# Children with Recurrent Infections

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# Host Immune Defense Mechanisms

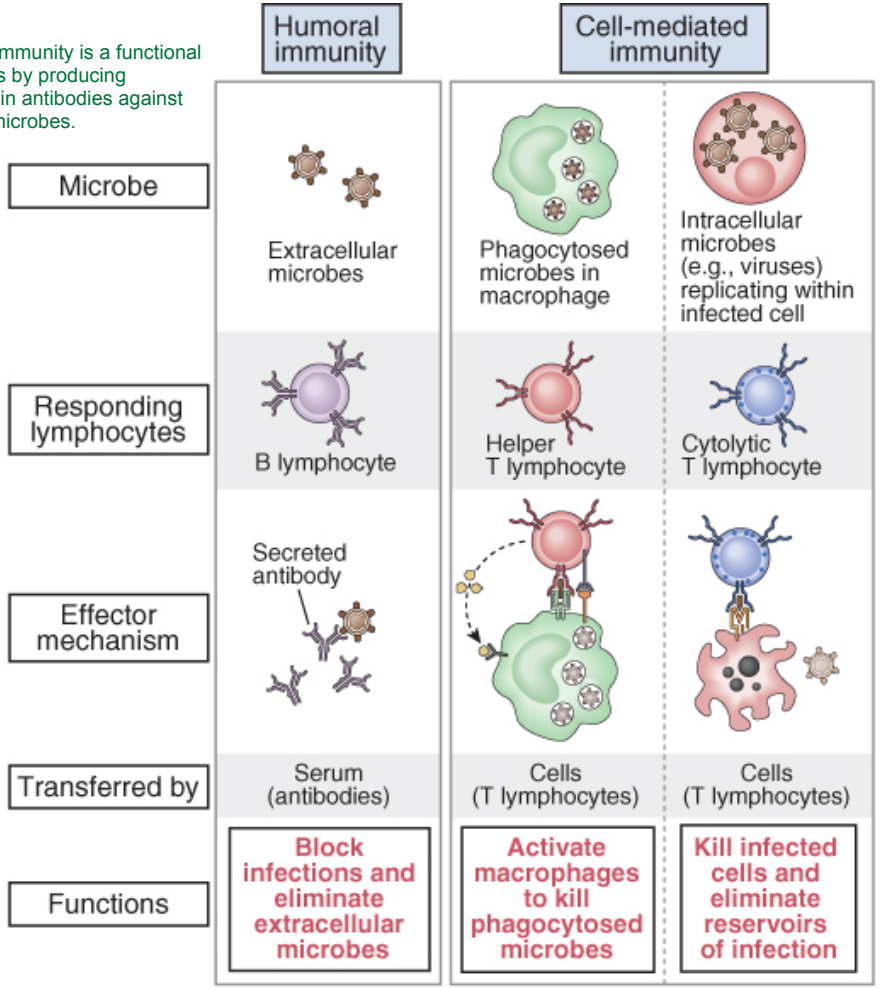
## Non-specific (innate)

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

## Specific (adaptive)

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

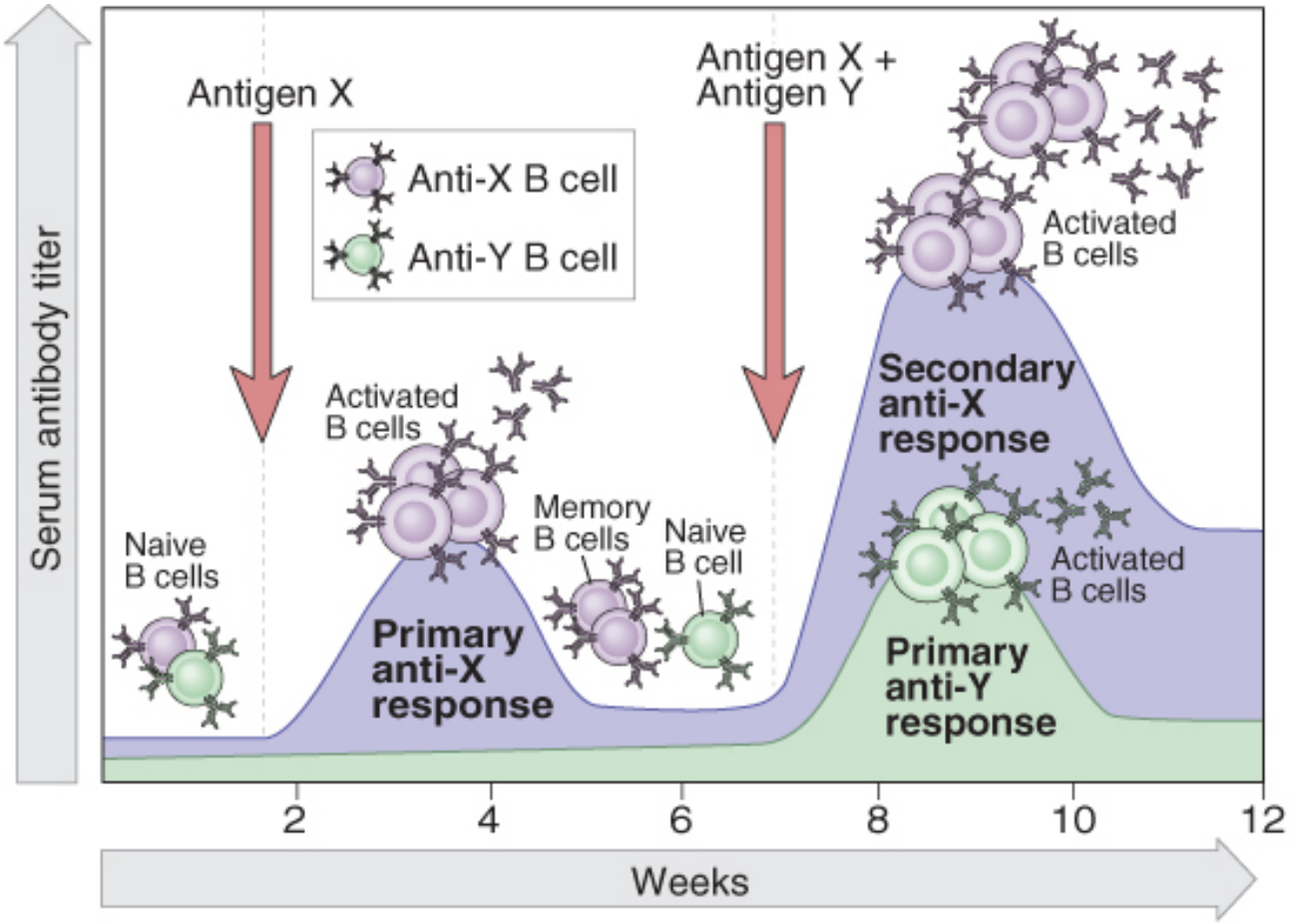
The humoral immunity is a functional B lymphocytes by producing immunoglobulin antibodies against extracellural microbes.




The cell mediated immunity is further divided into: helper T lymphocytes and cytolytic T lymphocytes.

- T helper cells: activates macrophages and neutrophils which phagocytosed microbes in order to kill ingested microbes.
- Cytotoxic T cells: identify, recognize viral infected cells so they can destroy those cells and prevent the existence of any reservoirs.

This illustrate the main difference between the adaptive and innate immunity






- If you inject a mouse with an antigen X, it will develop antibody to that antigen within 4 weeks = Anti-X
- And after weeks later if you inject the same mouse with two antigens X & Y, the mouse will develop a quicker and strong immune response to the x antigen that will also be more sustained. While the response to the Y antigen will be similar to the response to the X antigen in the first time. This indicates two major feature: 1-memory. 2- the immune system can differentiate between antigens.

# Immunodeficiency

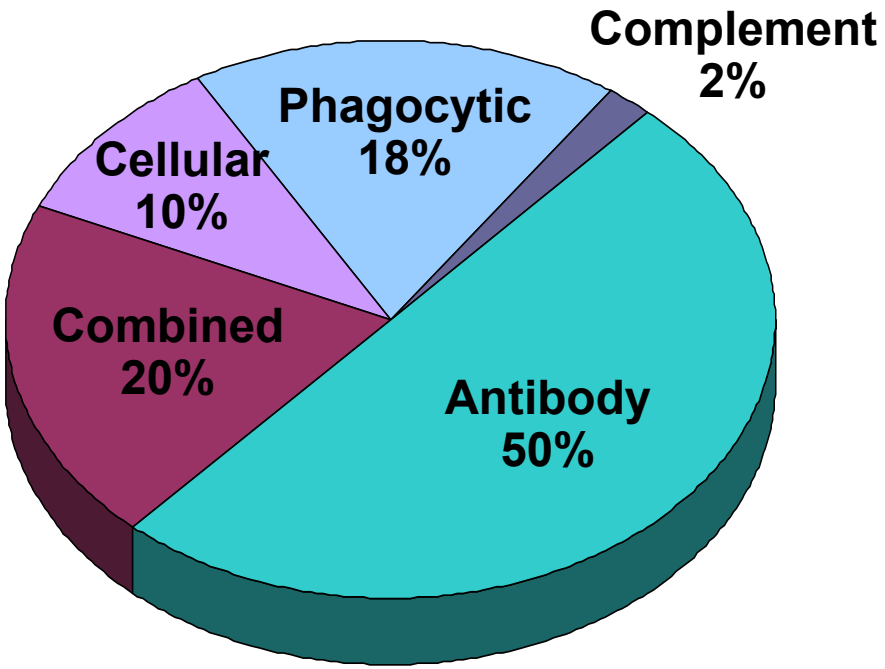
- Definition:
  Immunodeficiency represents a diverse group of abnormalities of the immune system resulting primarily in an increased susceptibility to infection.

- Primary Immunodeficiency:
  Congenital (inherited).

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

primary immunodeficiency is the main focus of this lecture

# Primary Immunodeficiency: Frequency




Most defect that affect the cellular immune system will indirectly affect the humoral immune system.

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

The prevalence in Saudi Arabia though to be significantly higher than that.

# 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.
  not every patient presenting with recurrent infection necessarily will have an immune defect, maybe the defect is anatomical.

- Many PIDs are complicated by autoimmunity and malignancy.
  Mainly hematological malignancy: hematoma, lymphoma...

- 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 The least common

- 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: Under each category there are different genetic causes you don't need to be concern about just know these category.
   - Cyclic neutropenia and severe congenital neutropenia.

B. Disorders of adhesion:
   - Leukocyte adhesion defect.

C. Disorders of chemotaxis : Affect the ability of cells to migrate to the site of inflammation
   - Chediak-Higashi syndrome. (also have abnormal intracellular killing)

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

# Chronic Granulomatous Disease

Some organisms (like: staph aurus and aspergillum) can produce catalase+ which will destroy H2O2, so the infected cell will no longer be able to produce HOCl.

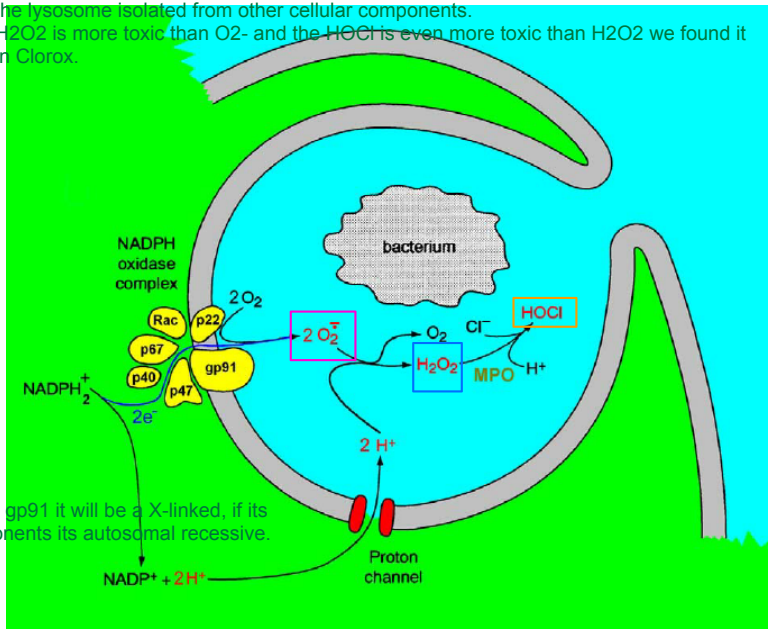
NADPH oxidase enzyme oxidase NADPH give rise of NADPH+ and reduce oxygen species
An electron will move from NADPH to an O2 leading to = oxygen radicals.
Oxygen radicals will subsequently converted into another enzyme hydrogen peroxide, and this can be further converted into hypochlorous acid.
All these molecules are toxic to the bacteria and to the cell but they are produce inside the lysosome isolated from other cellular components.
H2O2 is more toxic than O2- and the HOCl is even more toxic than H2O2 we found it in Clorox.

- 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.

recurrent pneumonia can present with bronchiectasis. deep seated abcesses (subcutaneous or muscles abcesses, lung abcesses, brain

If the defect is affecting gp91 it will be a X-linked, if its affecting other 4 components its autosomal recessive.

NBT is an old test.




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

BMT = bone marrow transplantation

# 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. Because of the sickness.
- GVHD may develop secondary to blood product transfusion or in-utero from materno-fetal transfusion. Manifest as rash, diarrhea, vomiting, hepatitis, others
- Often associated with humeral (B-cell) defect because of lack of T-cell help.

# Deficiencies in T-cell immunity - Causes

- I- Acquired:

- Severe malnutrition. Most common cause.
- Immunosuppressive drugs
- Radiation.
- Infections: like HIV. Primarily affect CD4

# Deficiencies in T-cell immunity - Causes

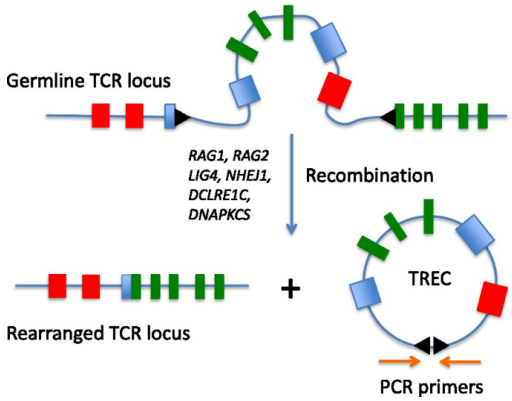
- II- Congenital:

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. Even if the patient looks completely healthy.
  - 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.

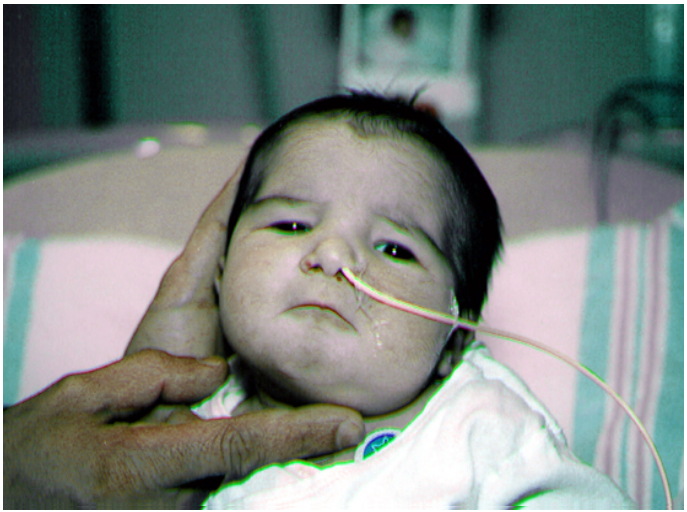
And many others……

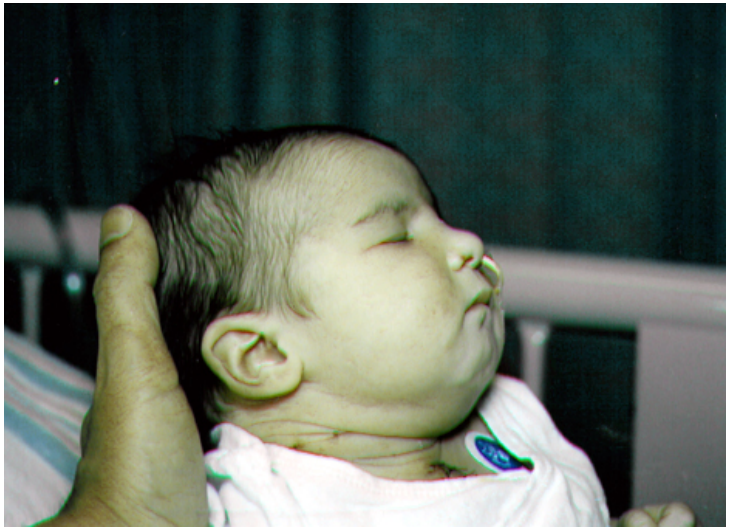
# Deficiencies in T-cell immunity

- **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.

There're very few patients will have thymic aplasia and they will have severe lymphopenia and need to be managed in specialized centers for thymic transplantation.
Diagnosis of microdeletions is commonly by Fluorescence In Situ Hybridization (FISH) or microarray chromosome analysis.

dysmorphic features: bulbous nose, frontal bossing, sometimes anti-slant of the eye, micrognathia, low set ear, sutures in the chest indicating cardiac surgery.





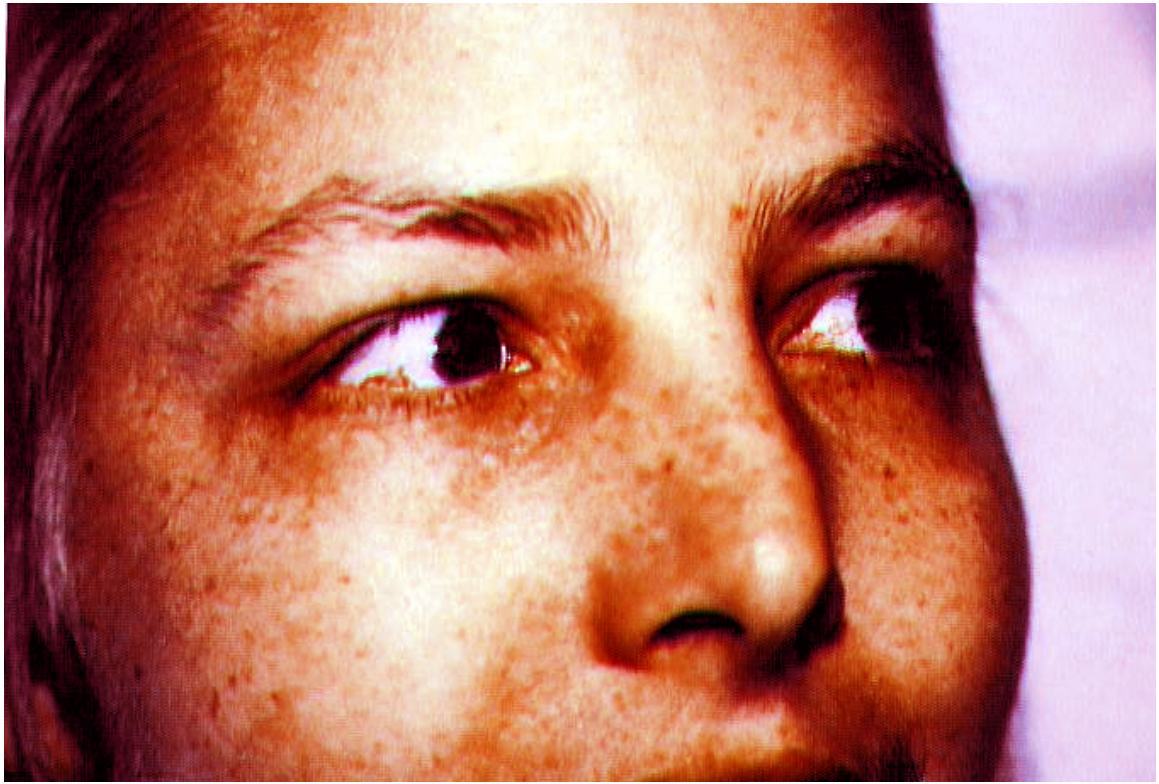
# Deficiencies in T-cell immunity

- **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. Because they have a defect in a gene called ATM
  - Patients have elevated $\alpha$-fetoprotein.

Cutaneous and ocular telangiectasia.



# 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. Also called Bruton 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. Positive IgM = indicates acute infection.
  Positive IgG = indicates subacute or chronic infection.

# General Approach to Patients with Suspected Immunodeficiency

# History:

History and physical examination are key in identifying those patients

- 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!

  For example history of recurrent infections, or early neonatal deaths.

# 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. Especially neisseria

- 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. Invasive encapsulated bacteria only with no intracellular organisms 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

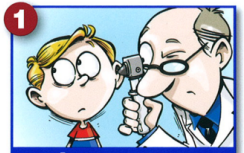
Imp point to remember

Live attenuated vaccines like: BCG, MMR, varicella, oral polio, rotaviruses vaccine.
Most other vaccines are killed 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. 

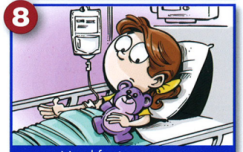
Two or more pneumonias within one year.

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)

National Heart, Lung, and Blood Institute (NHLBI) | National Institute of Allergy and Infectious Diseases (NIAID) | National Institute of Child Health and Human Development (NICHD)

Baxter BioScience | CSL Behring Biotherapies for Life™ | GRIFOLS | octapharma | PPTA Plasma Protein Therapeutics Association | Talecris Biotherapeutics

These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board. Consultation with Primary Immunodeficiency experts is strongly suggested. 

For information or referrals, contact the Jeffrey Modell Foundation: 866-INFO-4-PI | **info4pi.org**

# Physical Examination

- Absent tonsils ---------- B cell defect
  - Bc tonsils are mainly composed of B cells
  - Patients with agammaglobulinemia usually will have absent tonsils.
- Absent lymphnodes -------- T/B cell defect
- Lymphnode hyperplasia ---- CVID, CGD
- Absent BCG scar ---------- T cell defect
  - After 2 months of BCG vaccine there will be a local inflammation (T cells infiltration) will heal by scar formation.
- Delayed separation of the umbilical cord ---------- Leukocyte adhesion defect
  - Normally the umbilical cord will separate within 1 to 2 weeks
  - The umbilical cord may not separate until 6 weeks
- Others ……

# Assessment of the Immune System

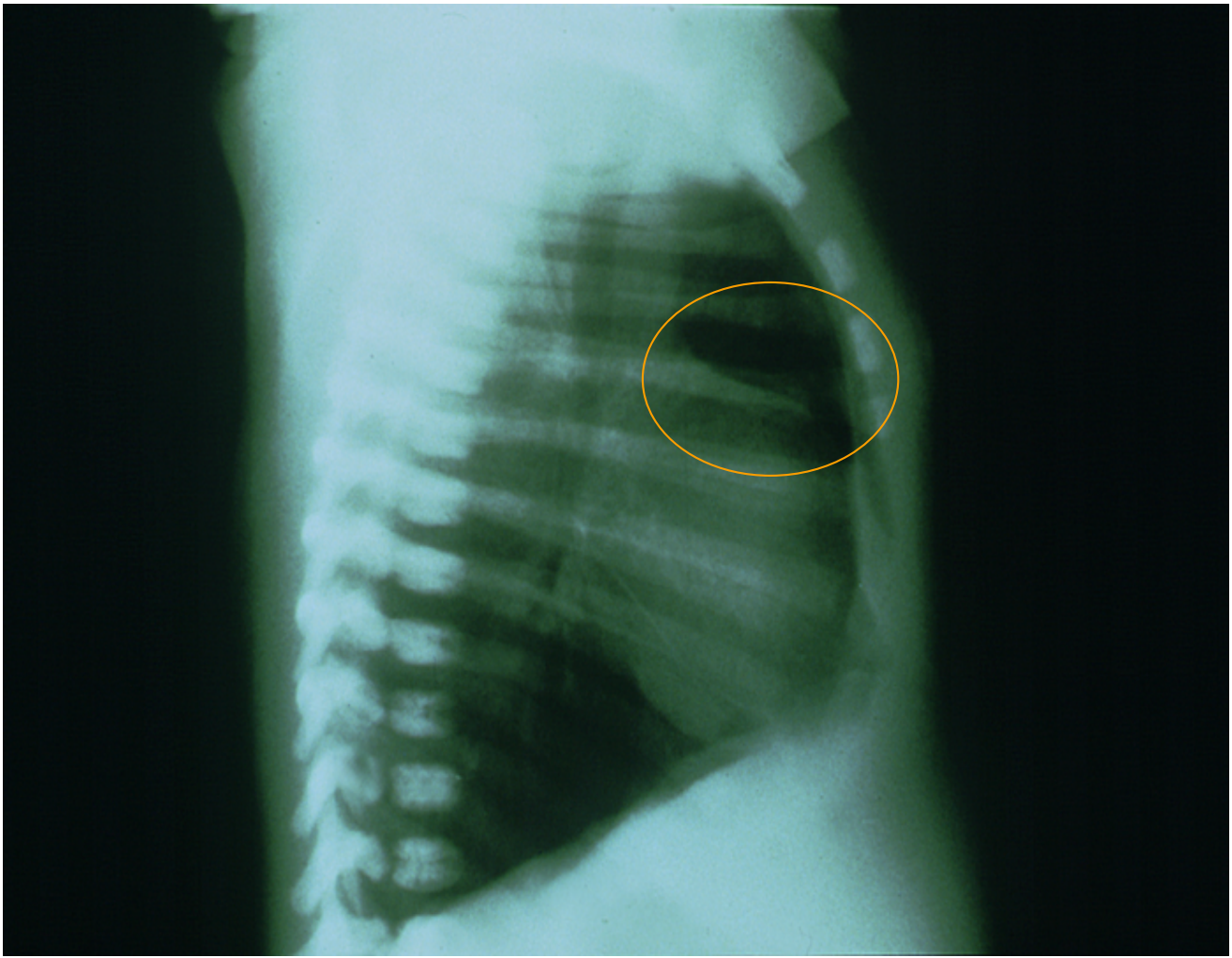
# **STAGE-I:** General non-specific evaluation.

- ✓ CBC, differential and blood film.

you need to look at lymphocytes count is the most imp thing.
Neutrophil count, platelets bc in some conditions they will have thrombocytopenia.

- ✓ Quantitative immunoglobulin levels.
- ✓ In newborns, CXR for thymic shadow.

This is not very sensitive.



Chest x-ray lateral film will be more useful, showing there's radiolucency retrosternal. between the heart and the sternum usually there is a thymic shadow normally appear as a white shadow (opaque), but here its radiolucent which indicates absent thymus.

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

## A. Innate immunity:

- ✓ Phagocytic function study (NBT, or oxidative burst).
- ✓ CH50, AH50. For complement pathway.
- ✓ Flowcytometry for adhesion molecules. If you suspect leukocyte adhesion defect.
- ✓ Chemotaxis. Chemotaxis is the ability of the cell to migrate through the tissue to the site of inflammation.

light microscope can't differentiate between different types of lymphocytes, therefore these cells can be differentiated by using markers and these markers can be identify by using antibodies against these markers that are fluorescent labeled antibodies, and the fluorescent can be detected by Flowcytometry.

# **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. To test the function of B cells.
    2. Isohemagglutinins. IgM antibodies against AB blood groups (anti-A, anti-B), this also can be used as indicator of B cells function.
    3. IgG subclasses. Is not necessary but sometimes it can be helpful.

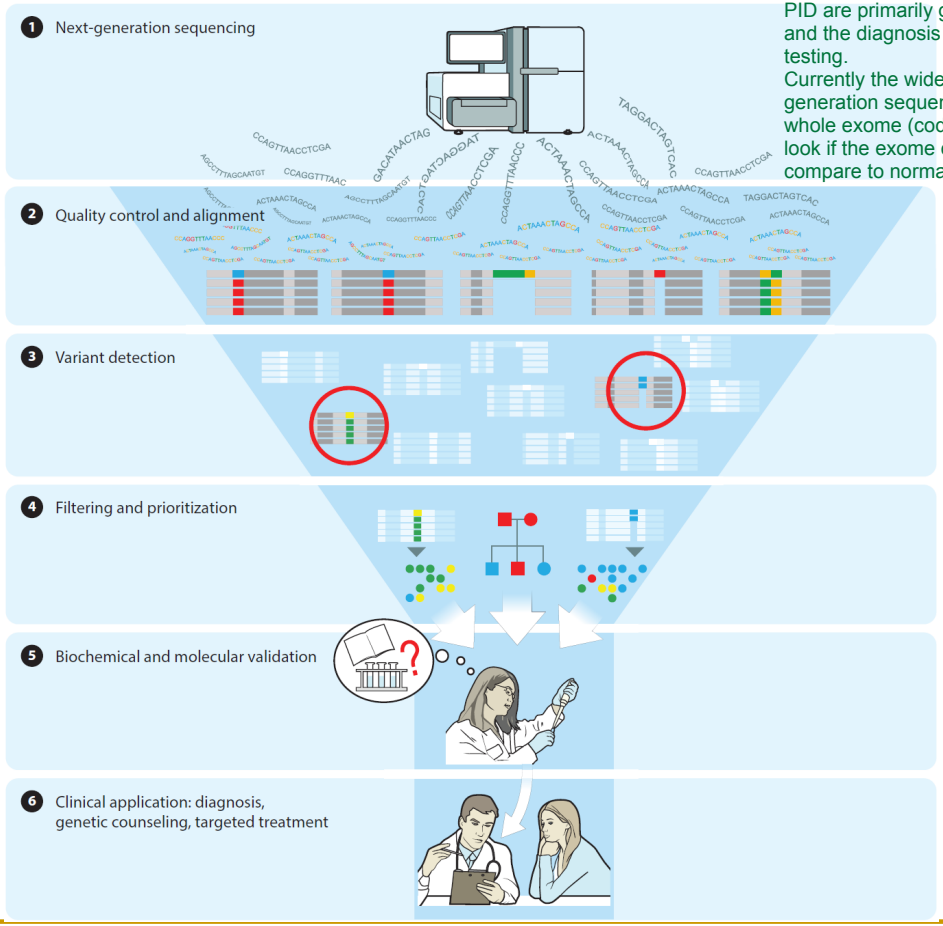
# **STAGE-II:** Evaluation based on the suspected type of immune deficiency

2. Cellular Component:

CD3 regardless of its function in real life it used as marker for T cells.
Positive CD3 and CD4 are marker for T helper cells.
Positive CD8 marker for cytotoxic T cells.
CD19 and CD20 are markers for B cells.
CD16/56 are marker for natural killer T cells.

   1. Lymphocyte subsets (CD3,CD4,CD8,CD19,CD16/56)
   2. Delayed skin hypersensitivity reaction to intradermal candida or tetanus (not sensitive with limited availability). Rarely used, typical example: PPD test for TB.
   3. Lymphocyte proliferation assays in vitro. Standard test.
   4. HIV testing. If we're suspecting T cells defect.

# **STAGE- III:** More detailed investigations



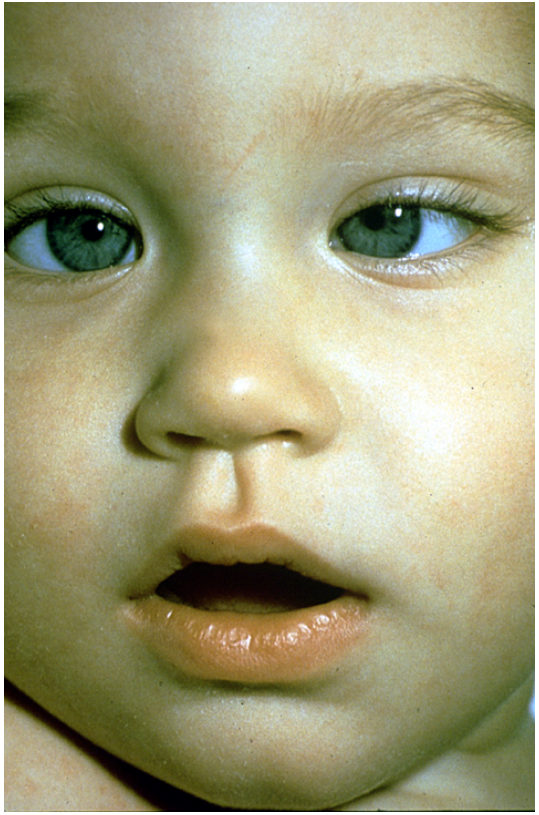

PID are primarily genetic diseases for most part and the diagnosis is achieve by doing a genetic testing.
Currently the widely used genetic method is Next generation sequencing which can sequence the whole exome (coding part of the genome), and we look if the exome contains any mutations that compare to normal data base.

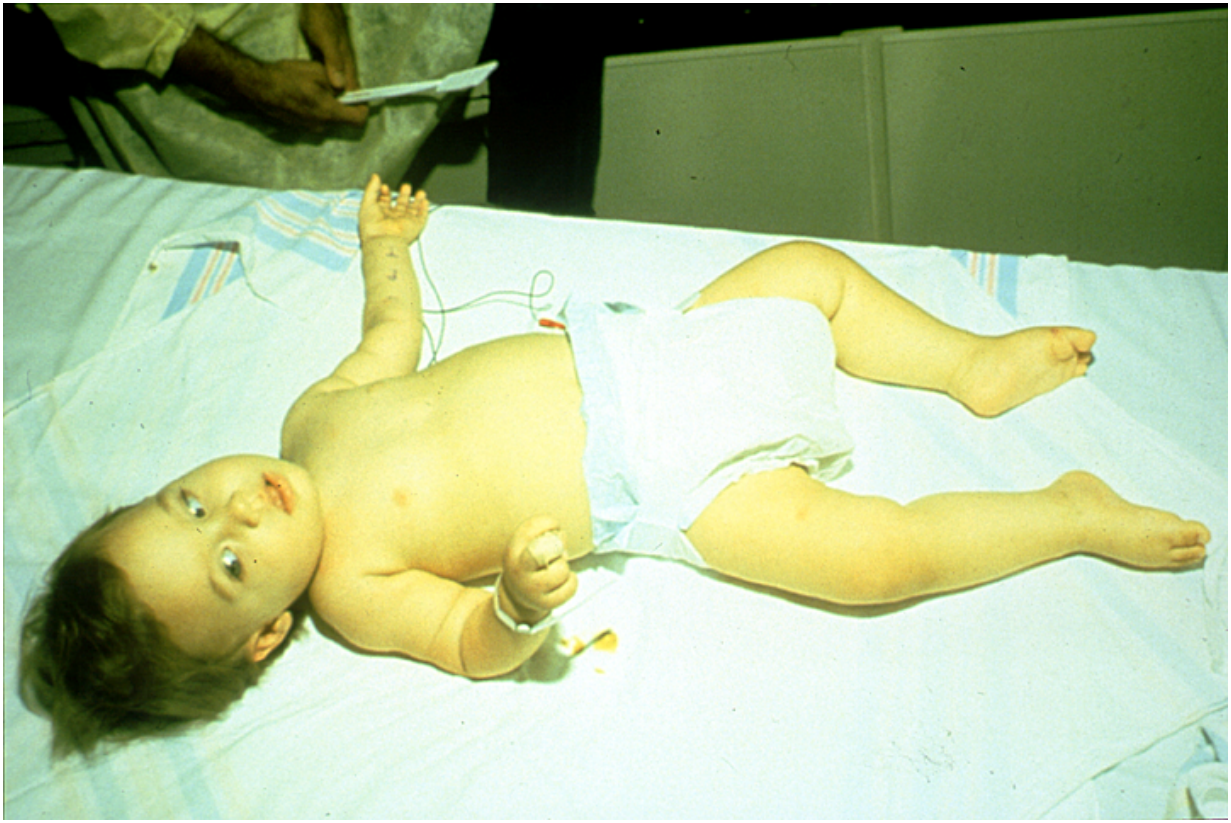
Annu. Rev. Immunol. 2016. 34:121–49

# 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.

aseptic meningitis = Increase cells but negative culture.





# Case Study-1 Cont…

- Two months earlier, the child had received an oral poliovirus immunization. A presumptive diagnosis of post-infectious polyneuritis was made. Polio infection can cause meningoencephalitis and bulbar palsy

- What should be done next? We should not forget that this patient might have immunodeficiency bc of complications to a live attenuated vaccine and investigate the patient immunologically.

# 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…

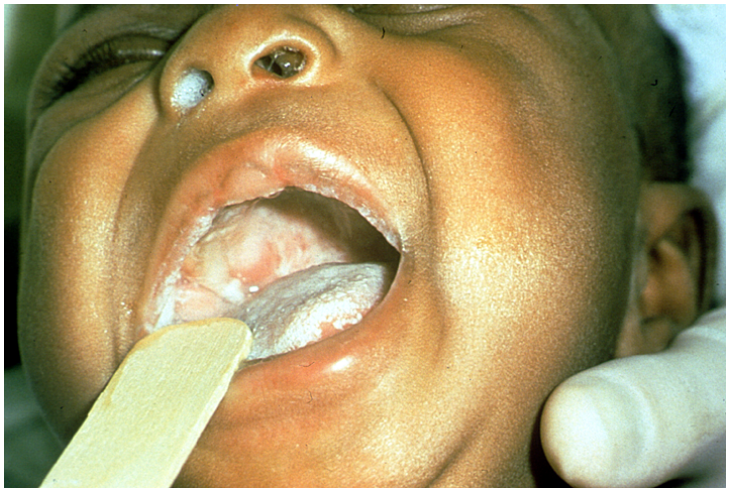
- Based upon the absence of mature B-cells in the circulation and a state of panhypogammaglobulinemia, a diagnosis of **Agammaglobulinemia** was made.

- 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!**

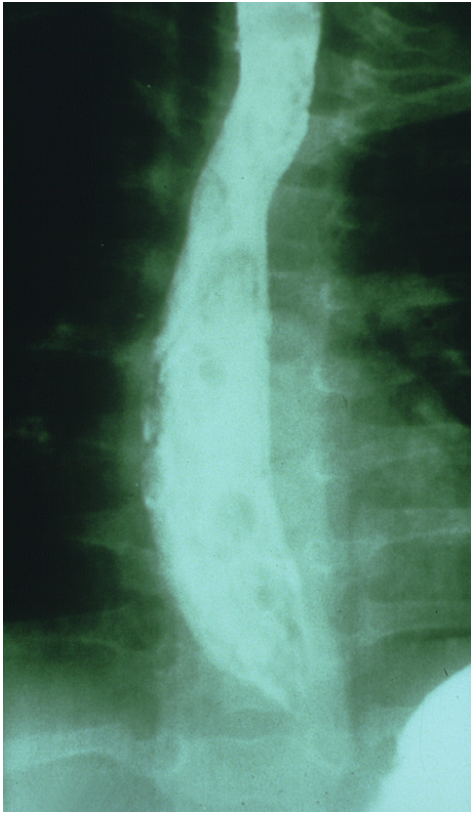
# Case Study-2

- A four-month-old infant was noted to have persistent oral thrush due to *Candida albicans.* Which doesn't respond to treatment



# 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? persistent fungal disease and oral thrush should raise the possibility of T cells defect.
- What to do next? Investigation:
  Basic CBC, differential and blood film and immunoglobulin levels.
  Lymphocyte subsets and T cell function.

# 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.

  - IgA and IgM were virtually absent = this is bc some of the IgG the patient having is still maternal.
  - Few mature T-cells could be detected by flow cytometry, and there was no response = severe lymphopenia.
  - T lymphocyte function and number are severely impaired and this is diagnostic of severe combined immunodeficiency.

# 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 is a replacement therapy in Agammaglobulinemia.

- 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