

Approach to a child with recurrent infections

CHEO TELEHEALTH ROUNDS

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January 29, 2016

Why do we care?

- A common concern
- Clinical dilemma

Healthy?



Not Healthy?

Objectives

- Develop a systematic approach to the evaluation and management of a child with recurrent infections
 1. Recognize the major causes of recurrent infections in children
 2. Determine the important findings on history and physical exam
 3. Recognize the 10 worrisome features suggestive of primary immunodeficiency
 4. Develop an understanding of the appropriate diagnostic testing that may be required
- We will not go through specific PIDs



What is a “recurrent infection”?

- No single definition
- Infections that are too...
 - Great in number
 - 3 or more infections in one year
 - Severe
 - 2 or more severe infections in one year
 - IV antibiotics, hospitalization, unusual pathogen or unusual complications
 - Long lasting
 - The need for antibiotics for 2 months/year



CAUSES OF RECURRENT INFECTION

Instead of thinking like this...

Normal

Child with
Immunodeficiency

4 Major Causes

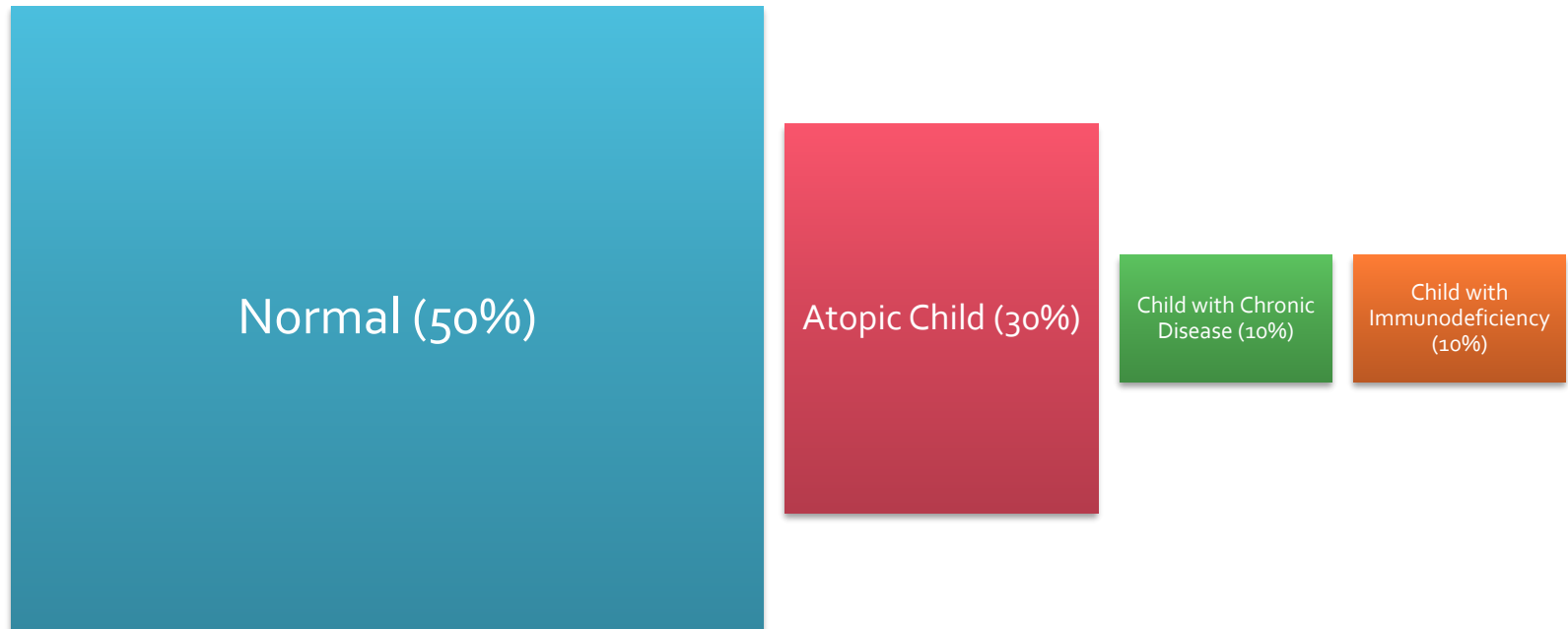
Normal

Atopic Child

Child with Chronic
Disease

Child with
Immunodeficiency

4 Major Causes

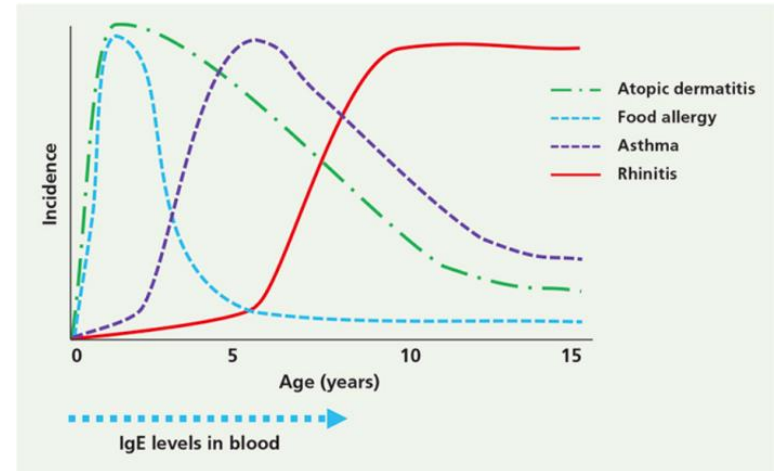


1. The normal child (50%)

- Average child has 4 to 8 respiratory infections per year (some: 10-12)
 - A child can be sick for nearly one-half of the year
- Risk factors
 - Immunologic immaturity (until school age)
 - Day care attendance
 - School-aged siblings
 - Over-crowded homes
 - Second-hand smoke (Maternal and passive)
- Mild, self-limiting viral infections
- Growth and development are not affected
- Physical exam and investigations are normal

2. The atopic child (30%)

- Chronic allergic rhinitis or persistent asthma symptoms can be mistaken for recurrent respiratory infections
 - Diagnosis can be difficult in young children
- Adherence of pathogens to the respiratory epithelium
- History may reveal suggestive symptoms:
 - Recurrent cough
 - Recurrent wheezing
 - Personal or family history of atopy
- Growth and development are typically not affected

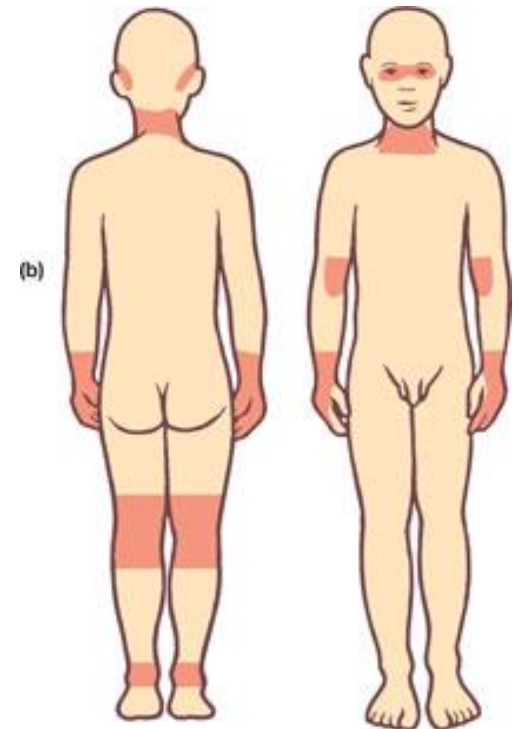


2. The atopic child (30%)

- Physical Exam may have findings of atopy



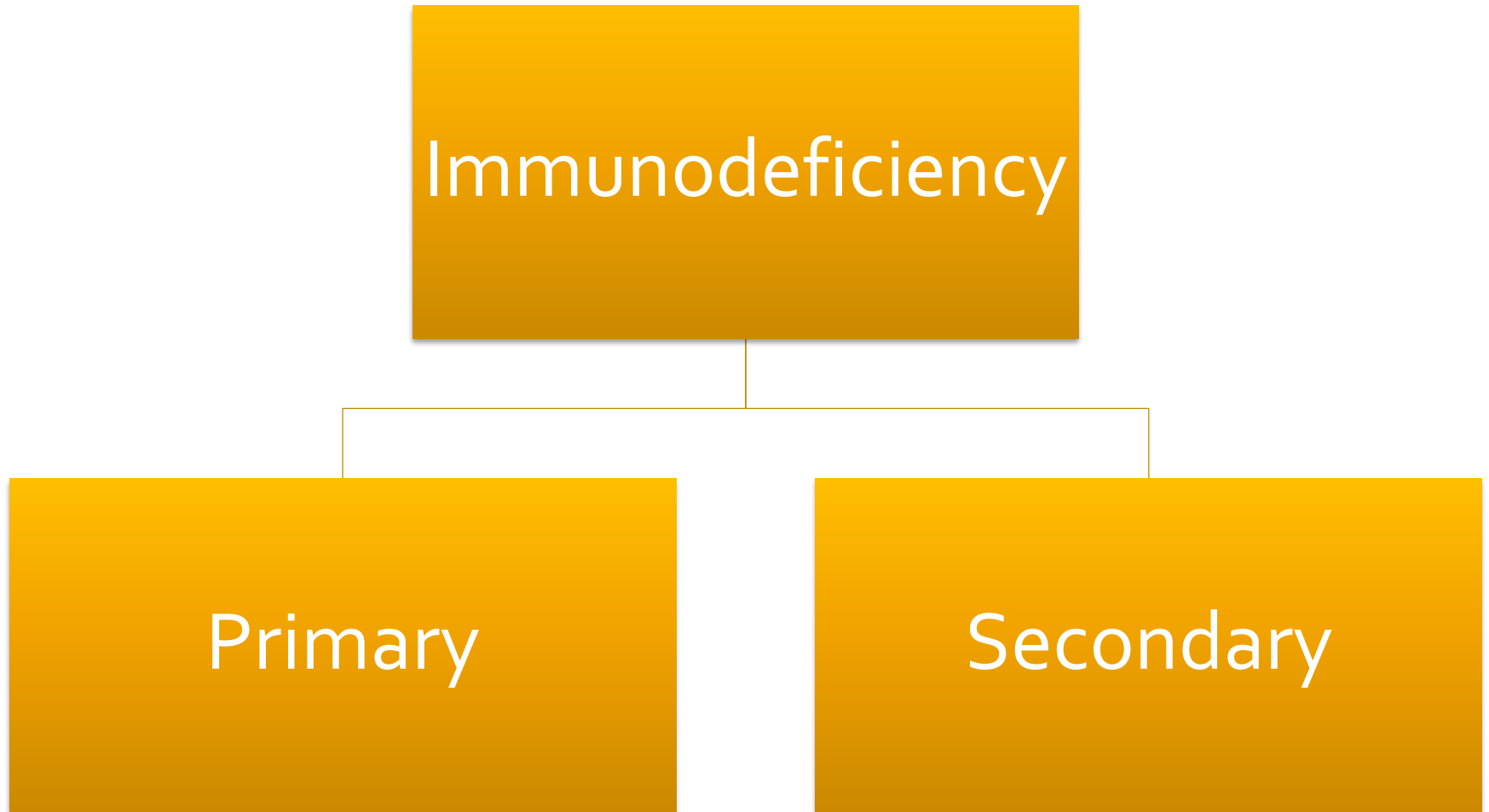
- Work-up may show an elevated IgE
 - Pulmonary Function Test
 - Therapeutic Trial



3. A child with chronic disease (10%)

- Underlying chronic disease or etiology that predisposes a patient to recurrent infections
- Reasons may include:
 - Barrier failure
 - Structural defects of the sinuses
 - Breakdown of the skin (e.g. burns)
 - Inadequate clearance of secretions
 - Hypotonia
 - Abnormal cilia
 - Obstruction
 - Eustachian tube dysfunction
 - Tonsillar/Adenoid hypertrophy
 - Foreign body
 - VP shunts, CVL, or indwelling catheter
 - Noniatrogenic foreign body
 - Resistant organisms
 - CA-MRSA

4. The child with immunodeficiency (10%)

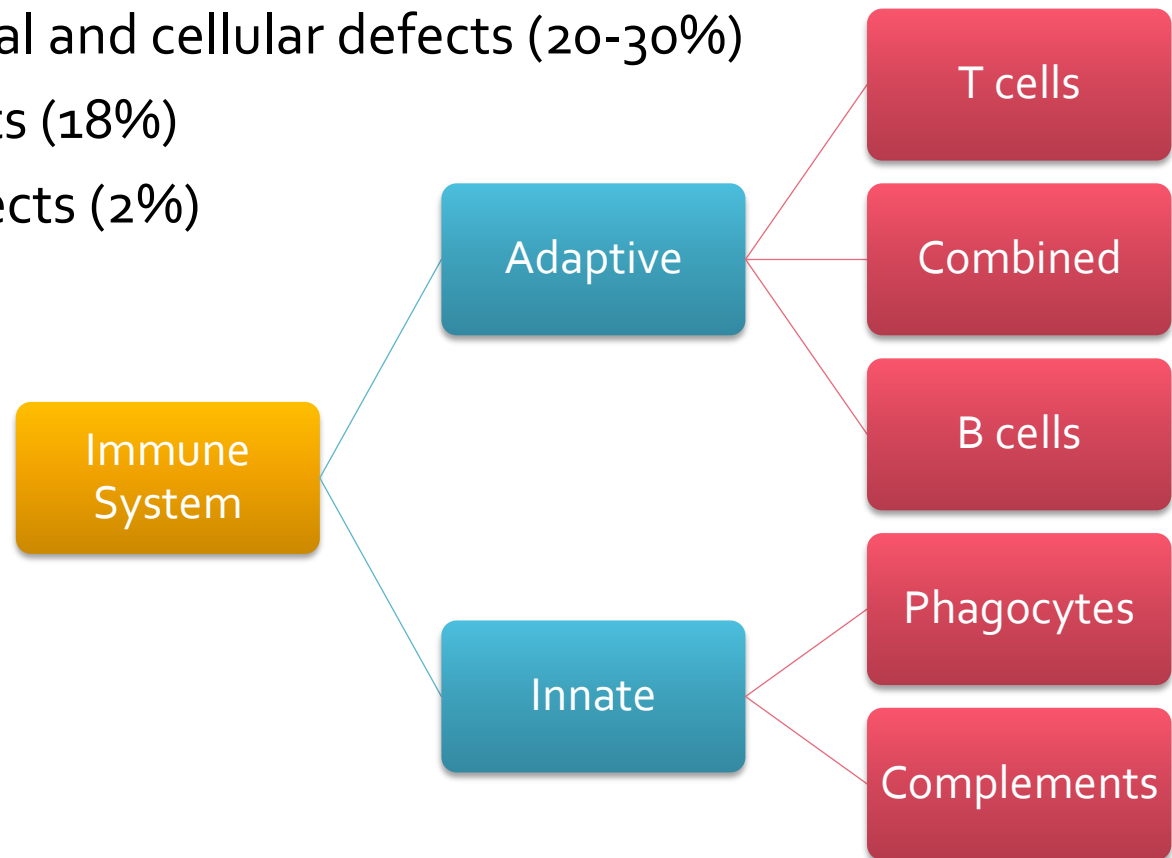


4. The child with immunodeficiency (10%)

- Primary Immunodeficiencies (PID)
 - Genetic defects that interfere with the immune system
 - Rare (1: 10,000 – 1:200,000) except IgA deficiency
 - >150 diseases
 - Early diagnosis improves quality of life and are treatable

Primary Immunodeficiency

- 120 defects identified
 - B-cell immunity defects (>50%)
 - Combined humoral and cellular defects (20-30%)
 - Phagocytic defects (18%)
 - Complement defects (2%)



4. The child with immunodeficiency (10%)

- Secondary/Acquired Immunodeficiency
 - 50 disorders have been identified
 - More common than PID
 - Causes may include:

Infectious

- HIV/AIDS

Splenic Disorder

- Functional asplenia
- Congenital asplenia

Malnutrition

Malignancy

Chronic Disease

- Diabetes
- Chronic lung/kidney/liver

Protein-loss

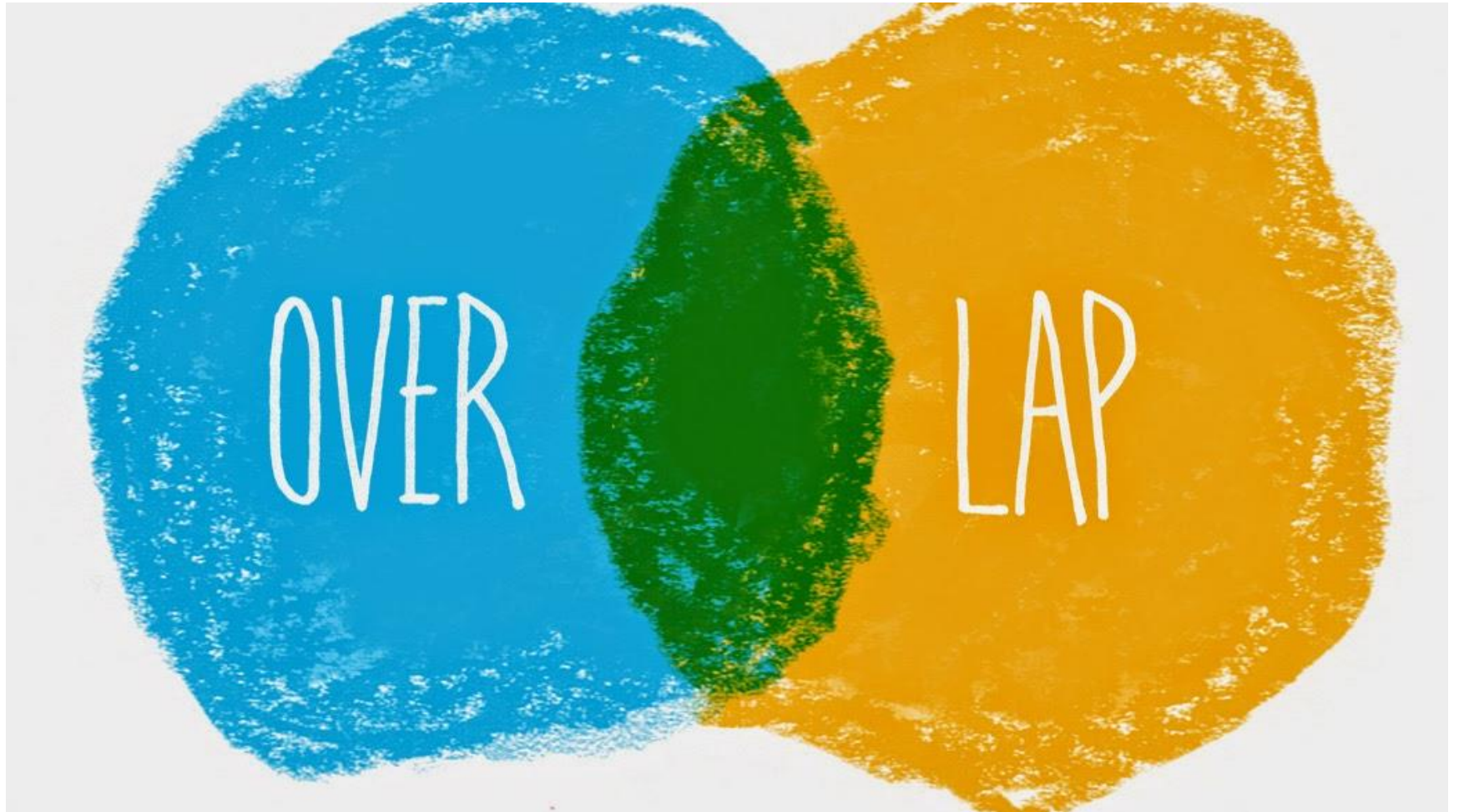
- Protein losing enteropathy
- Nephrotic syndrome
- Burns

Other causes in the differential

- Immunosuppressive-iatrogenic agents
 - Chemotherapy
 - Organ transplantation
 - Chronic Corticosteroid therapy
 - Anticonvulsant



Let's be thorough!



MEDICAL HISTORY & EXAMINATION



History

- Describe each infectious episode in detail:
 - Age at onset
 - How the diagnosis was established
 - Severity
 - Hospitalization
 - Duration
 - Etiology
 - Bacterial
 - Viral
 - Fungal
 - Opportunistic infection
 - Organs affected
 - Severe locations: meninges, bone/joint, bacteremia/sepsis
 - Response to therapy
 - Complications
 - Need for surgical intervention



What's the organism?

Organism	Type of Defect
Encapsulated organisms	B cells/ Humoral
Viruses, protozoa, mycobacteria	T cells / Cellular
Staphylococcal, gram negative	Phagocytic Defects
Encapsulated, Neisserial species	Complement

Red Flags on HPI

- An atypical presentation
- Unusually severe course
- An unexpected pathogen
- Unusual complications
- Recurrent or persistent



History

- Family History
 - Ethnic heritage
 - Consanguinity
 - Early unexplained deaths
 - Maternal male relatives
 - Autoimmune disorders
 - Malignancy

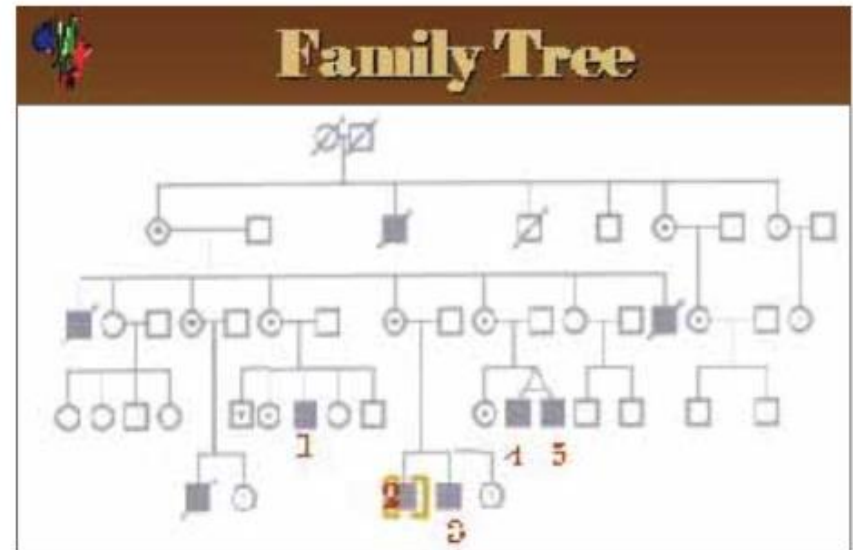


Fig. 2. X-linked agammaglobulinaemia – family tree (S Pienaar).

History

- Birth History and Development
 - Maternal Illness & Risk Factors
 - Neonatal complications
 - Delayed separation of umbilical stump
- Social History
 - Siblings
 - Daycare
 - Tobacco smoke
 - Bottle feeding
 - Travel history

History

- Response to events throughout childhood:
 - Live vaccines
 - Vaccine failures
 - Transfusions
- Medications, Allergies
- Complete review of systems
 - Recurrent fevers
 - Failure to thrive
 - Chronic diarrhea, malabsorption
 - Poor wound healing
 - Rashes
 - Arthritis
 - Gingivitis, retained primary teeth, aphthous stomatitis

Warning signs for PID

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 1 year.
- 2** Two or more serious sinus infections within 1 year.
- 3** Two or more months on antibiotics with little effect.
- 4** Two or more pneumonias within 1 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.

Most predictive of PID

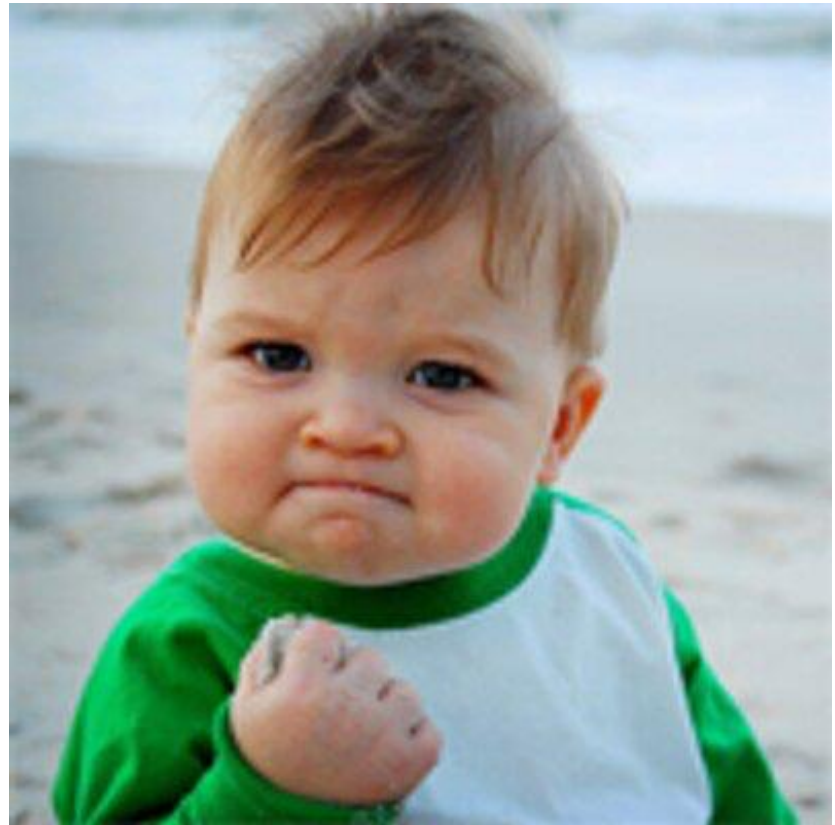
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Reassuring Features

- Thriving child
- Older child/adolescent
- No “severe infections”
- No opportunistic infections
- No family history



Physical Exam

- Thorough physical exam is required to evaluate the various causes
- A normal exam does not exclude significant immune defects



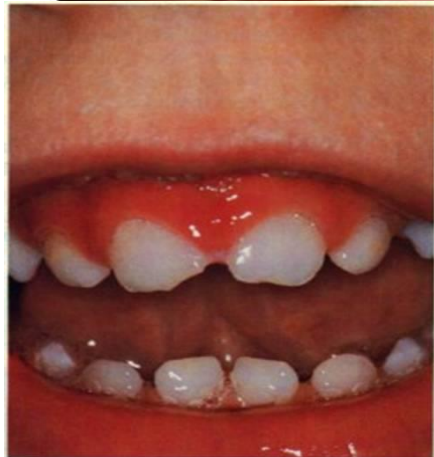
Physical Exam

- The initial look:
 - General appearance
 - Vitals
 - **Height**
 - **Weight**
 - Dysmorphic features



Physical Exam

- Pay particular attention to:
 - Head and Neck Exam



Oral ulcers	Chronic granulomatous disease, severe combined immunodeficiency, congenital neutropenia
Periodontitis, gingivitis, stomatitis	Neutrophil defects
Oral or nail candidiasis	T-cell immune defects, combined defects, mucocutaneous candidiasis, hyper-IgE syndrome

Physical Exam

- Pay particular attention to:
 - Head and Neck Exam
 - Lymph Node Exam

Usually present

Recurrent upper respiratory infections

Severe bacterial infections

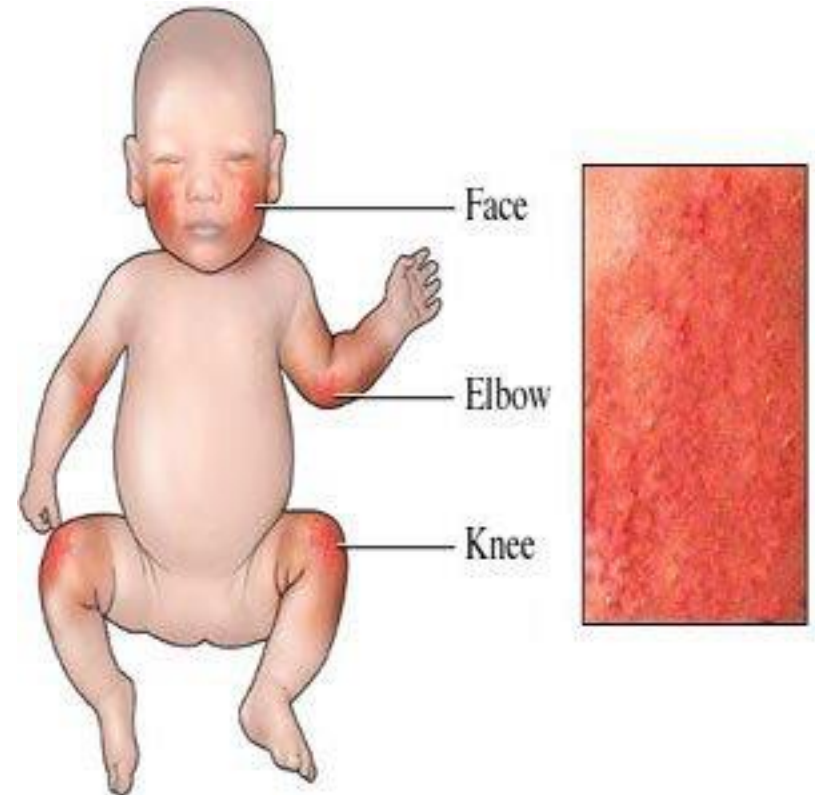
Persistent infections with incomplete or no response to therapy

Paucity of lymph nodes and tonsils



Physical Exam

- Pay particular attention to:
 - Head and Neck Exam
 - Lymph Node Exam
 - Findings of Atopy



Physical Exam

- Pay particular attention to:
 - Head and Neck Exam
 - Lymph Node Exam
 - Findings of Atopy
 - Skin Exam

Table 3. CHARACTERISTIC SKIN MANIFESTATIONS OF IMMUNODEFICIENCY

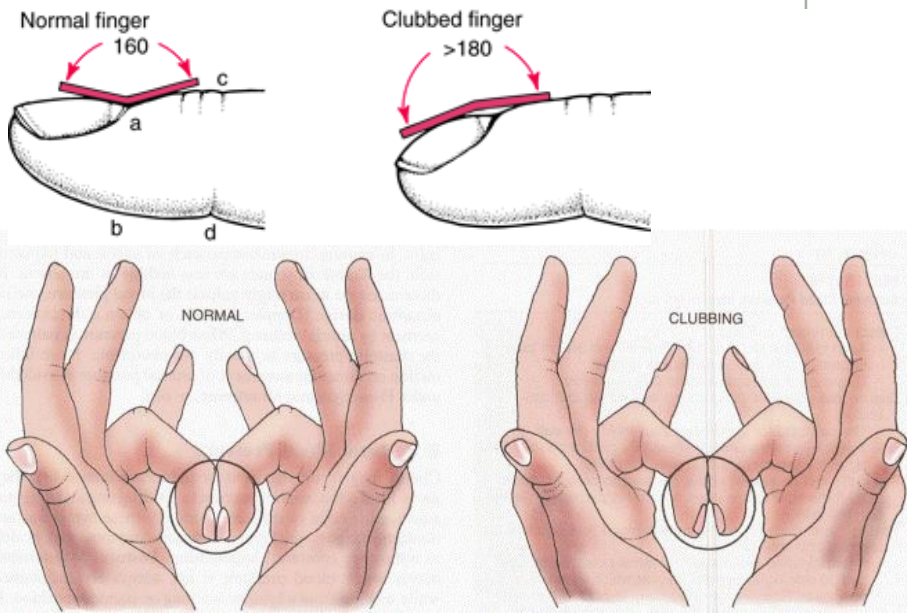
Skin Findings	Associated Immune Defect
Eczema and petechiae	Wiskott-Aldrich syndrome
Telangiectasia	Ataxia-telangiectasia syndrome
Oculocutaneous albinism	Chédiak-Higashi syndrome
Dermatomyositis-like rash	B-cell dysfunction (XLA)
Chronic dermatitis	Hyper-IgE syndrome
Lupuslike rash	Complement deficiency (early components)
Cutaneous scars	Phagocytic cell defect
Generalized molluscum contagiosum	T-cell deficiency
Extensive warts	T-cell deficiency
Candidiasis	T-cell deficiency

XLA = X-linked (Bruton's) immunodeficiency.

Physical Exam

- Pay particular attention to:
 - Head and Neck Exam
 - Lymph Node Exam
 - Findings of Atopy
 - Skin Exam
 - Extremities

SKELETAL	
Short-limb dwarfism	Short-limb dwarfism with T- and/or B-cell immune defects
Bony dysplasia	ADA deficiency, cartilage hair hypoplasia



INVESTIGATIONS

Infection Evaluation

- Appropriate cultures
- Radiographic imaging of areas of suspected infection
- ESR or CRP



Laboratory Screening

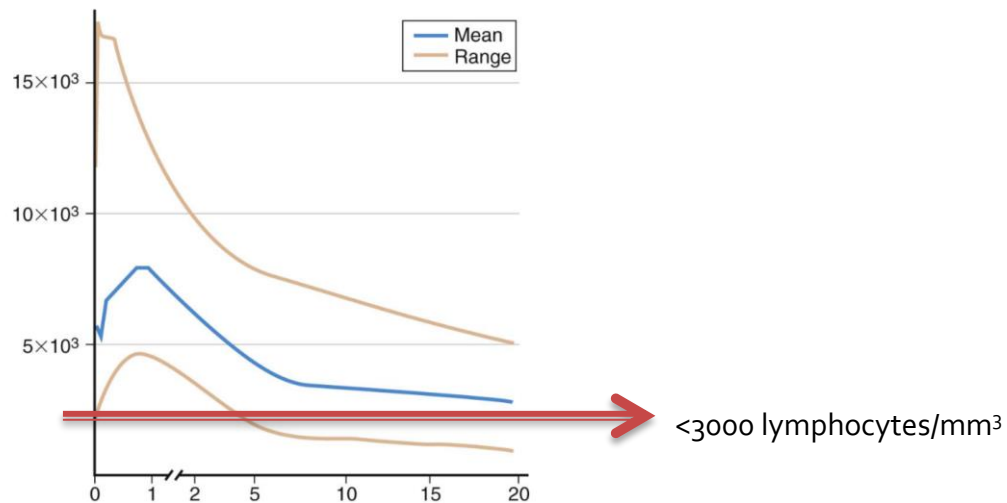
- Most immunologic defects can be excluded at minimum cost
- Basic work-up:
 - CBC and diff
 - Neutrophils: Congenital/Acquired neutropenias, leukocyte adhesion defect
 - Absolute lymphocyte count: T-cell defects
 - Platelets: Wiskott-Aldrich Syndrome
 - Peripheral Blood Smear
 - Howel-Jolly bodies: Congenital asplenia
 - ESR
 - Normal: Chronic bacterial or fungal infection unlikely

Screening Tests for B-cell Defects

- Immunoglobulins (IgA, IgM, IgG, IgE)
 - Low levels may be due to GI or renal losses as well
 - Utility of IgG subclasses are debatable and not recommended
- Antibody titers to tetanus, diphtheria, haemophilus influenzae and strep pneumococcal
 - To evaluate specific and functional antibody production
 - Protein Antigens
 - Polysaccharide Antigens
 - Live vaccines

Screening Tests for T-cell Defects

- Absolute Lymphocyte Count
 - Lymphopenia in a neonate is almost always abnormal
 - Normal lymphocyte counts are higher in infancy and early childhood than later in life



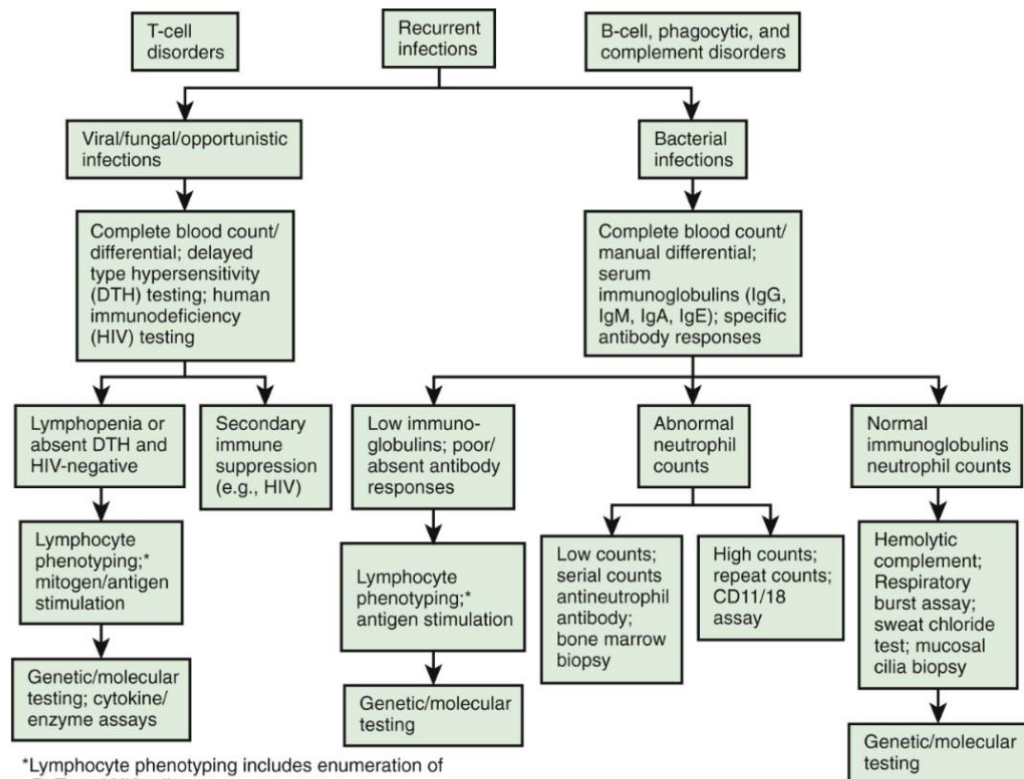
Screening Tests for Complement Deficiency

- C₃, C₄
- Total hemolytic complement (CH₅₀) assay
 - Evaluates the functional integrity of the classic complement pathway
 - Test when the patient is well to rule out consumption
 - Normal CH₅₀ excludes nearly all hereditary complement deficiencies

Definitive Testing

- Abnormalities should be characterized fully before treatment
- Undertaken in consultation with a pediatric immunologist

SCREENING TESTS	ADVANCED TESTS	RESEARCH/SPECIAL TESTS
B-CELL DEFICIENCY		
IgG, IgM, IgA, and IgE levels	B-cell enumeration (CD19 or CD20)	Advanced B-cell phenotyping
Isohemagglutinin titers		Biopsies (e.g., lymph nodes)
Ab response to vaccine antigens (e.g., tetanus, diphtheria, pneumococci, <i>Haemophilus influenzae</i>)	Ab responses to boosters or to new vaccines	Ab responses to special antigens (e.g., bacteriophage φX174), mutation analysis
T-CELL DEFICIENCY		
Lymphocyte count	T-cell subset enumeration (CD3, CD4, CD8)	Advanced flow cytometry
Chest x-ray examination for thymic size*	Proliferative responses to mitogens, antigens, allogeneic cells	Enzyme assays (e.g., ADA, PNP) Thymic imaging
Delayed skin tests (e.g., <i>Candida</i> , tetanus toxoid)	HLA typing	Mutation analysis
	Chromosome analysis	T-cell activation studies Apoptosis studies Biopsies
PHAGOCYtic DEFICIENCY		
WBC count, morphology	Adhesion molecule assays (e.g., CD11b/CD18, selectin ligand)	Mutation analysis
Respiratory burst assay	Mutation analysis	Enzyme assays (e.g., MPO, G6PD, NADPH oxidase)
COMPLEMENT DEFICIENCY		
CH ₅₀ activity	AH50, activity	
C3 level	Component assays	
C4 level	Activation assays (e.g., C3a, C4a, C4d,	








In Summary

1. The four major causes of recurrent infections in children are: the healthy child, the atopic child, the child with chronic diseases, and the child with immunodeficiency
2. A high index of suspicion is needed for PID. Although rare, early treatment leads to improved morbidity and mortality
3. The most predictive features of PID are:
 1. Failure to thrive
 2. The need for IV antibiotics
 3. A family history of PID
4. Most immunologic defects can be excluded at minimum cost

Thank you!

Resources

1. Hernandez-Trujillo VP. Approach to children with recurrent infections. *Immunol Allergy Clin N Am* 35(2015):625-636.
2. Ballow M. Approach to the patient with recurrent infections. *Clinic Rev Allerg Immunol* 34 (2008):129-140.
3. Esser M. Approach to the child with recurrent infections – presentation and investigation of primary immunodeficiency. *Current Allergy & Clinical Immunology* 21 (2008):8-12.
4. Up to date
5. Nelson's Pediatrics Textbook
6. Infectious Disease Department at CHEO

Microbiology	Associated PID
Streptococcus pneumoniae Streptococcus pyogenes Haemophilus influenzae Ureaplasma urealyticum Giardia lamblia	 Humoral Immunodeficiency
Mycobacteria Salmonella Listeria monocytogenes Toxoplasma gondii Pneumocystis carinii Fungi Viruses	 Cellular immunodeficiency
Candida albicans Pneumocystis carinii Aspergillus species Viruses (especially herpes viruses)	 Combined – Cellular and humoral immunodeficiency
Staphylococcus aureus Klebsiella Escherichia coli Enterobacter Serratia marcescens Salmonella Pseudomonas	 Phagocytic defects
Neisseria meningitidis S pneumoniae H. influenzae Neisseria gonorrhoeae	 Complement deficiencies

Physical Examination

Usually present	Recurrent upper respiratory infections
	Severe bacterial infections
	Persistent infections with incomplete or no response to therapy
	Paucity of lymph nodes and tonsils
Often present	Persistent sinusitis or mastoiditis (<i>Streptococcus pneumoniae</i> , <i>Haemophilus</i> , <i>Pneumocystis jiroveci</i> , <i>Staphylococcus aureus</i> , <i>Pseudomonas</i> spp.)
	Recurrent bronchitis or pneumonia
	Failure to thrive or growth retardation for infants or children; weight loss for adults
	Intermittent fever
	Infection with unusual organisms
	Skin lesions: rash, seborrhea, pyoderma, necrotic abscesses, alopecia, eczema, telangiectasia
	Recalcitrant thrush
	Diarrhea and malabsorption
	Hearing loss due to chronic otitis
	Chronic conjunctivitis
	Arthralgia or arthritis
	Bronchiectasis
	Evidence of autoimmunity, especially autoimmune thrombocytopenia or hemolytic anemia
	Hematologic abnormalities: aplastic anemia, hemolytic anemia, neutropenia, thrombocytopenia
	History of prior surgery, biopsy