Children with Recurrent Infections

Abdullah Alangari

http://fac.ksu.edu.sa/aangari

Host Immune Defense Mechanisms

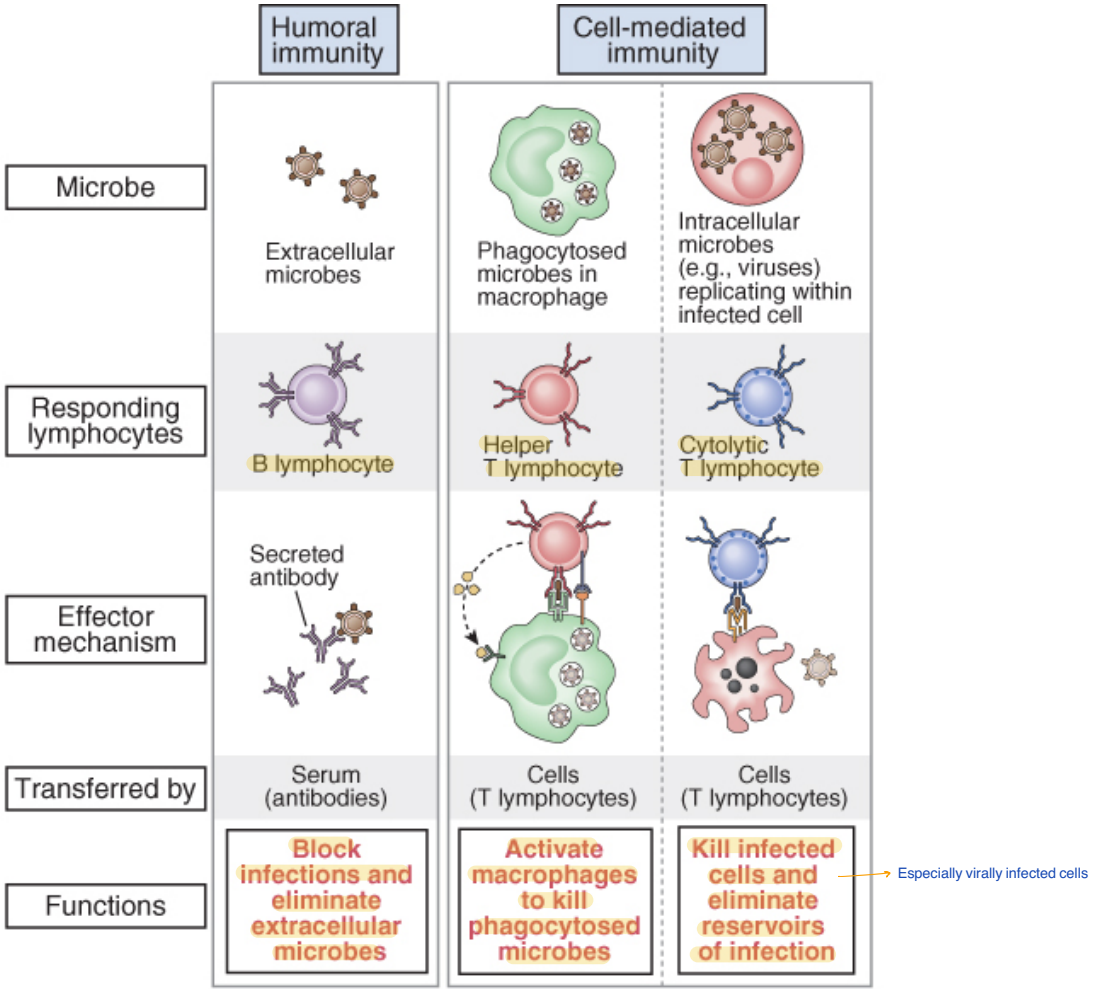
Non-specific (innate)

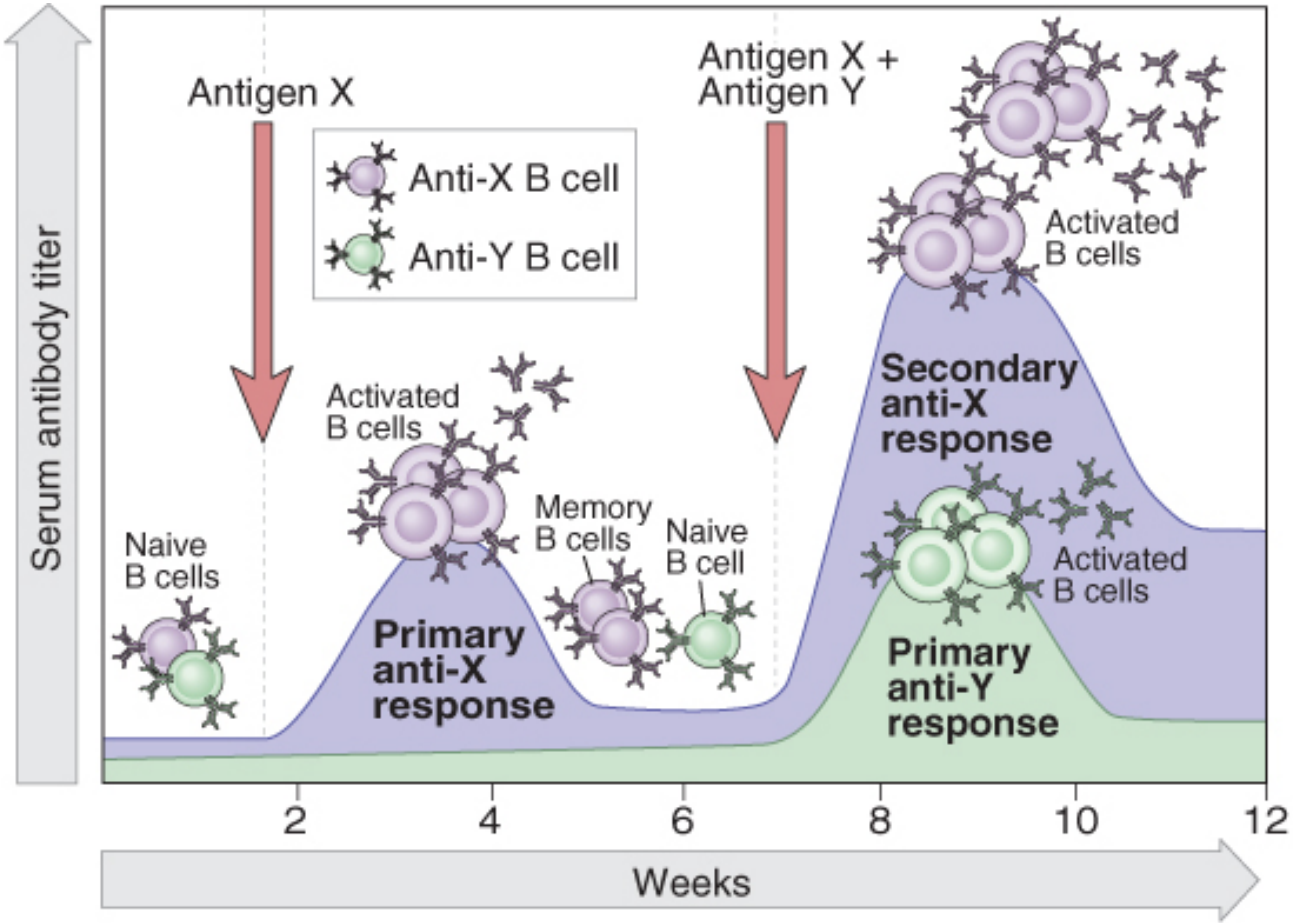
- Barriers
  - Skin
  - Secretions (mucous, tears, saliva)
  - Mucociliary clearance, peristalsis
- Phagocytes
  - Neutrophils
  - Macrophages
- Complement
- Cytokines

Specific (adaptive)

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

What is the major difference between the adaptive and immune system ?
The adaptive immune system has memory for future infections and B and T cells are very specific they can differentiate specific antigens and microbes while the innate can identify them as groups only





- This is an experiment if you bring a mouse and inject it with antigen X , after four weeks the mouse will develop antibodies then it will go down.

After 4 weeks if you inject the same antigen X and another antigen Y you will see the response to X is more exaggerated and more sustained (this exaggeration represents memory they remember the previous exposure)

The response to Y mean specificity since it can differentiate between X and Y.

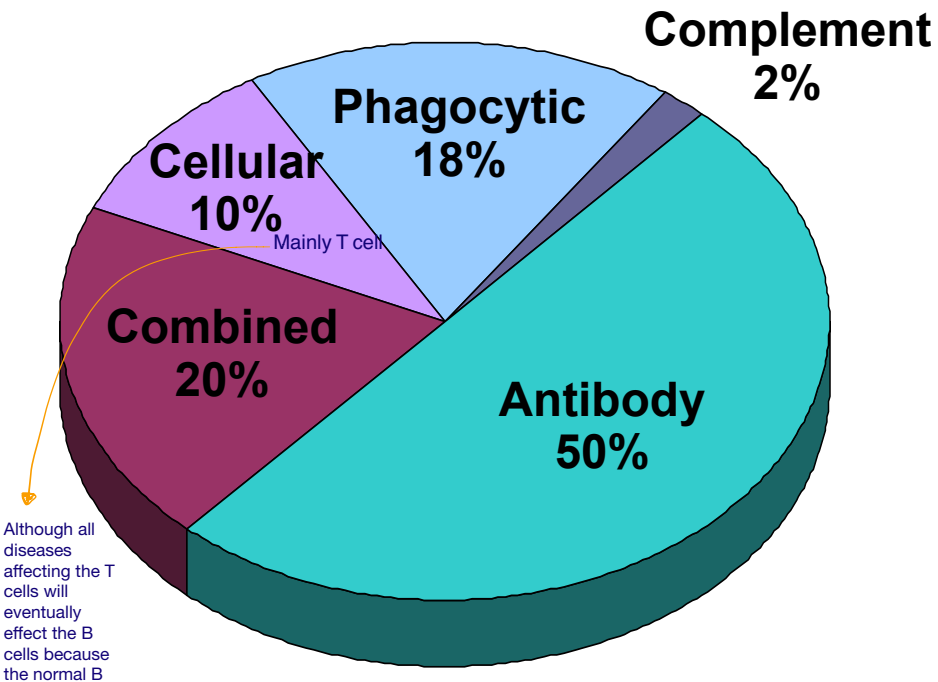
Immunodeficiency

- 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. Example radiation and infection

Primary Immunodeficiency: Frequency



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

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. And Glomerulonephritis

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

Phagocytic Defects: Types and examples

A. Disorders of neutrophil number: <500 neutrophils
   - Cyclic neutropenia and severe congenital neutropenia.

B. Disorders of adhesion: Therefore neutrophils can't reach the site of infection
   - Leukocyte adhesion defect.

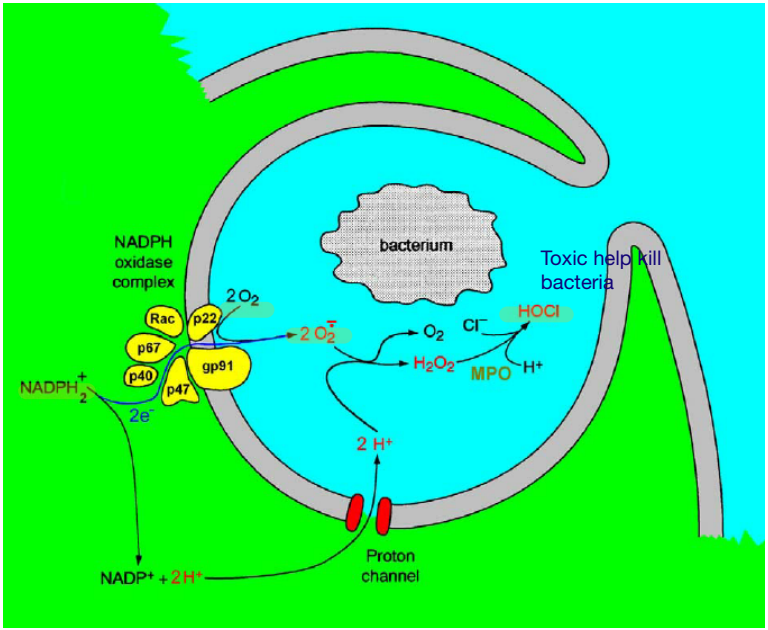
C. Disorders of chemotaxis :
   - Chediak-Higashi syndrome. (also have abnormal intracellular killing)

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. All are catalase +ve
- Can be inherited as X-linked or autosomal recessive.
- Diagnosis: NBT or oxidative burst assay. → Old no longer used
- Patients are put on bactrim and itraconazol prophylaxis. BMT is recommended for some patients.

Why catalase +ve ?
because a lot of the bacteria produce their own H2O2 and the cell can use it to produce HOCL to toxic to the bacteria but in catalase +ve the catalase enzyme will destroy the H2O2 and the cell can't use it. BUT this is not exclusive to these.



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

BMT is the definitive treatment the prophylaxis will only decrease the severity of the infections

Most common cause of death In these patients ? Disseminated Aspergillosis .

The infections most commonly caused by Staph aureus

Why does it have different modes of inheritance? Because the genes are encoded in different places for example gp91 is encoded in the X chromosome.

Deficiencies in T-cell immunity

The most devastating

- **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* When a child has it you should think of T cell deficiency right away.
- 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. World wide this is the most common cause
- Immunosuppressive drugs
- Radiation.
- Infections: like HIV. It affects the helper T cells

Deficiencies in T-cell immunity - Causes

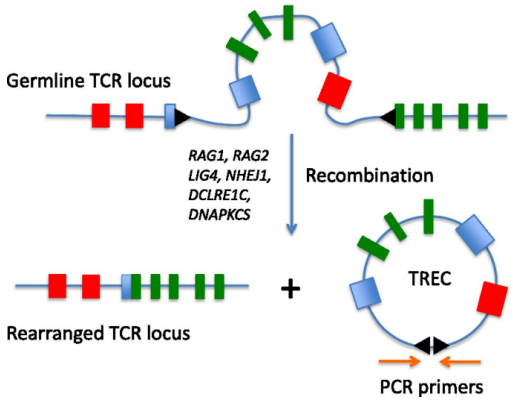
- II- Congenital:

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. Red Flag
  - 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.
  - The droplets of the blood are put on the guthrie card (it is also used for metabolic diseases)
- 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.

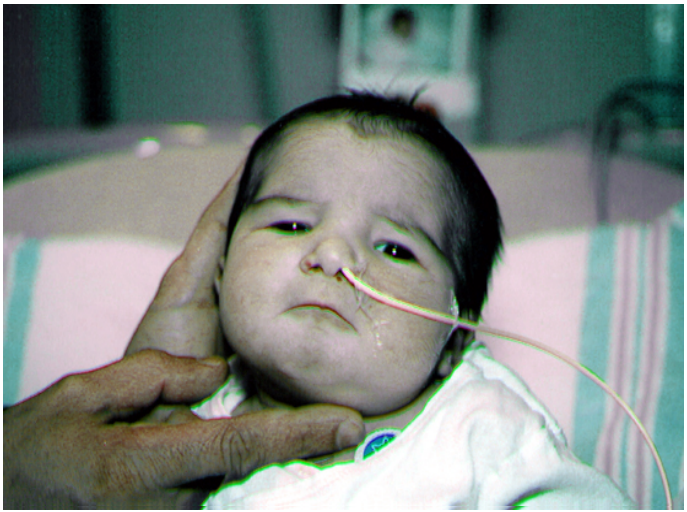
And many others……

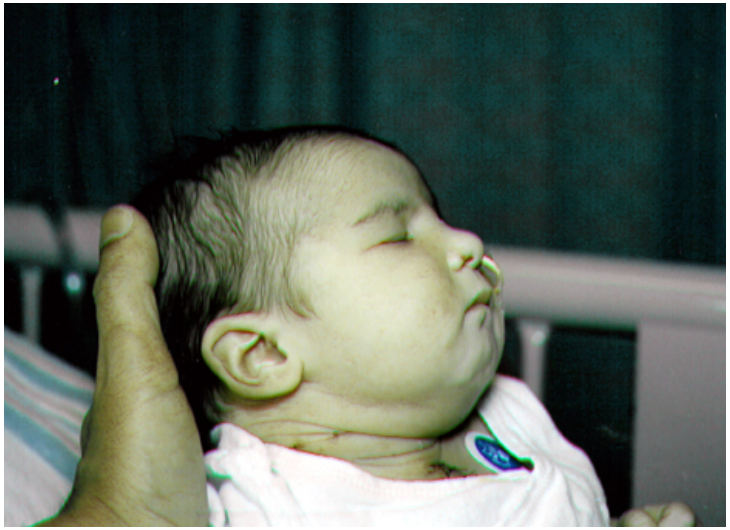
Deficiencies in T-cell immunity

- **DiGeorge Syndrome:**
  - Features: congenital cardiac malformation involving large vessels, hypoplastic thymus, parathyroid deficiency, velopharyngeal insufficiency, cleft palat, and dysmorphic features. They can have tetralogy of fallot.
  - 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.

So the majority we don't need to worry about them or do anything except the small group that has thymic aplasia they have severe immunodeficiency

- DiGeorge the abnormalities seen in the pictures:
  - Bulbous nose
  - Short phlitrum
  - Micrognathia
  - Low set ears





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.

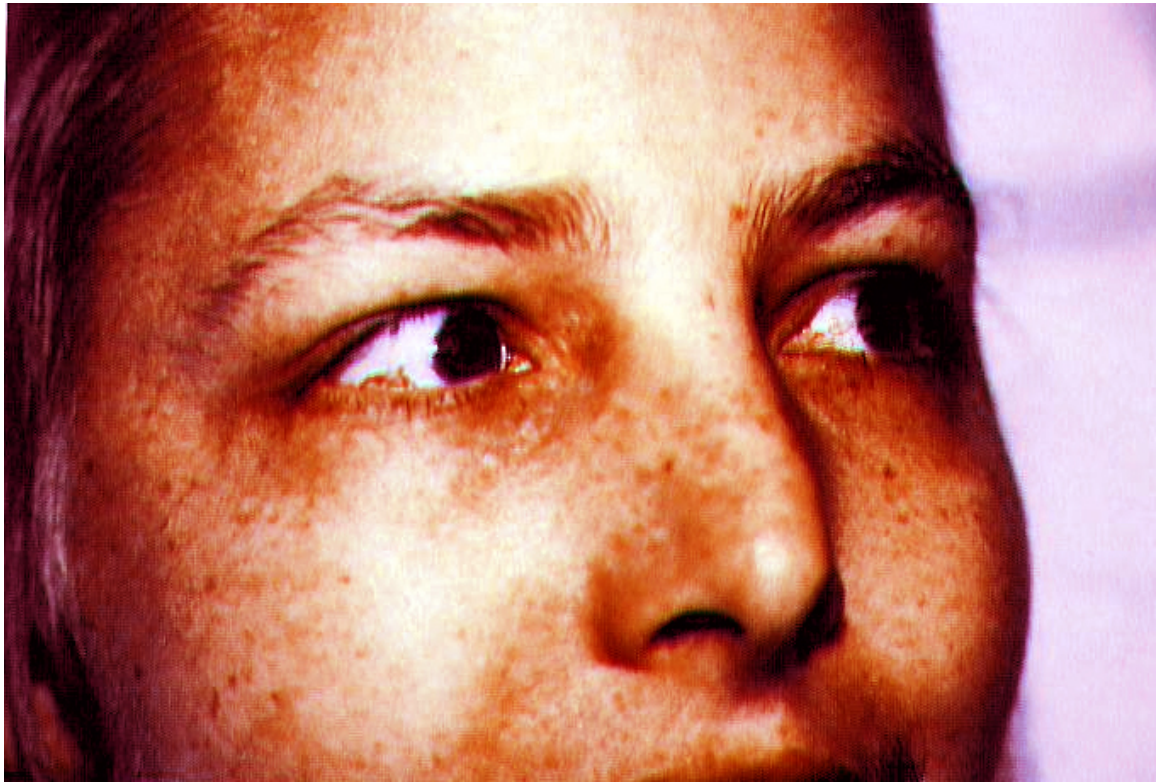
Unlike ITP that have Thrombocytopenia will Large platelets

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.

Cerebellar Ataxia

The Ataxia talangiectasia mutations has a function in DNA repair in the T and B cell receptors formation so the receptor formation is affected.



- Ocular and cutaneous Talangiectasia

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.

Due to Maternal IgG passing through the placenta so they are protected in the first few months

IgG has a 3 weeks half life

Because it can come as pure B cell deficiency unlike T cell deficiency which is usually combined.

They have variable response to vaccines patients will agammaglobulinemia they do not respond to vaccines they can have some T cell activation but it isn't enough either way they are treated with immunoglobulins so we don't vaccinate them

Deficiencies of B-cell immunity – major causes

- X-linked agammaglobulinemia.
- AR agammaglobulinemias.
- Common variable immunodeficiency (CVID): hypogammaglobulinemia with poor antibody responses to antigens.

  It is a group of conditions
- Hyper-IgM syndromes: High-normal IgM with low IgG and IgA.

  Because normally the naive B cells produce IgM and when they are exposed to an infection they switch and become IgG producing to the same antigen.
  So if we have a problem in the switching mechanism between IgM and IgG we will have a lot of IgM.

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.
    - 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.
- Recurrent infections with bacteria of low virulence (e.g: staph) suggest a neutrophil abnormality.
- Recurrent Nisseria infections suggest terminal complement defect.

Always look for anatomical causes prior to immunodeficiency except when the organism is clearly pointing towards an immunodeficiency like pneumocystis jiroveci

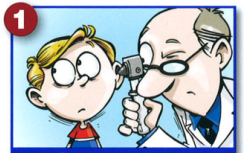
History of Adverse Reactions to Vaccines

- 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.

- Also MMR and BCG vaccines
  Especially BCG immunodeficient patients present with pneumonia and disseminated infection if given the vaccine.

10 Warning Signs of Primary Immunodeficiency

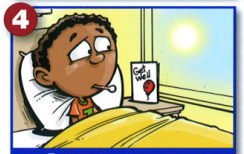
Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. **If you or someone you know is affected by two or more of the following Warning Signs, speak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

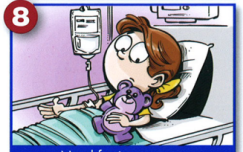
Two or more pneumonias within one year.

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
- 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 ……

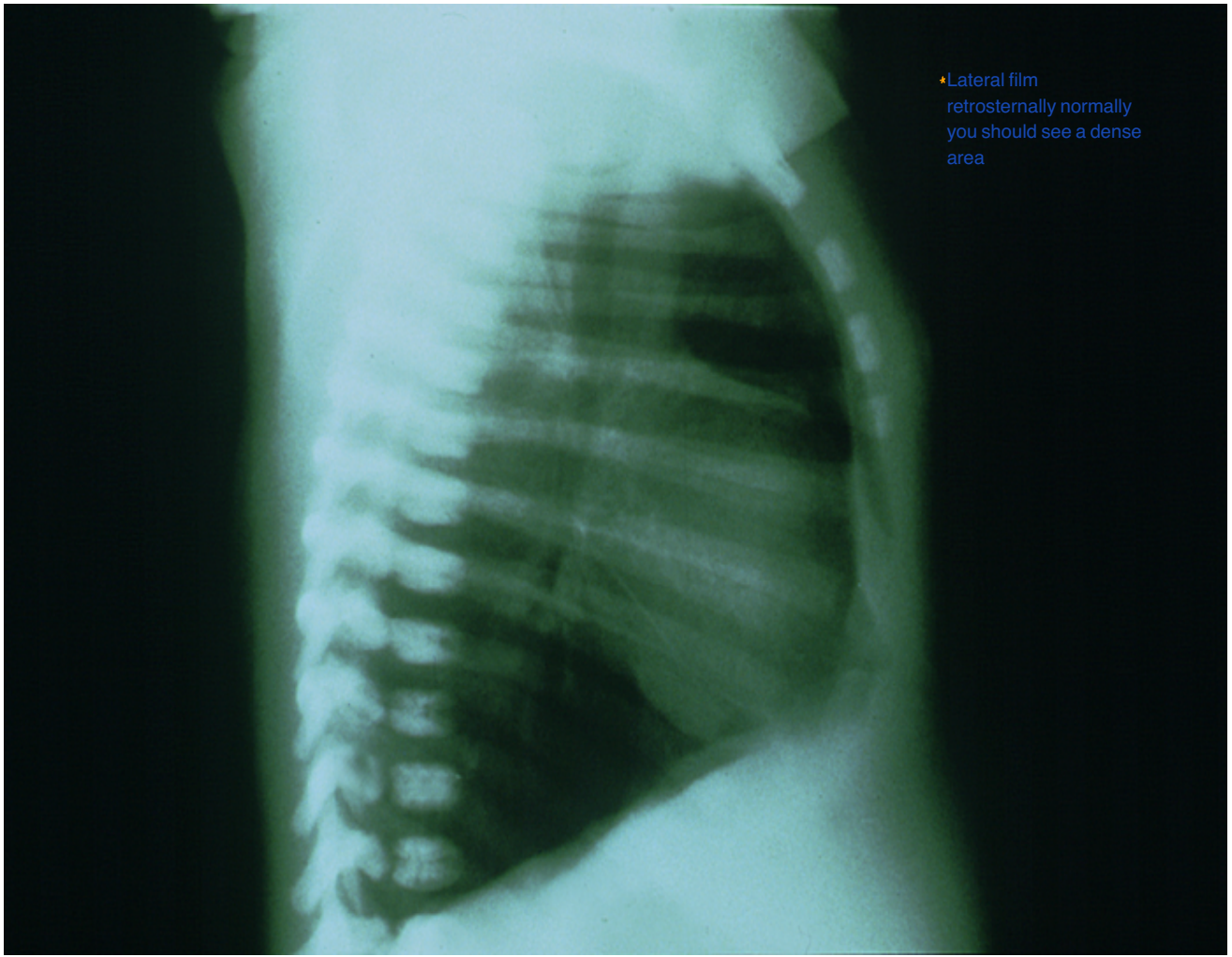
Normally separates at 1–2 weeks

When you get BCG vaccinated the area is infiltrated with helper T cells and inflammation will lead to induration and scar formation in the left deltoid.

Assessment of the Immune System

STAGE-I: General non-specific evaluation.

- ✓ CBC, differential and blood film.
  - We look WBC count , platelet count, neutrophils and most importantly lymphocytes it might be the first clue.
  - SCID will have lymphopenia
- ✓ Quantitative immunoglobulin levels.
- ✓ In newborns, CXR for thymic shadow.
  - Not a sensitive method



- Lateral film retrosternally normally you should see a dense area

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

A. Innate immunity:

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

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

B. Specific immunity:

The quantitive immunoglobulin gave the overall concentration of immunoglobulins not the function or its ability to respond to specific antigens.
we can do the specific immune response to measure the function for example tetanus we can look at the specific antibodies against tetanus if it is not an immunoprotective level we can vaccinate the patient for tetanus them measure it again in 4–6 weeks normally should increase by 10 folds . (normal B cells response to antigens)

1. Humeral component:

1. Specific antibodies responses to tetanus, hemophilus influenzae, and pneumococcus.
2. Isohemagglutinins. ABO blood groups for example A blood type has anti- B this is IgM mainly they are called Isohemagglutinins
3. IgG subclasses. It has 4 subgroups. Subgroup is 1 is the main one.

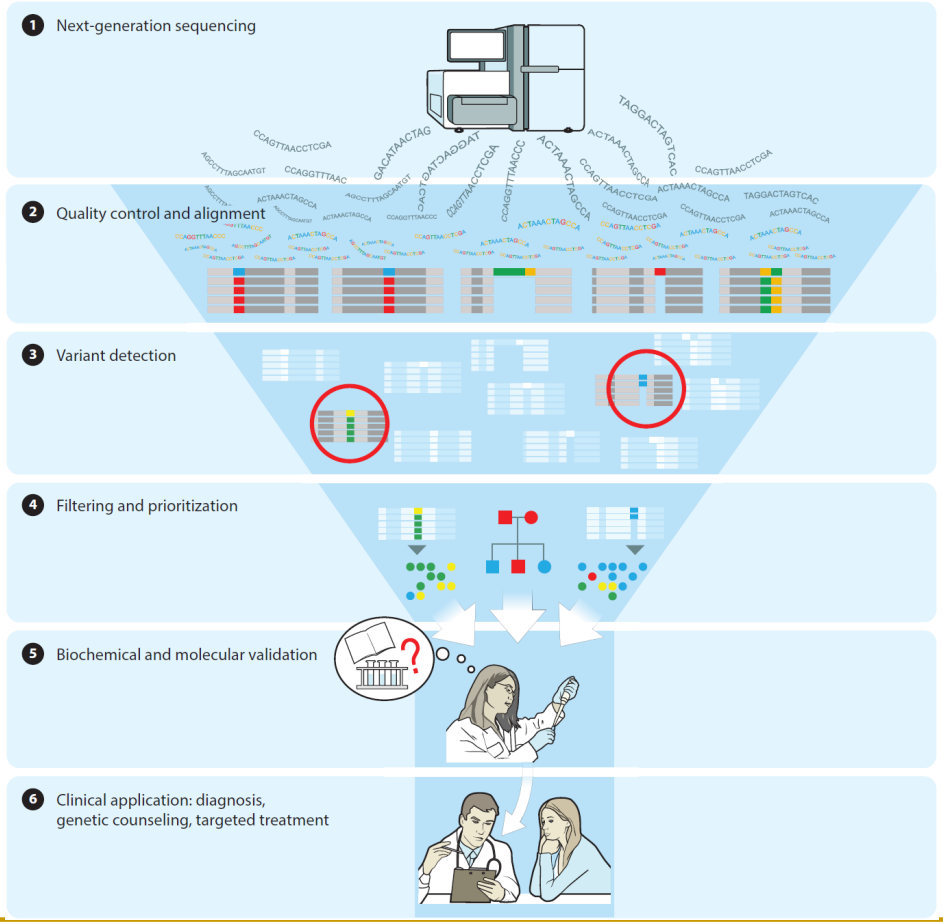
STAGE-II: Evaluation based on the suspected type of immune deficiency

- To differentiate between the sub-types of lymphocytes (T-cell,B-cell,natural killer cell) we use the flow cytometry to see the antibodies against these CD cluster of differentiation.
- Helper cells should be dual positive CD_3 and CD_4 and the cytolytic should be both CD_3 and CD_8

2. Cellular Component:

   1. Lymphocyte subsets (CD3,CD4,CD8,CD19,CD16/56)
      - CD3: T-cells
      - CD4: Helper T cell
      - CD8: Cytolytic T cell
      - CD19: B cells and sometimes CD_{20}
      - CD16/56: NK cells
   2. Delayed skin hypersensitivity reaction to intradermal candida or tetanus (not sensitive with limited availability).
   3. Lymphocyte proliferation assays in vitro.
   4. HIV testing.
      - Why does it hit the CD_4 specifically ?
      - Due to the GP_{120} expressed on the HIV it's ligand is CD_4
      - Other viruses do the same like EBV it ligand is CD_{21} so it affects the B cells.

STAGE- III: More detailed investigations

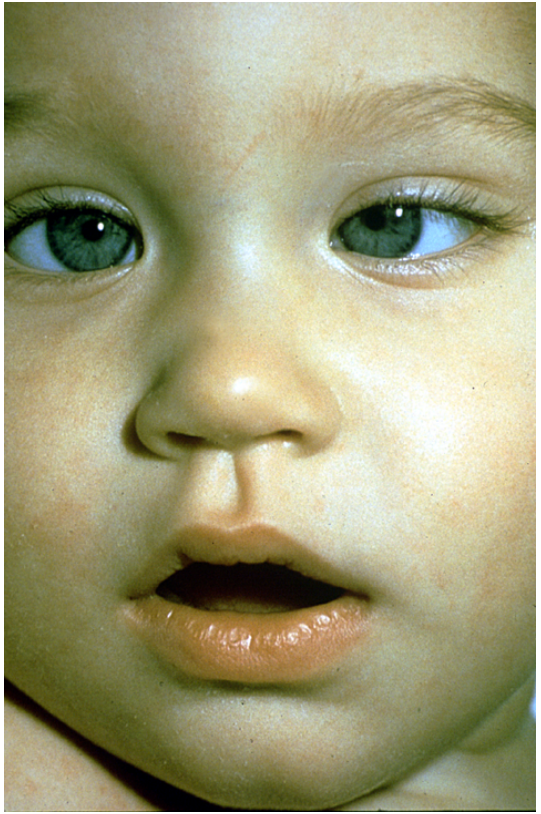


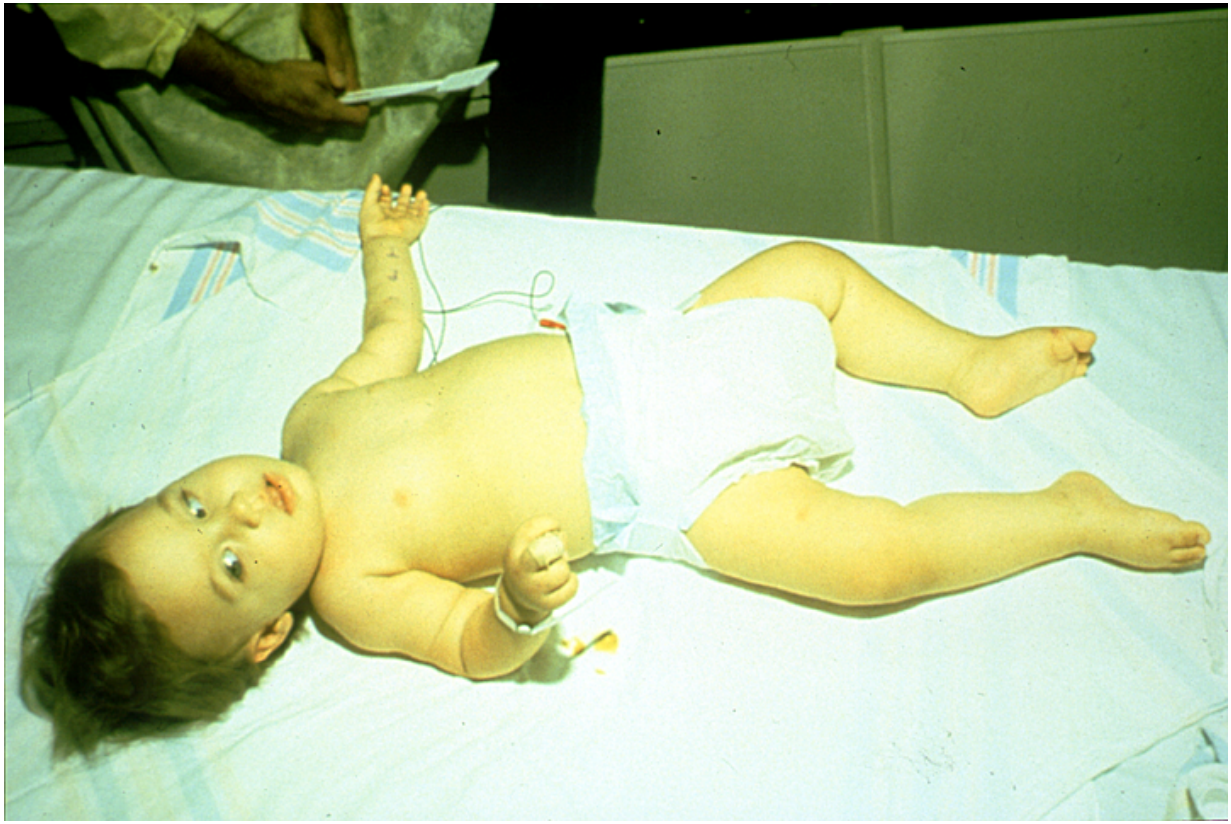
- The doctor talked about the human genome project that took place in the 90's and the breakthrough technologies that lead to us being able to sequence the entire genome in only three days using the Exome (it is the coding part of genome that codes for protein)
- What is the percentage of the coding region in the genome ? 1–2 percent

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.
  - Meaning 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.
- 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.

CD19 cells

Case Study-1 cont…

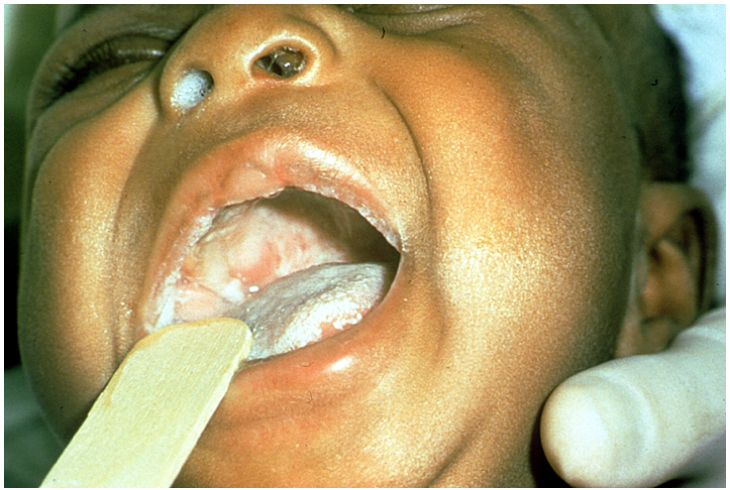
- Based upon the absence of mature B-cells in the circulation and a state of panhypogammaglobulinemia, a diagnosis of **Agammaglobulinemia** was made.

- 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!**

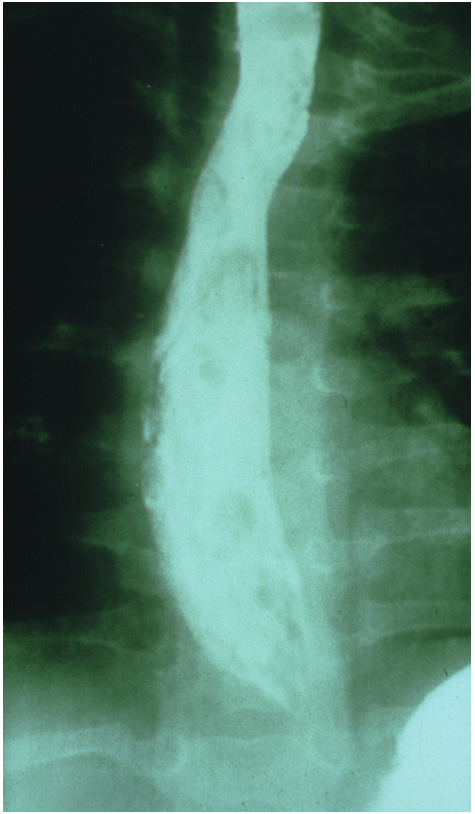
Case Study-2

- 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?

  Candida is fungal and it is mostly T cell immunodeficiency

- What to do next?

Case Study-2 Cont…

- The few IgG present currently are of maternal origin

- 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 is used in two ways :
  1- **Replacement** in patients with hypogammaglobenemia or agammaglobenemia or even T cell deficiency while they wait for the bone marrow transplant
  2- **Immunomodulatory agent** (the most common) and used as the first line in these diseases:
  a-ITP
  b-GBS
  c-Kawasaki

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

- <u>Mechanism of action</u>: 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

- In general it is very safe

- Adverse Effects: non-specific generalized reactions are usually reported in 1-10% of patients, mostly mild.

- during the infusion we start slowly then increase over the next hour then we maintain so on average it takes 4 hours but is some immunodeficiency we use higher doses so it may take up to 8 hours

  - **Mild**: flushing, headache, back pain, chills, myalgia, nausea. Intervention: slow infusion and treat symptoms.
  - **Moderate**: urticaria, bronchospasm, vomiting. Intervention: stop infusion and treat symptoms.
    - We can try again after pre-treating the patient and doing it more slowly next time
  - **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.
  - Taken from at least 10,000 donors so theoretically there is a risk of disease transmission but it goes through a lot of processing to eradicate any organism so the risk of disease transmission is very unlikely.
  - There has been no recorded case of HIV transmission with IVIG

THE END