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Approach to the Pediatric Patient with Recurrent Infections

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BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT RANKED IN 10 SPECIALTIES 2021-22

MAGNET RECOGNIZED AMERICAN NURSES CREDENTIALING CENTER

Audience Response Question

- A 3 yo patient is brought to the pediatrician's office due to concern for recurrent infections. She has had 4 viral RTIs in the past 2 months. Her parents are concerned because she is not in daycare and avoids most public indoor activities due to COVID-19 related concerns. What other aspects of her clinical history may be helpful?
  a. Older Siblings
  b. Atopy
  c. Parental Smoking
  d. Nutritional Status
  e. All of the above

Audience Response Question

- Infection with which of the following infections would NOT warrant an Immunologic evaluation in a child?

a. *Pneumocystis Jirovecii* Pneumonia
b. Recurrent Herpes Simplex Encephalitis
c. *Burkholderia cepacia* septicemia
d. Atypical Mycobacterium lymphadenitis

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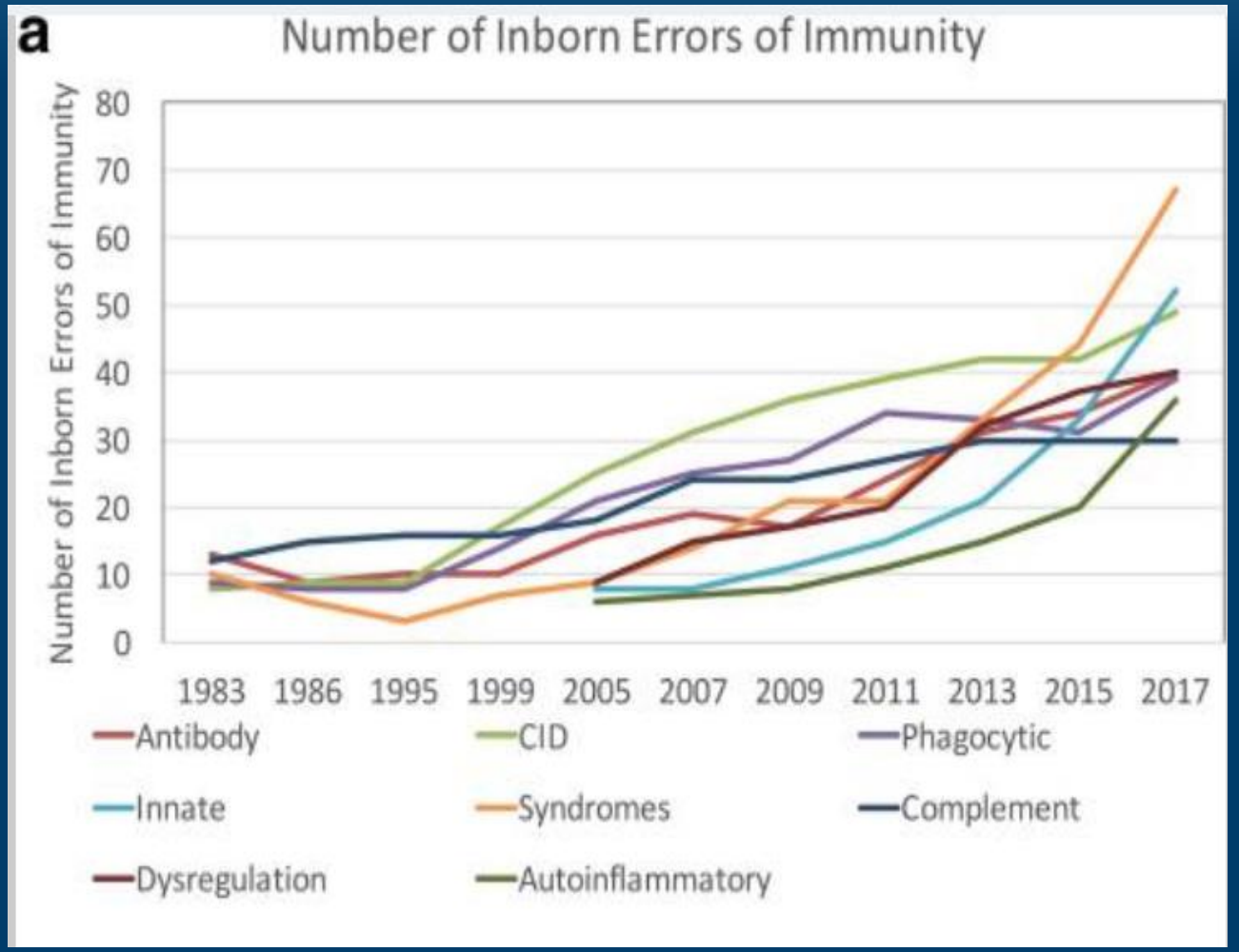
Outline

- What are Inborn Errors in Immunity (IEI)?
- Defining "Normal"
- Differential Diagnosis
- Features Concerning for IEI

Inborn Errors of Immunity

- >450 genes identified that contribute to disorders of the immune system.
- IEI – more encompassing term
- Prevalence 1 in 2000 patients in the United States
- 20% of patients seeking care in Immunology clinic.



Picard C, Gaspar HB, Al-Herz W, et al. J Clin Immunol. 2018. 38:97
Tangye SG, Al-Herz W, Bousfiha A, et al. J Clin Immunol. 2021. 41:666
Benjamin Prince et al. "Incidence of Primary Immunodeficiency Disorders at a Tertiary Care Immunology Clinic"[Abstract] JACI 2020; 142:1

Defining "Normal" – Physiologic Immunodeficiency of Immaturity

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Decreased Neutrophil number and function	• Low bone marrow reserves • Reduced chemotaxis
Low complement level and function	• Classical and Alternative Pathways affected
Decreased Cellular Responses	• Poor responses to antigen • More difficult to stimulate • Decreased CD40L expression • Th2 skewing
Decreased Humoral Responses	• Physiologic nadir of IgG • Delayed IgG2 subclass production • Low IgA during childhood

Slatter MA, Gennery AR. *Clin Exp Immunol*. 2008;152(3):389-396.

Defining "Normal" Frequency

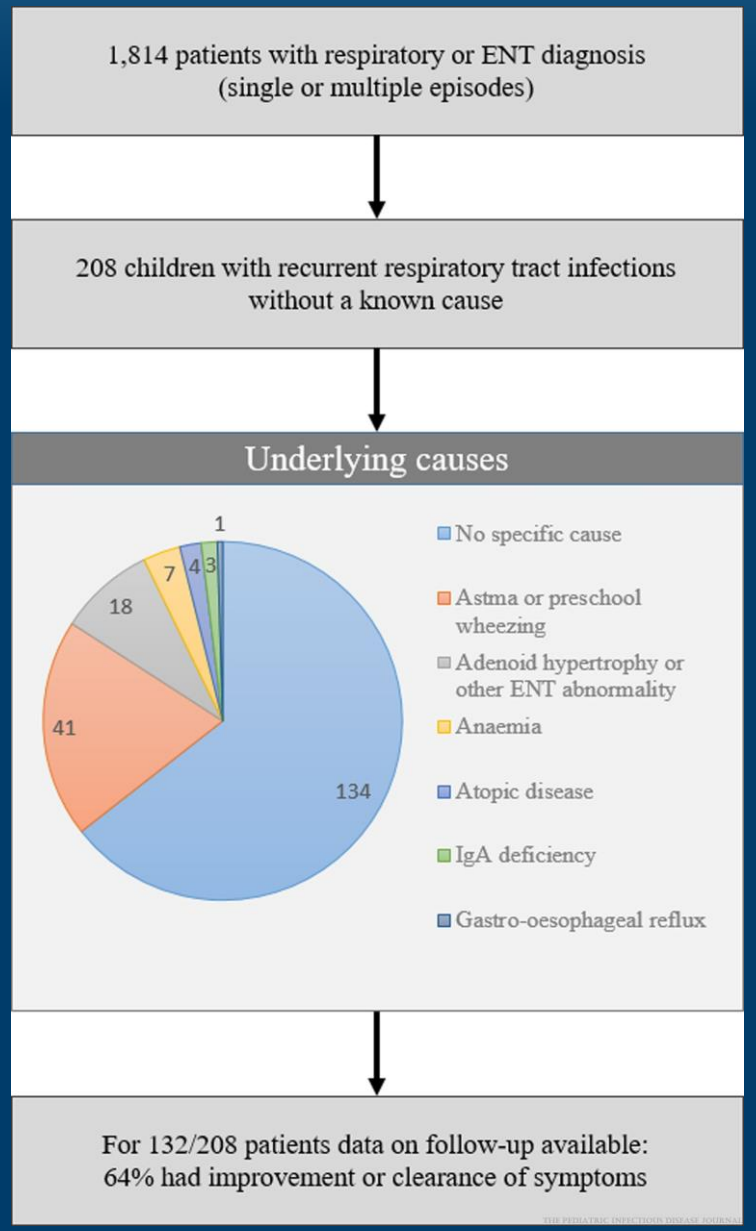
- 6 infections/year, lasting 1-2 weeks (25-50% of the year)!
- RRTI – 10-20% of the population between 0-10 years

- Risk factors:
  - Siblings
  - Day care attendance
  - Poor nutrition
  - Cigarette smoke
  - Overcrowded living conditions

Gray PE, Namasivayam M, Ziegler JB. J Paediatr Child Health. 2012 Mar;48(3):202-9.

Defining "Normal"

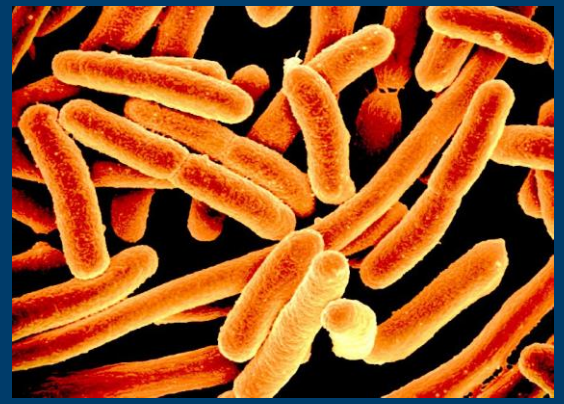
- Common Things are Common, Ex. Vomiting Infant
- Peeters study showed 64% patients did not have an underlying pathology.
- Key factors distinguish healthy children
  - Growth
  - Response to treatment
  - Interim health



Peeters, D et al. The Pediatric Infectious Disease Journal 40(11):e424-e426, November 2021.

Non-immune Differential Diagnosis

- Atopy
- GER
- Resistant Organism
- Continuous Reinfection

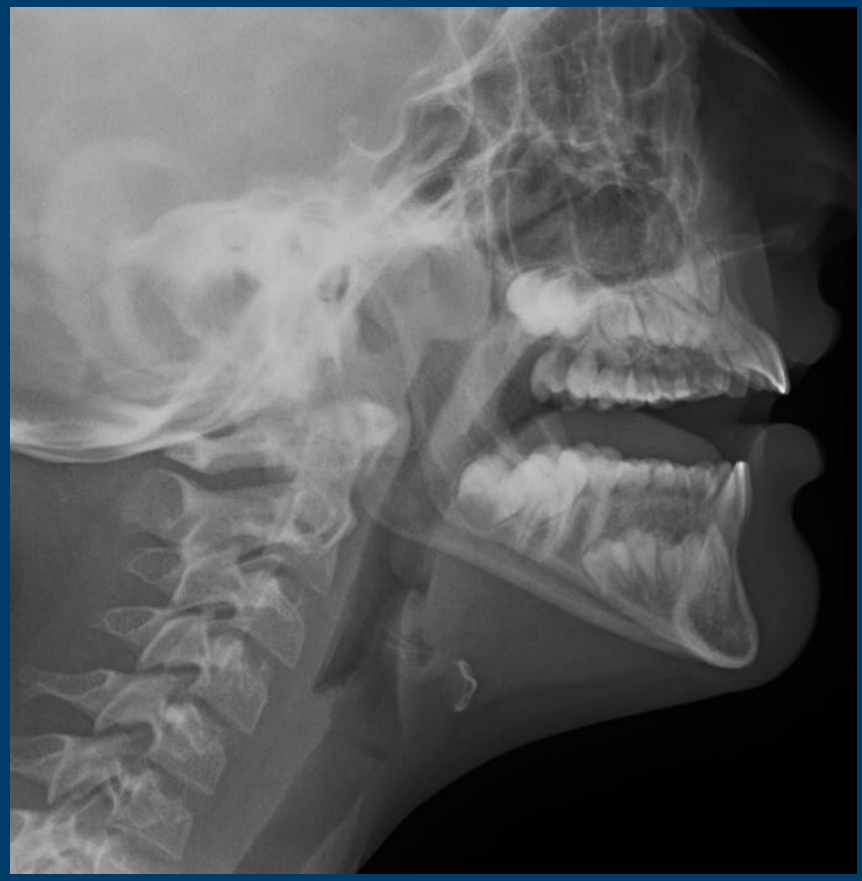


Non-immune Differential Diagnosis

- Secondary Immunodeficiency
  - Nutrition
  - HIV
  - Iatrogenic (immunosuppressant or immunomodulatory treatment)
- Systemic/Chronic Diseases
- Cardiac Disease

Non-immune Differential Diagnosis

- Physical/Anatomic issues
  - Ex. Orbital cellulitis patient
  - Vesicoureteral reflux
  - Adenoid Hypertrophy
  - Cystic Fibrosis
  - Primary Ciliary Dyskinesia
  - Eustachian Tube Dysfunction
  - Disrupted Epithelial Tissue
  - Foreign body



Case courtesy of Dr Servet Kahveci, Radiopaedia.org, rID: 83587

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:

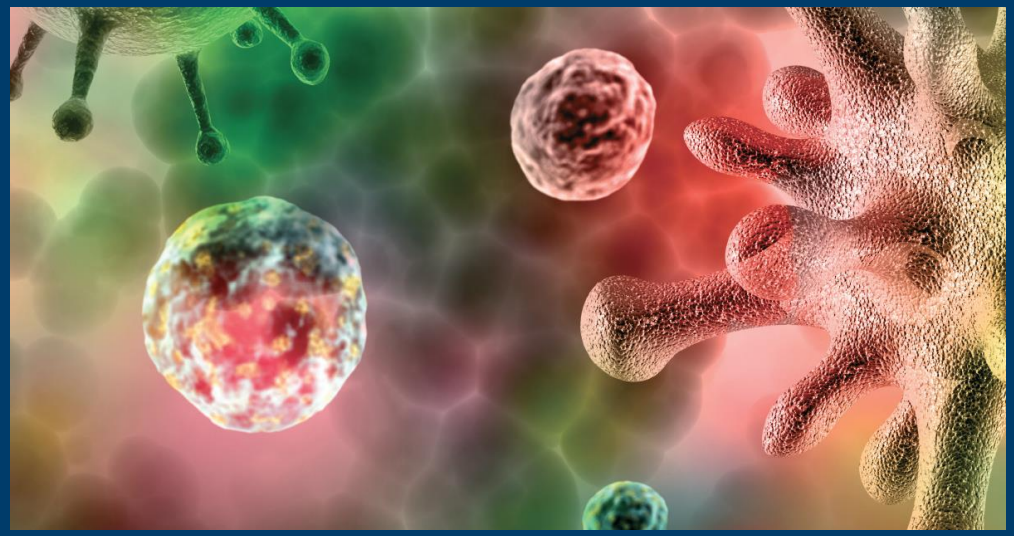
When to look for Zebras

- Age of Presentation and Associated PID
  - Neonatal period – delayed separation of the cord, perianal ulcers, omphalitis, erythroderma w/ associated LAD, cardiac defects or other syndromic features
  - < 6 months – cellular defects
  - 6 months to 5 years – antibody and complement defects, late presentation of CID, antibody deficiency, DNA repair defects
  - > 5 years – humoral immunodeficiency

Slatter MA, Gennery AR. *Clin Exp Immunol*. 2008;152(3):389-396

Unusual or recurrent pathogen

- Disseminated atypical mycobacterial infection
- Invasive Staphylococcal or Streptococcal infection
- PJP
- *Burkholderia cepacia* septacemia
- Fungal abscesses
- Human herpes virus infections
- Recurrent meningococcal infection
- *S. pneumonia* or *Hemophilius influenzae* causing sinopulmonary infections
- Several enteroviral infection
- HSV encephalitis



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When to suspect PID- Organ Specific Complications

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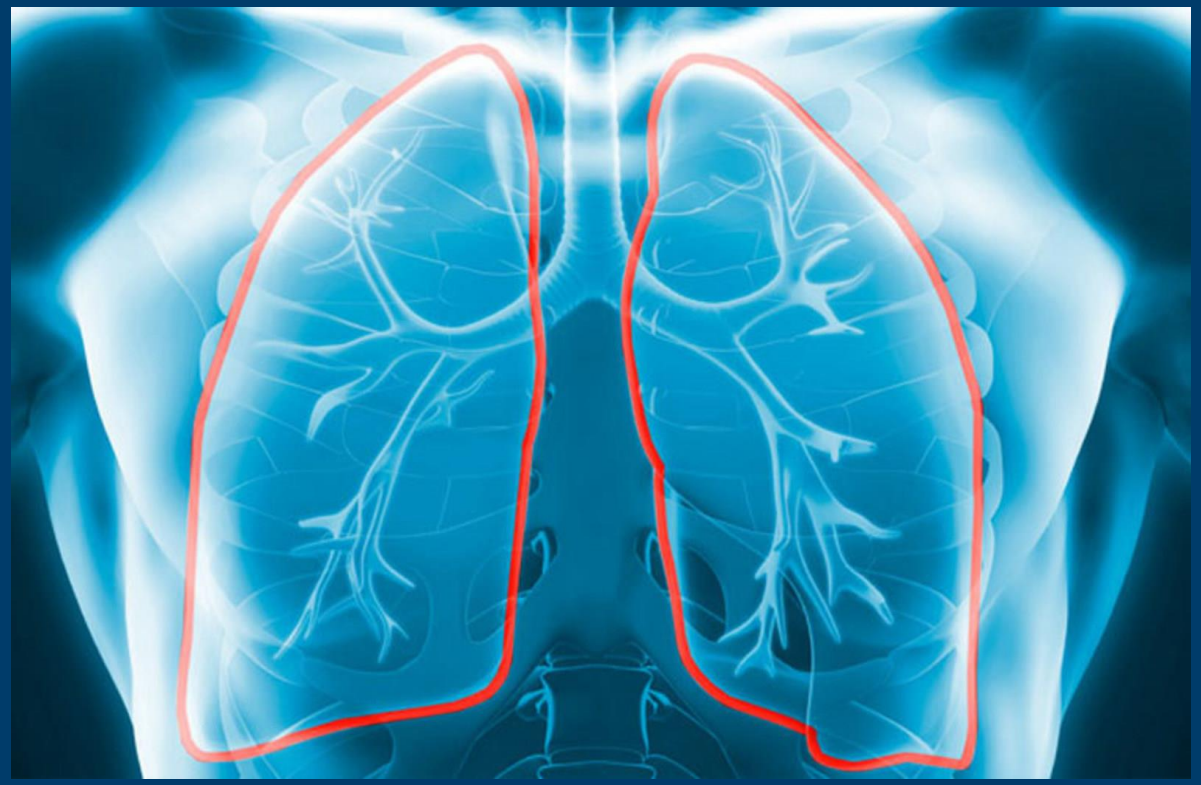
Respiratory tract

- persistent/recurrent bronchiolitis in infancy
- interstitial pneumonia
- PJP
- Recurrent sinobacterial infections
- Staphylococcal lung abscesses w/ pneumatocele
- Fungal pneumonia



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Gastrointestinal Tract

- FTT and malabsorption
- Very Early Onset IBD
- Hepatic abscesses
- Exocrine pancreatic insufficiency
- *Cryptosporidium parvum* associated sclerosing cholangitis

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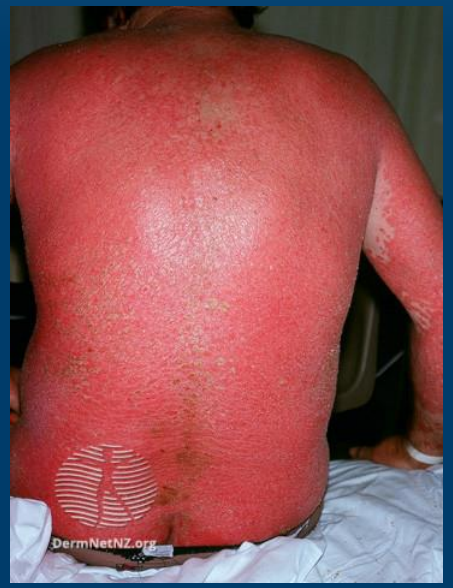
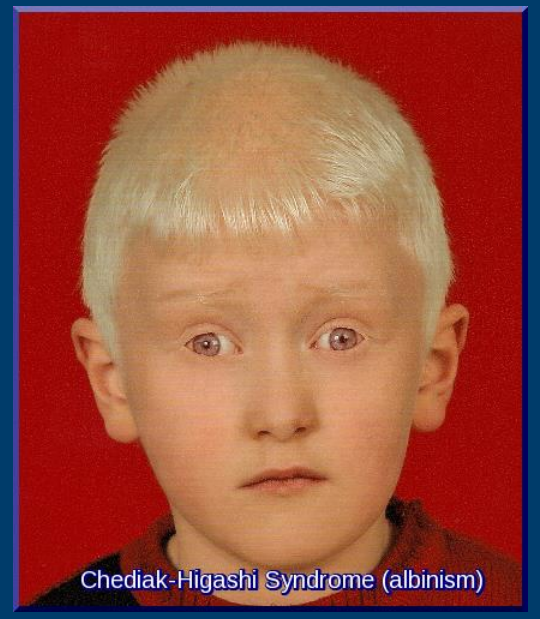
Dermatologic

- Severe eczema + petechiae
- Erythroderma
- Pyoderma
- Mucosal candidiasis
- Oculocutaneous albinism
- Telangiectasias





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Neurologic

- Neurodevelopmental delay
- Unsteady gait
- Microcephaly
- Enteroviral meningoencephalitis

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Hematologic

- Primary HLH
- Neutropenia
- Autoimmune cytopenia (esp. Evan's syndrome)
- Myelodysplasia

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Hadjadj et al. Blood. 2019 Jul 4;134(1):9-21.
Slatter MA, Gennery AR. *Clin Exp Immunol*. 2008;152(3):389-396

When to suspect PID- Organ Specific Complications

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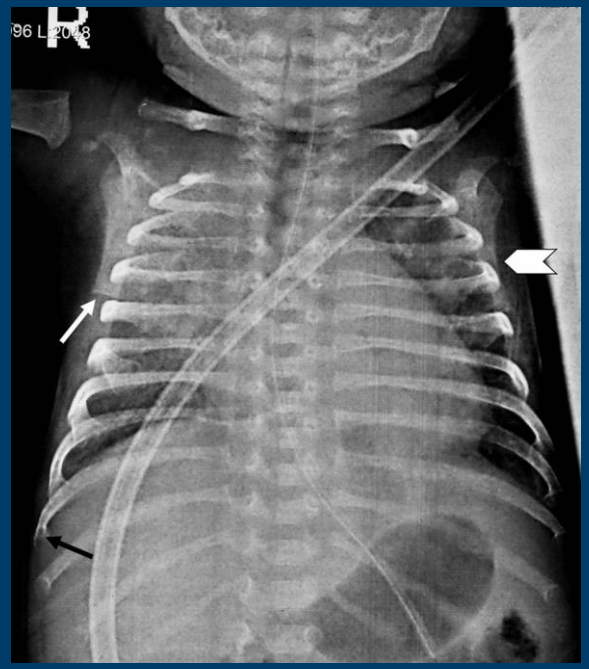
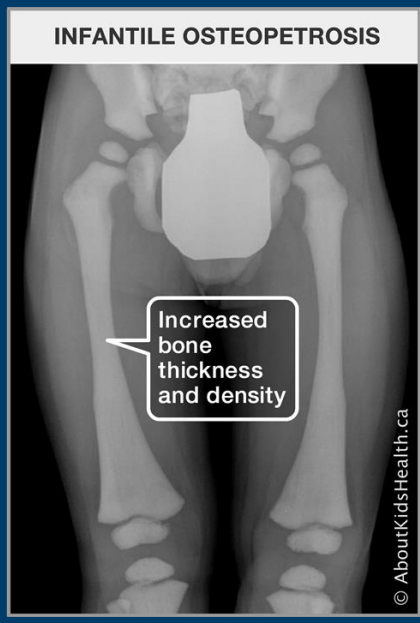
Skeletal abnormality

- Short-limb dwarfism
- Rib cupping
- Hypodense bone
- Delayed primary dental deciduation
- Osteopetrosis





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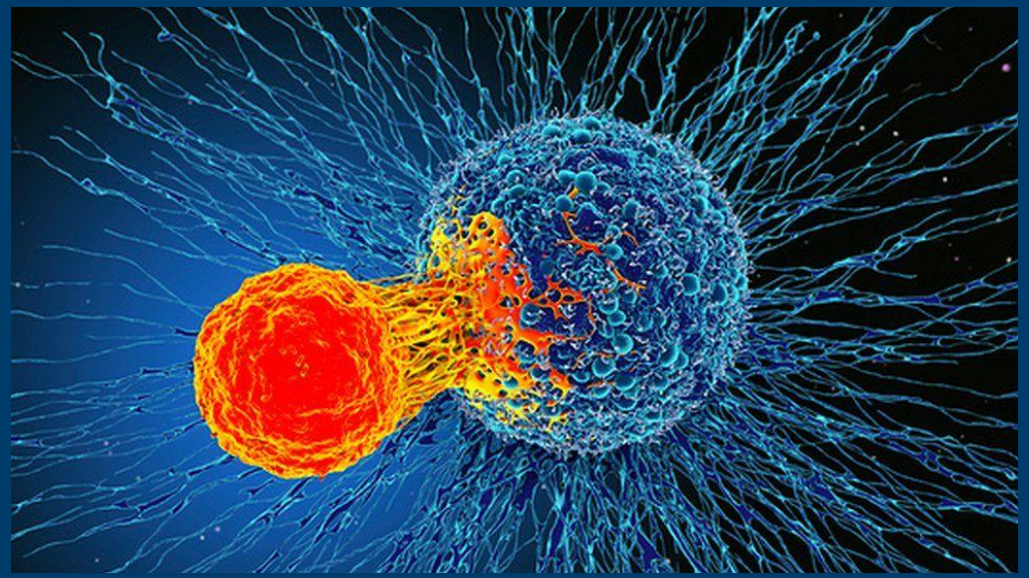
Slatter MA, Gennery AR. *Clin Exp Immunol*. 2008;152(3):389-396
Ankur Kumar Jindal, and Amit Rawat BMJ Case Reports 2017;2017:bcr-2017-220642

When to suspect PID- Organ Specific Complications

Lymphoreticular System

- Non-Hodgkin's lymphoma
- Hepatoma
- EBV associated lymphoma
- Early or unusual malignancy



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Initial Immunologic Evaluation

- CBC with Differential
- Humoral immunodeficiency suspected: Immunoglobulins (age adjusted), B cell quantification, S. Pneumoniae and Tetanus titers
- Cellular immunodeficiency suspected: Lymphocyte flow cytometry, lymphocyte proliferation studies
- Phagocytic defects: Neutrophil Oxidative Index
- Complement deficiency: CH50 or AH50
- Functional testing depending on history – ex. CD40L expression assay
- Push for early genetic testing

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