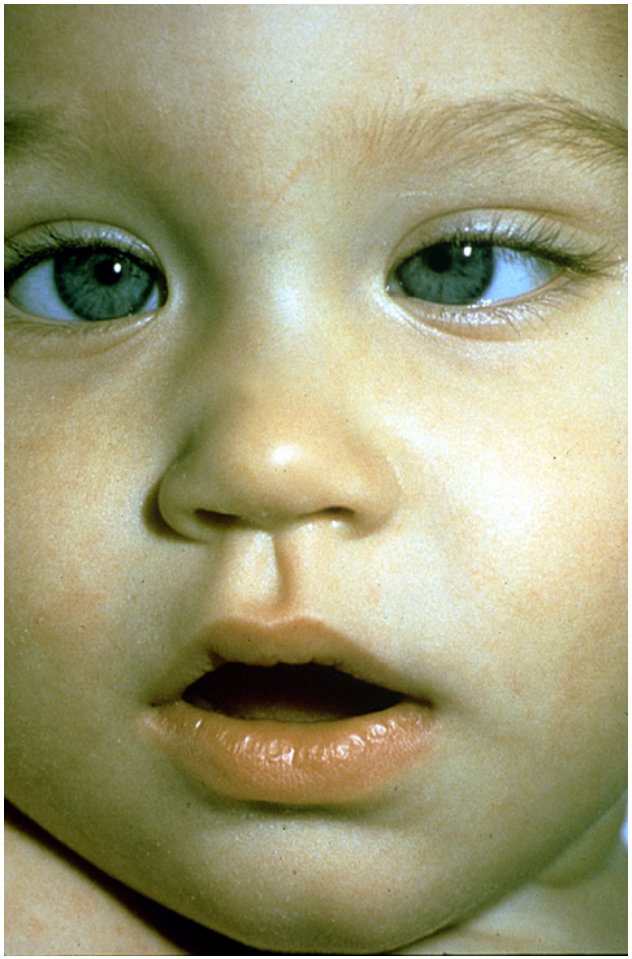
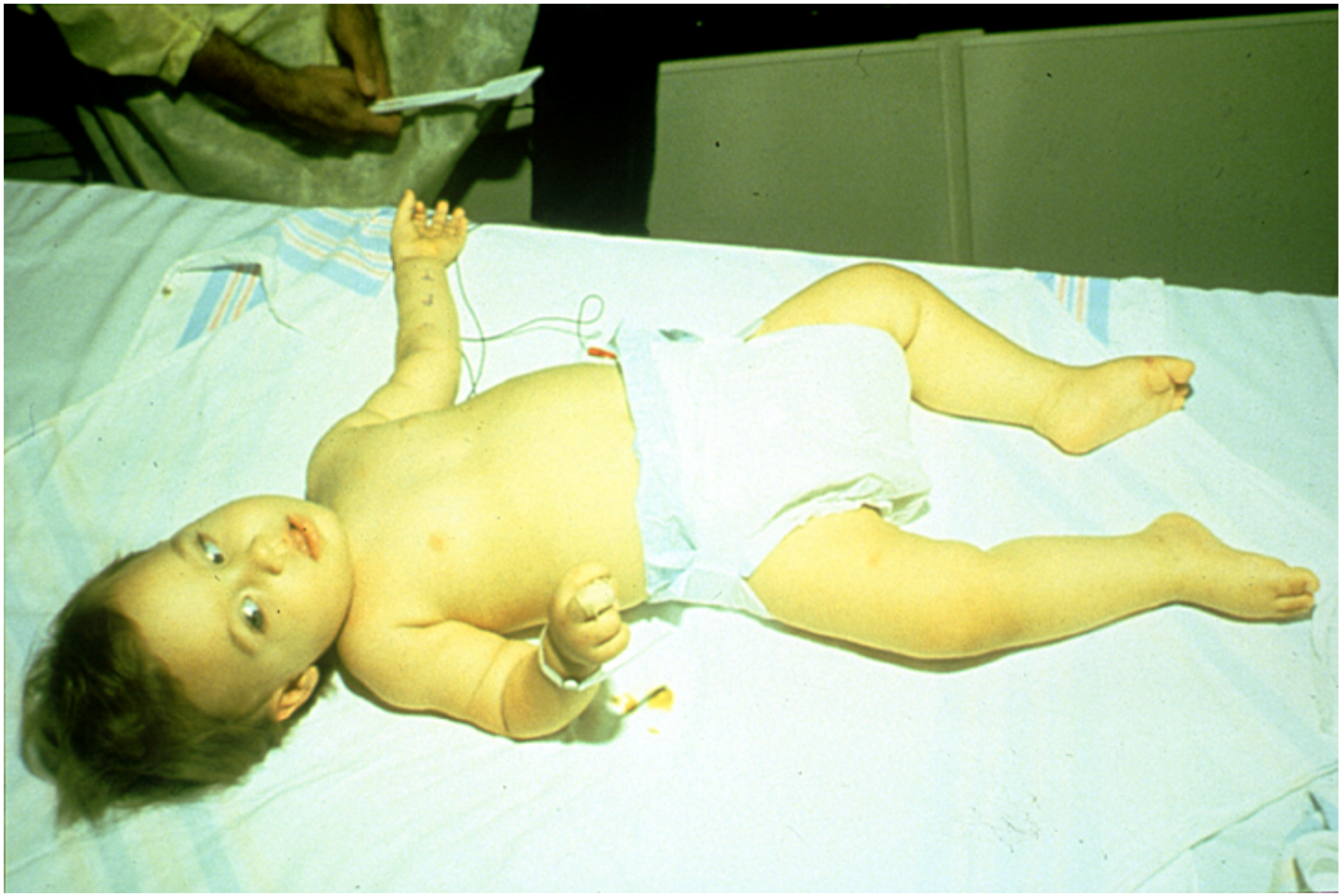
Case Study-1

- An eight-month-old boy was presented to a pediatrician with fever, lethargy, left ocular and facial palsy, and flaccid paralysis of the lower extremities. CSF showed a picture of aseptic meningitis.





Case Study-1 Cont…

- Two months earlier, the child had received an oral poliovirus immunization. A presumptive diagnosis of post-infectious polyneuritis was made.
- What should be done next?

Case Study-1 Cont…

- Serum IgG concentration was 9 mg/dl (extremely low). The infant was referred to a pediatric allergist-immunologist. Mature B-cells were absent from the circulation. T-cell immunity was normal. The spinal fluid subsequently grew the vaccine strain of poliovirus.

Case Study-1 cont…

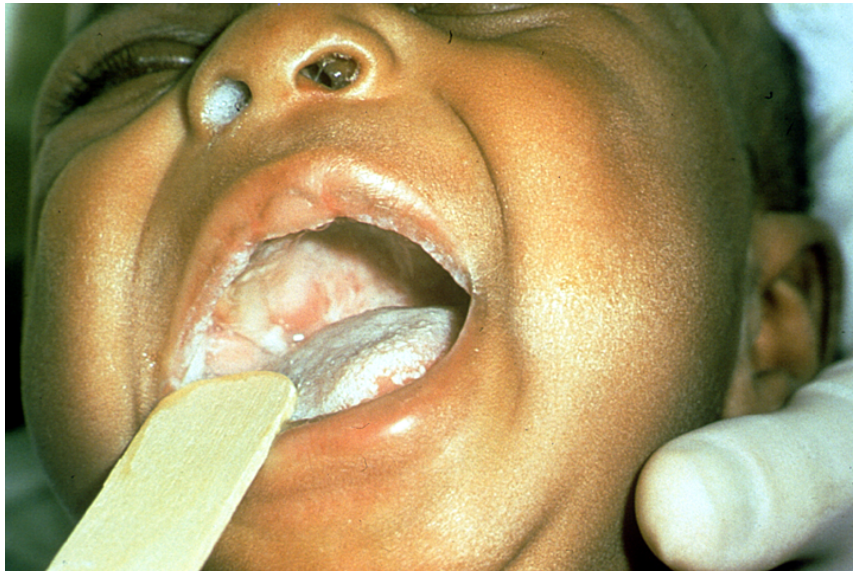
- Based upon the absence of mature B-cells in the circulation and a state of panhypogammaglobulinemia, a diagnosis of **Agammaglobulinemia** was made.

- The child has done well on monthly intravenous immunoglobulin replacement therapy, but is hemiplegic.

- **Individuals with a primary immunodeficiency should NOT be given live vaccines!**

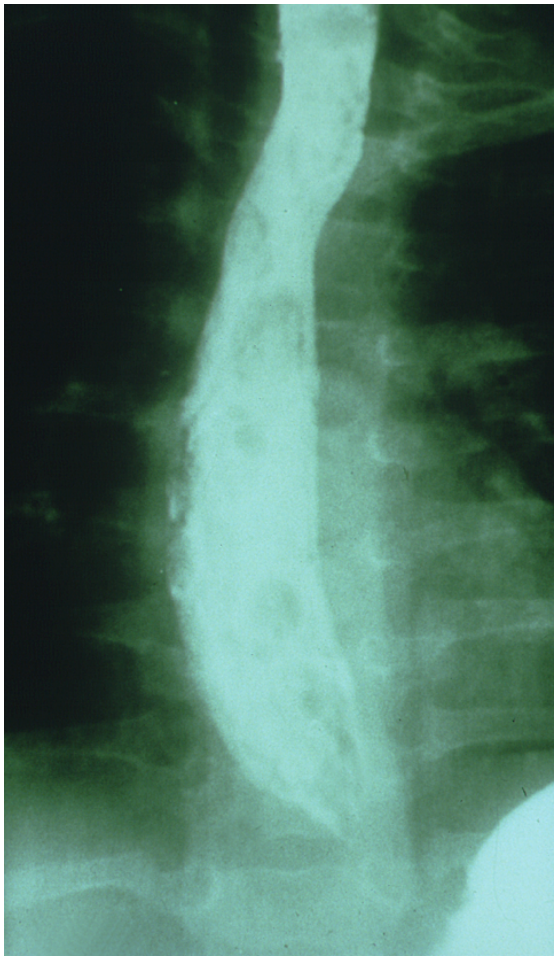
Case Study-2

- A four-month-old infant was noted to have persistent oral thrush due to *Candida albicans.*



Case Study-2 Cont…

- A consulting immunologist ordered a barium swallow x-ray, and ulcer craters due to this same organism were observed throughout the esophagus .



Case Study-2 Cont…

- Where could be the defect?
- What to do next?

Case Study-2 Cont…

- The child's serum IgG was low, but the IgA and IgM were virtually absent. Few mature T-cells could be detected by flow cytometry, and there was no response of peripheral blood lymphocytes to stimulation by mitogens.

Case Study-2 Cont…

- A diagnosis of **SCID** (Severe Combined Immunodeficiency) was made based on the very low T-cell number and their suppressed function.

- The child survived with a bone marrow transplantation from his HLA-compatible sister.

IVIG in PID

- IVIG (IntraVenousImmunoGlobulin) is purified human IgG prepared from pooled plasma of thousands of donors.

- Mechanism of action: It is estimated that an IVIG preparation contains ten million antibody specificities. This mechanism leads to:
  - Neutralization of viruses.
  - Opsonization of bacteria.
  - Neutralization of toxins.

IVIG in PID

- Indications:
  - Agammaglobulinemia.
  - CVID.
  - CID.
- Dosage: It is recommended to maintain a trough IgG above lower limit of normal. Infusion is given q 3-4 wks intervals.
- Monitoring: IgG trough level q3-6 months.

IVIG in PID

- Adverse Effects: non-specific generalized reactions are usually reported in 1-10% of patients, mostly mild.
  - **Mild**: flushing, headache, back pain, chills, myalgia, nausea. Intervention: slow infusion and treat symptoms.
  - **Moderate**: urticaria, bronchospasm, vomiting. Intervention: stop infusion and treat symptoms.
  - **Severe**: anaphylaxis/anaphylactoid. Intervention: stop infusion and resuscitate. Very rare. ? IgG or IgE anti IgA antibodies.
- Organ-Specific and idiosyncratic reactions are rare.
- Risk of disease transmission.

THE END