Children's Research Institute
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MEDICAL COLLEGE OF WISCONSIN

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Pulmonary Manifestations of Primary Immunodeficiencies (PID)

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SPUR: When to Suspect a PID

- Severe: complicated pneumonias (multilobar, pneumatocoeles, cavities, empyema) and/or unusual mediastinal/hilar adenopathy
- Prolonged/Persistent: failure to respond to usual therapy in a expected manner
- Unusual: unusual or opportunistic pathogens, lymphadenopathy
- Recurrent: repeated episodes of pneumonia

Diagnostic Studies in Patients with PID

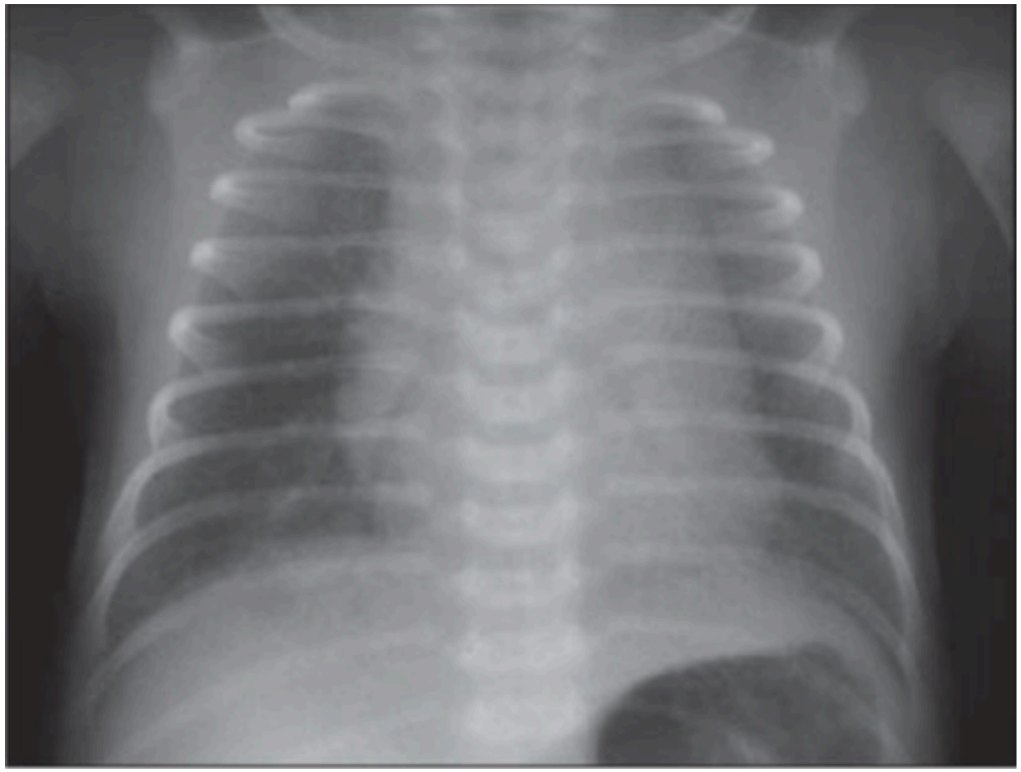
- DO NOT use serological assays for dx in pts. with PID: many forms of PID decreased/absent ability to make specific Abs
- Serological assays: measure antibodies in gammaglobulin in patients receiving IVIG
- Dx of infectious disease MUST be done by culture, PCR or other direct methods to directly test the presence of the pathogen

Severe Combined Immunodeficiency (SCID)
Combined Immunodeficiencies

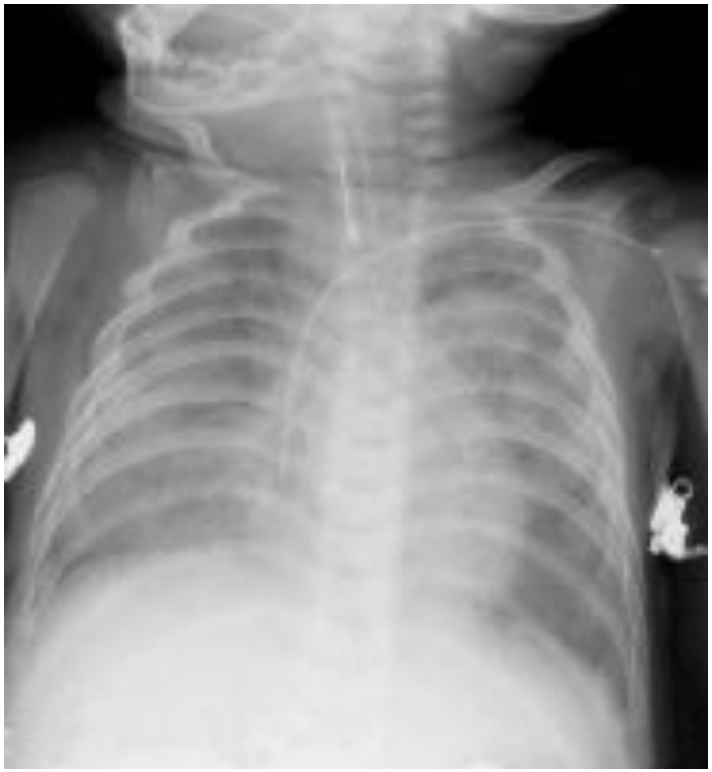
SCID

- Group of syndromes characterized by a profound decrease in T cells and concomitant B cell defects
- Pulmonary infections are common: opportunistic pathogens (*P. jirovecii*), viruses (AD, CMV, herpes virus, RSV, PIV-3 and others), atypical mycobacteria, fungi (aspergillus, scedosporium etc.)and common pathogens as well
- Absence of lymphoid tissue, absence thymic shadow and ALC<2500/mm3 (most)
- Newborn screening using TREC assay-early diagnosis and improved prognosi

SCID



- Normal CXR neonate
- Prominent thymic shadow

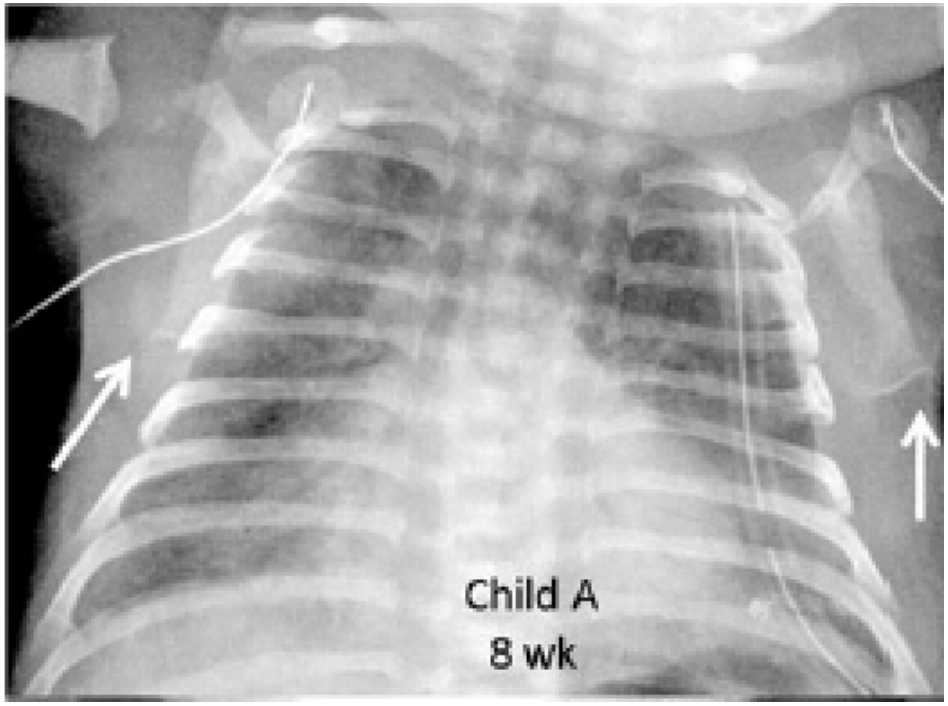


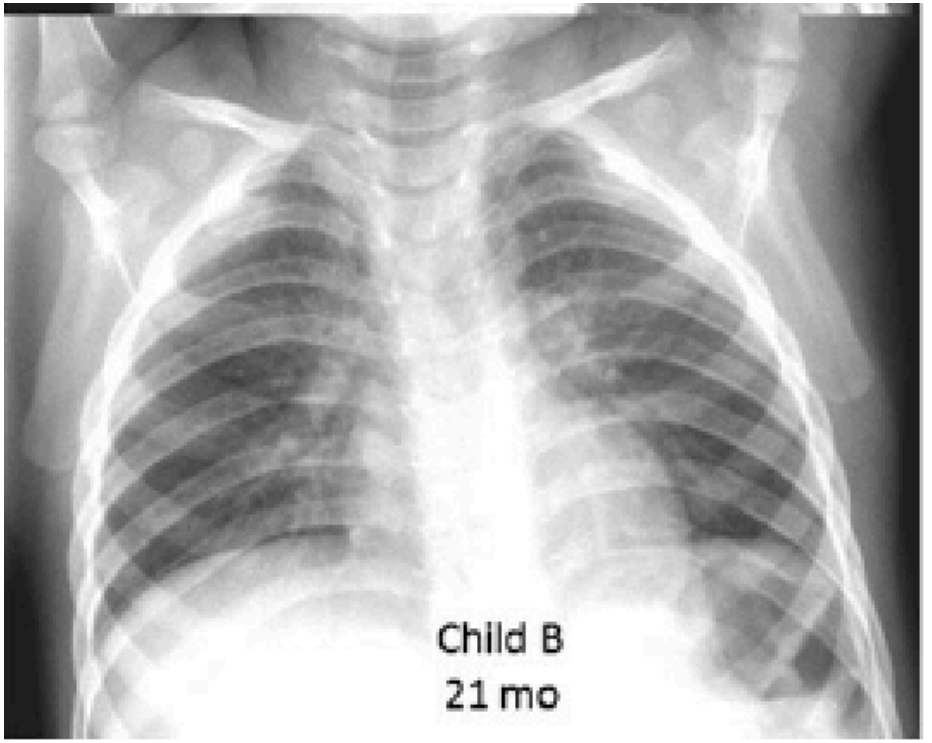
- SCID with diffuse infection secondary to. *P. jiroveci* (PCP)
- Absent thymic shadow

ADA Deficiency-SCID

- Increased incidence of non-infectious pulmonary abnormalities compared to X-SCID (metabolic abnormalities due to ADA deficiency leading to pulmonary problems)
- Pulmonary alveolar proteinosis, squaring of the scapula, cupping of ribs
- Reversible with definitive Rx (HSCT, gene therapy, ADA-replacement)

ADA Deficiency-SCID





Squared off scapula (white arrows) that normalize with ADA-replacement therapy

J Clin Immunol (2012) 32:449–453

Immunodeficiency due to Gain of Function (GOF) Mutations in Phosphatidylinositol-3-OH kinase-Activated PI3KD Syndrome (APDS)

Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110δ result in T cell senescence and human immunodeficiency

nature immunology

Nature immunology 2014;15:88-97.

Phosphoinositide 3-Kinase δ Gene Mutation Predisposes to Respiratory Infection and Airway Damage

Science

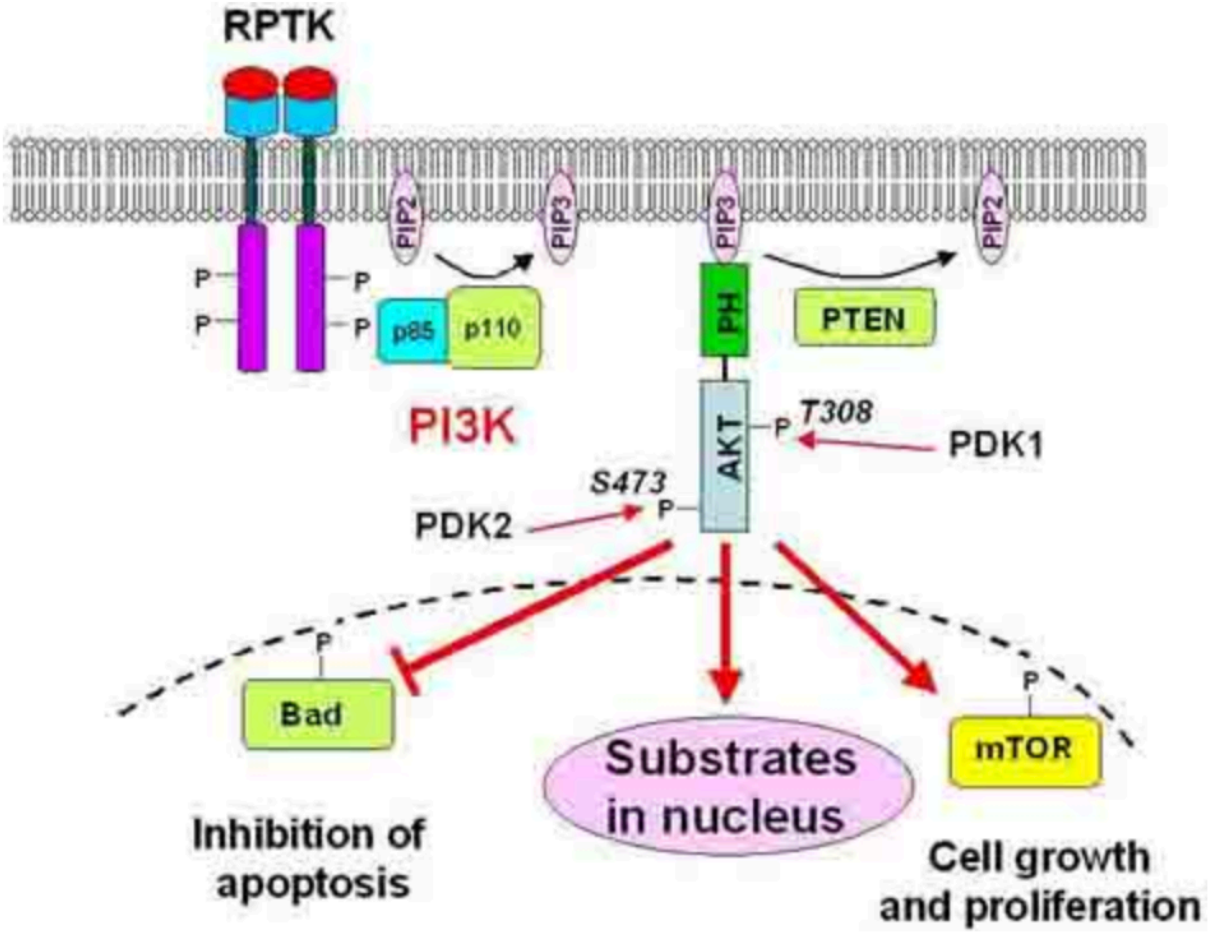
AAAS

Science 2013;342:866-71.

Phosphatidylinositol-3-OH kinase (PI3K)

- Function: Phosphorylation of PIP2 to generate PIP3, which leads to activation of AKT-mTOR pathways
- p110δ−PI3Kδ catalytic subunit: **only** expressed in lymphocytes
- PI3Kδ is activated by ligation of BCR and TCR and essential for T cell and B cell function
- Primary immunodeficiency disease (PI) due to activating mutations (gain of function-GOF) mutations of PI3KD
- Autosomal dominant-termed Activated PI3KD Syndrome (APDS)

PI3K Function



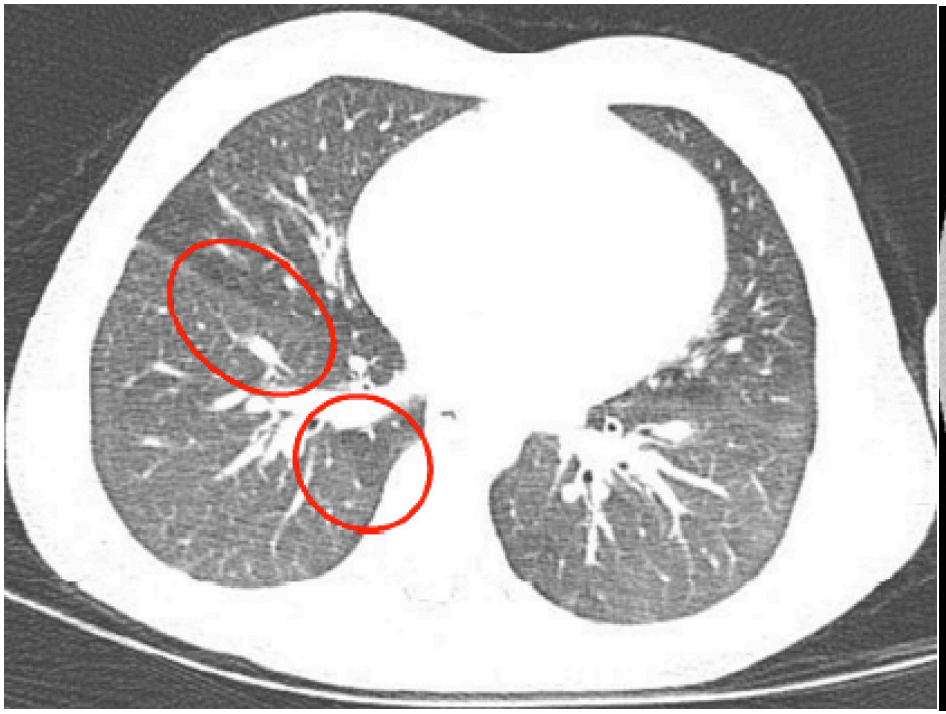
Clinical Features APDS

Clinical Features	Percentage
Sinopulmonary Infections	100%
Lymphadenopathy/splenomegaly	~75%/60%
Bronchiectasis/Bronchiolitis	~50%
EBV/CMV infections (also HSV, VZV)	~50%
Mucosal lymphoidal aggregates	~50%
Skin, salvary gland, lacrimal gland or dental carries	~40%
Other: Autoimmune cytopenias, IBD, EBV-induced lymphomas	

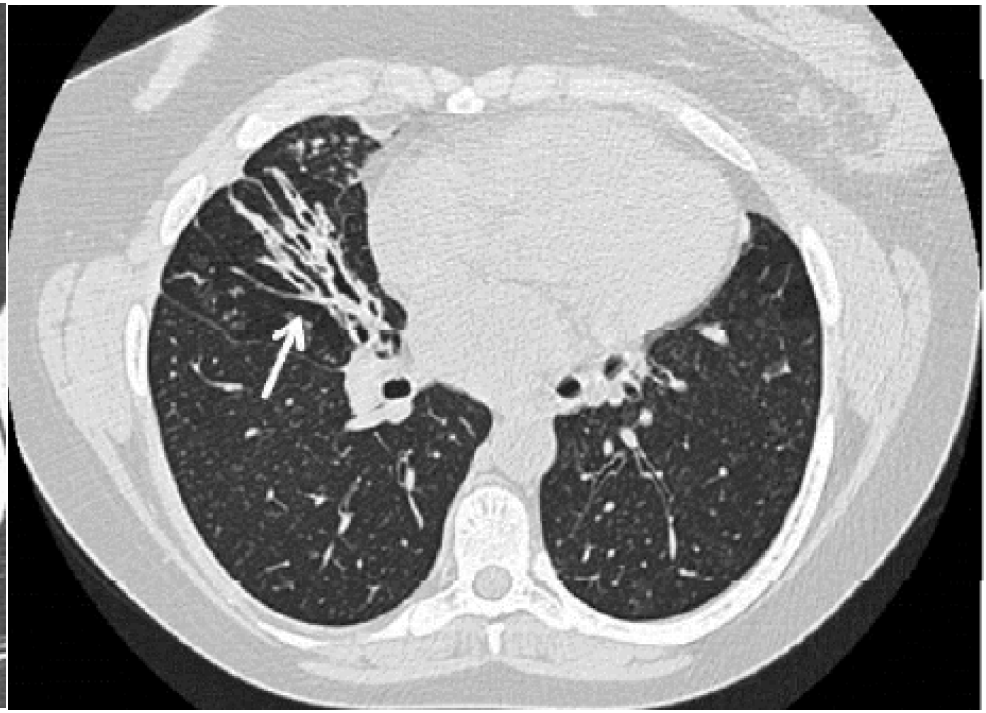
Immunological Abnormalities

Assay	Percentage
Serum IgG/IgA/IgM	Variable: IgG, IgA, ↑ IgM 80%
Low B cell numbers	~75%
Increased transitional B cells (CD19+CD38+ IgM^{lo}), decreased isotype class switched B cells	88% / 50%
Decreased specific Ab H.Infl./S. Pneum.	~70%
Decreased T cells (either CD4 or CD8)	~70%

Pulmonary Findings
APDS



Mosiac Attenuation (air trapping)

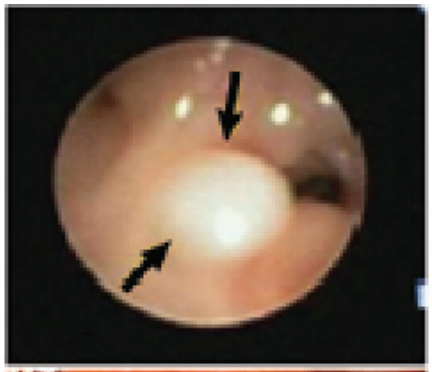


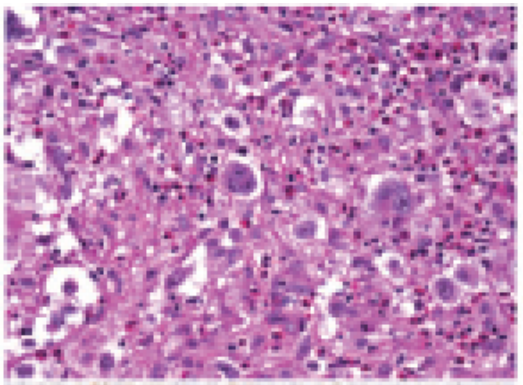
Bronchiectasis

Science 2013;342:866-71.

Lymphoproliferation in APDS

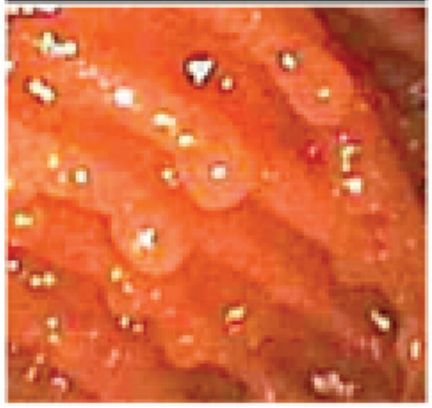
Lymphocytic Infiltrates Airway

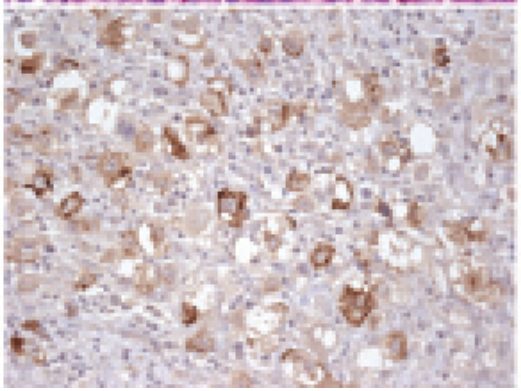




Hodgkin Lymphoma

Lymphocytic Infiltrates Gut





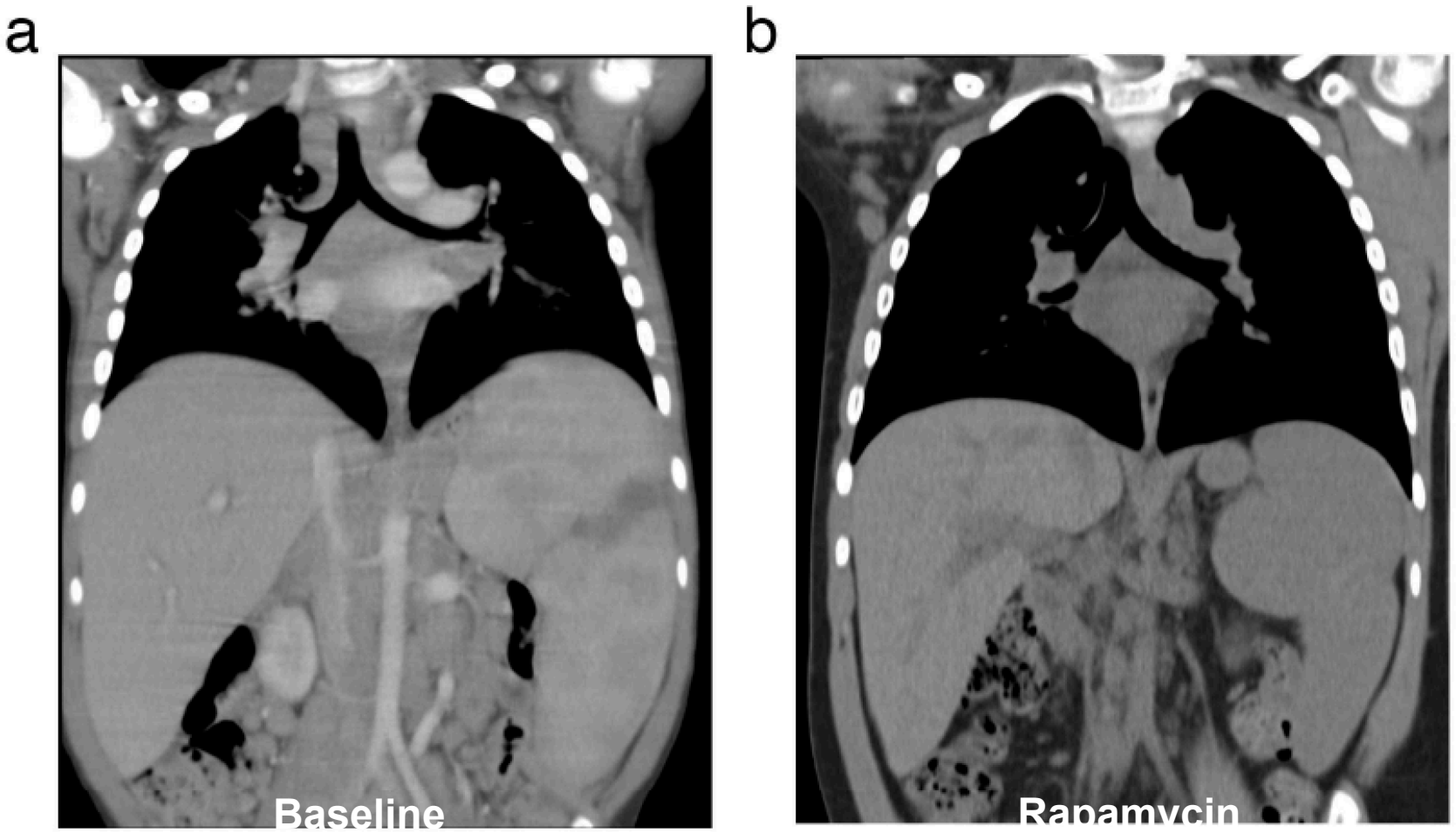
LMP1 (EBV Ag)

Nature immunology 2014;15:88-97.

Treatment of APDS

- Prognosis and optimal treatment is unknown
- PI3KD only in hematopoeitic cells--HSCT in one patient, alive and well
- Inhibitor mTOR pathway (rapamycin) clinical improvement in small number patients

Rx of APDS with Rapamycin



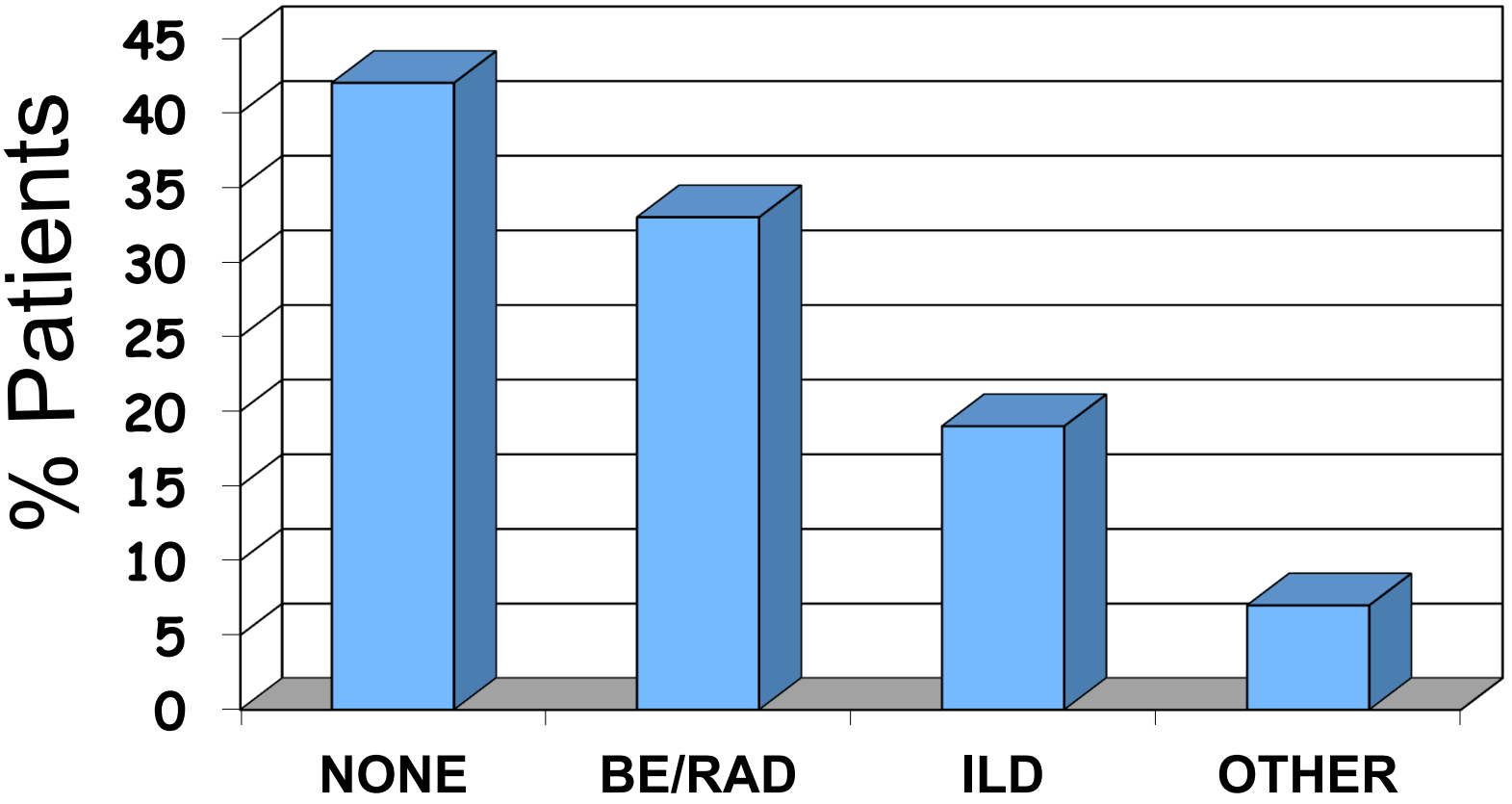
Nature immunology 2014;15:88-97.

Antibody Deficiencies:
CVID and Inherited Agammaglobulinemias

RT Pathogens in Antibody Deficiencies

- Encapsulated bacterial organisms (*e.g.* H. influenzae, S. pneumoniae)
  - Infection with other GNR (pseudomonas and others) may occur esp. in pts. Rx'd repeatedly with broad spectrum Abx
- Atypical bacteria: Mycoplasma /Ureaplasma sp.
  - Unique susceptibility--Antimicrobial Rx MUST cover "atypical" bacteria (URTI/LRTI)
- Viruses (enteroviruses, CMV, RV)

Lungs-the Good and the Bad in CVID



N=69 pts.

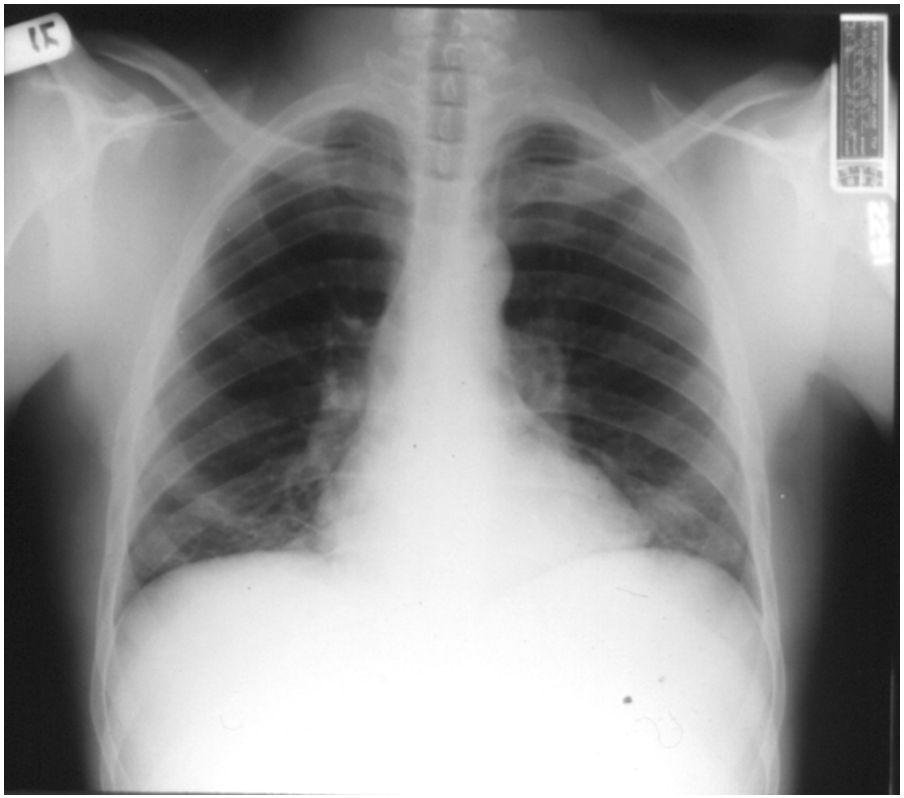
J. Allergy Clin. Immunol. 114: 246-51, 2004

Non-infectious Pulmonary Cxns of CVID

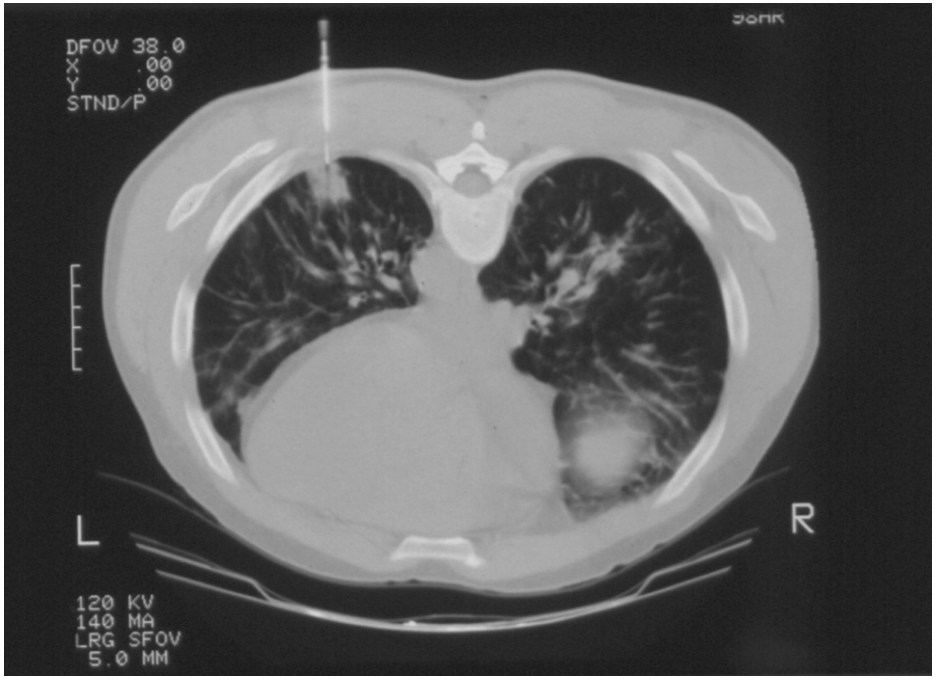
- Predominantly Obstructive lung disease
  - Bronchiectasis
  - Asthma/COPD
  - Bronchiolitis obliterans
- Predominantly restrictive lung disease and diffuse
  - Granulomatous and lymphocytic interstitial lung disease (GLILD)
  - Cryptogenic organizing pneumonia
  - Lymphoma (BALT, NHL) or metastatic carcinoma
  - Hypersensitivity pneumonitis

Our Approach to Diagnosis of Lung Disease in CVID

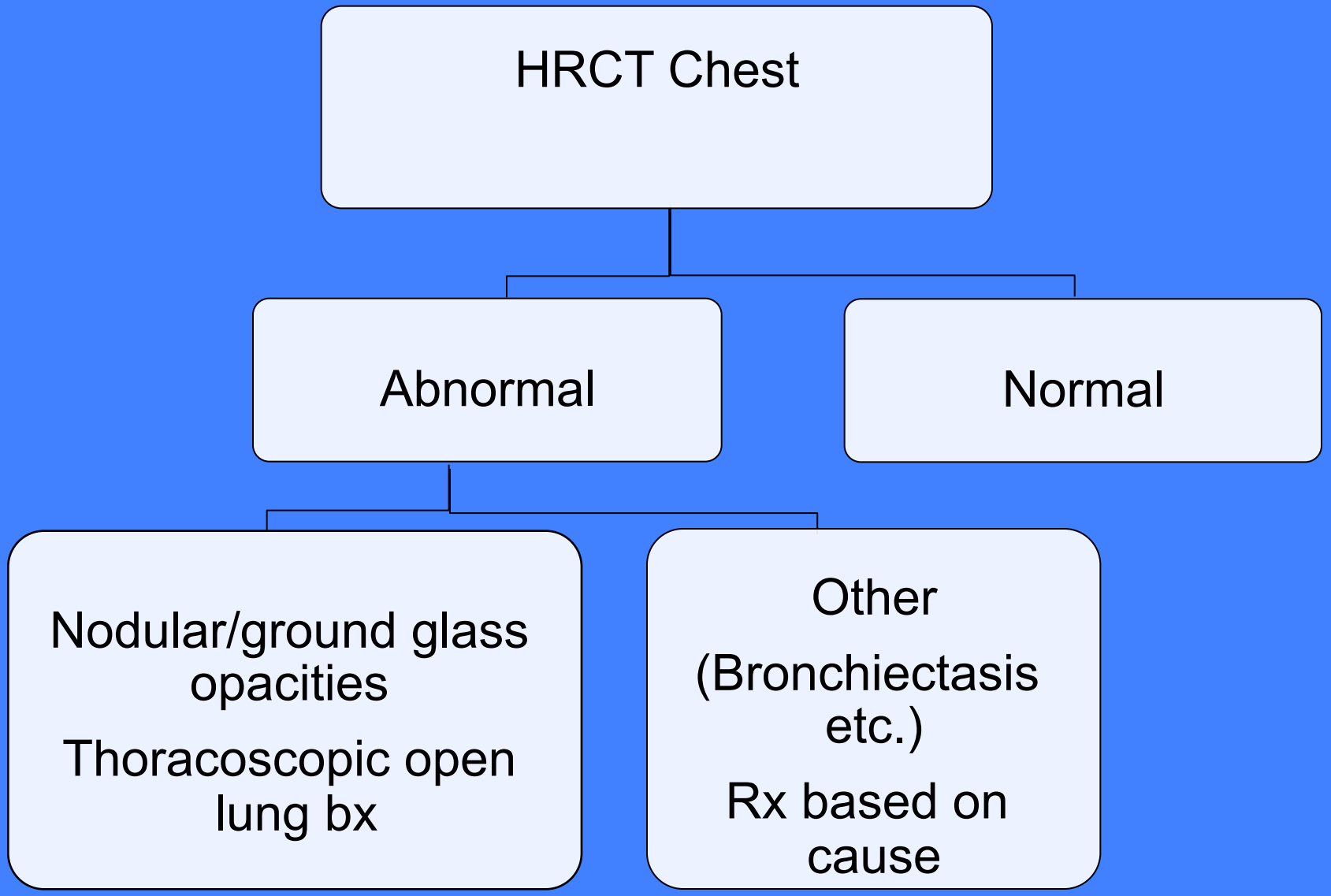
Chest X ray is NOT Sensitive for Lung Disease in CVID



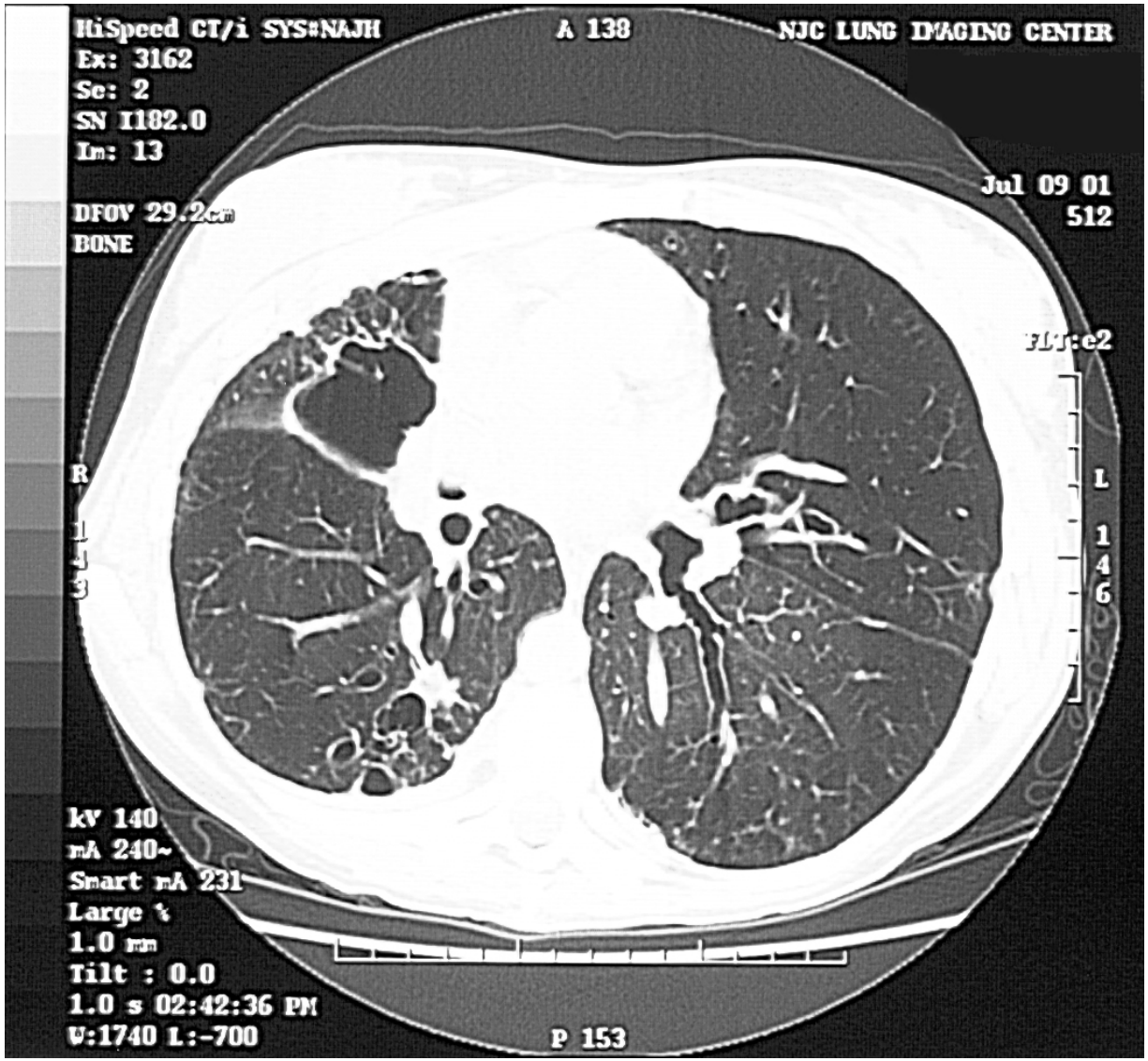
Normal CXR



Abnormal HRCT scan


HRCT Chest
Abnormal
Normal
Nodular/ground glass opacities
Thoracoscopic open lung bx
Other
(Bronchiectasis etc.)
Rx based on cause

Bronchiectasis in CVID



- 31 year-old female with hx “asthma”
- Frequent pneumonias
- Partial lobectomy of right lower lobe.
- CT scan: severe bronchiectasis.
- Patient died of progressive pulmonary failure.
- MOST COMMON pulmonary abnormality in CVID

Bronchiectasis in CVID

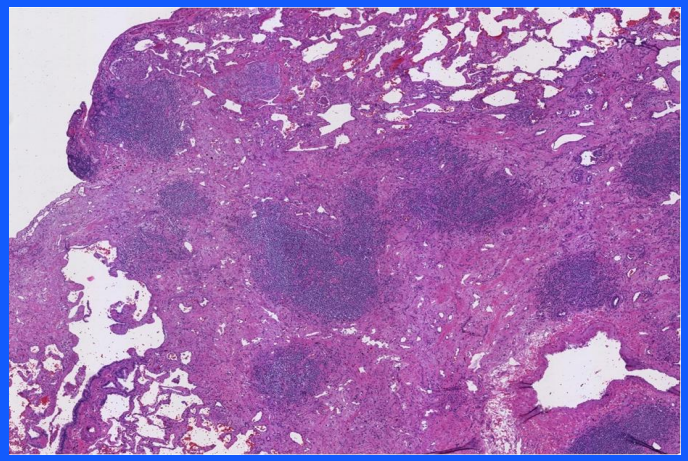
- Most common lung abnormality in CVID (20-35% overall)
- Abnormal mucous clearance-predisposes recurrent pneumonias
- Bronchiectasis may progress or occur despite IVIG/SCIG
- Requires higher dose replacement Ab
- Rx in manner similar to cystic fibrosis
  - Daily chest physiotherapy (acapella, vest in severe cases) w hypertonic saline if tolerated
  - Hospitalization with IV Abx for acute exacerbations
  - Chronic azithromycin Rx—decreases infectious exacerbations for bronchiectasis not associated with PID. (Lancet 2012;380:660-7; JAMA 2013;309:1251-9; Respiratory medicine 2013;107:800-15)
  - Culture for MAI prior to institution of chronic azithromycin

GLILD in CVID

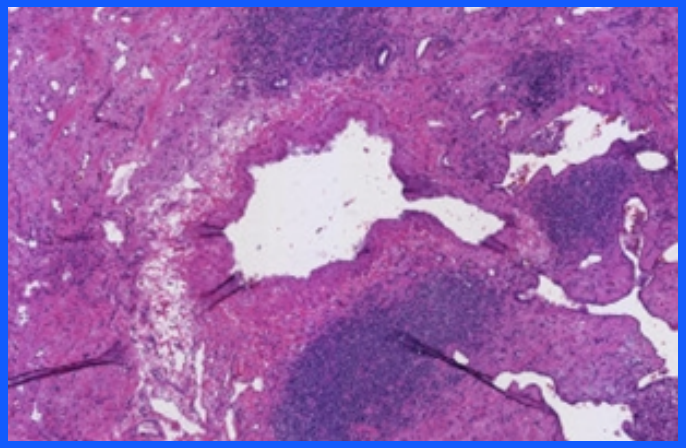
- Different histological patterns in same biopsy
  - Granulomatous disease
  - Lymphocytic interstitial pneumonitis
  - Follicular bronchiolitis
  - Frequently large areas of organizing pneumonia
- Granulomas lung, liver, lymph nodes, bone marrow
- Enlarged spleen and diffuse adenopathy
- Increased autoimmunity, B cell lymphomas
- Multisystemic lymphoproliferative disease

(*Clin Immunol*. 2010 Feb;134(2):97-103; Blood. 2008 Jul 15;112(2):277-86; *J Allergy Clin Immunol*. 2004 Aug;114(2):415-21, *J Clin Immunol*. 33(1):30-9, 2013)

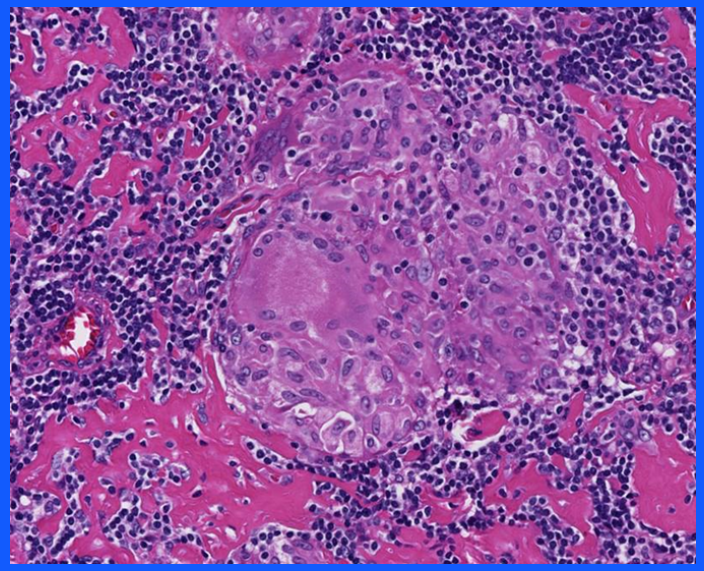
GLILD-Histology



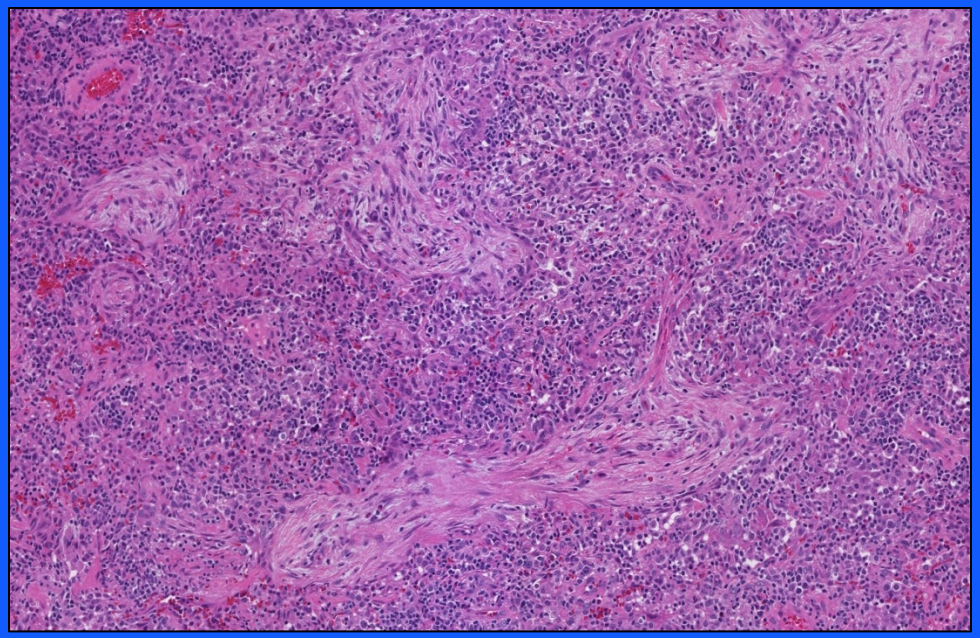
Lymphocytic interstitial pneumonitis



Follicular Bronchiolitis

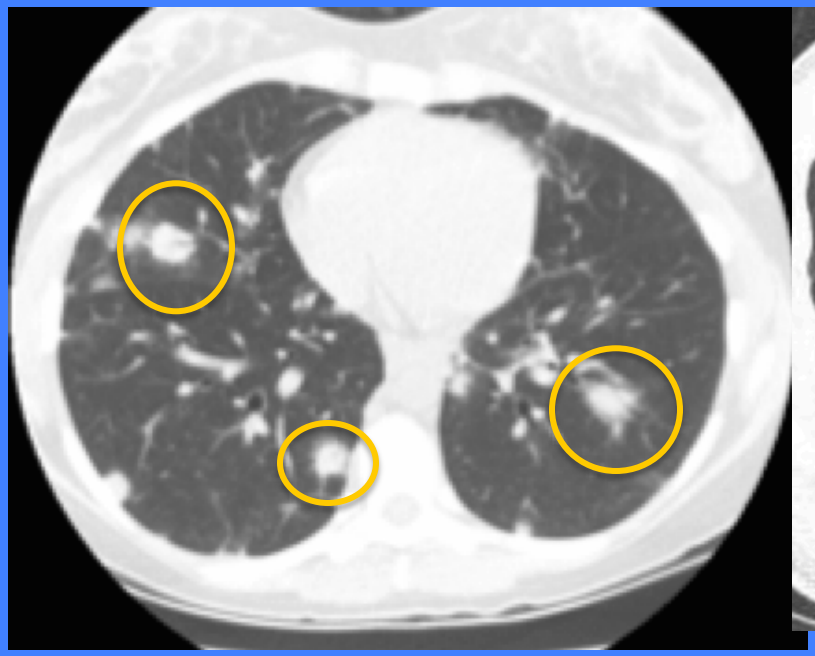


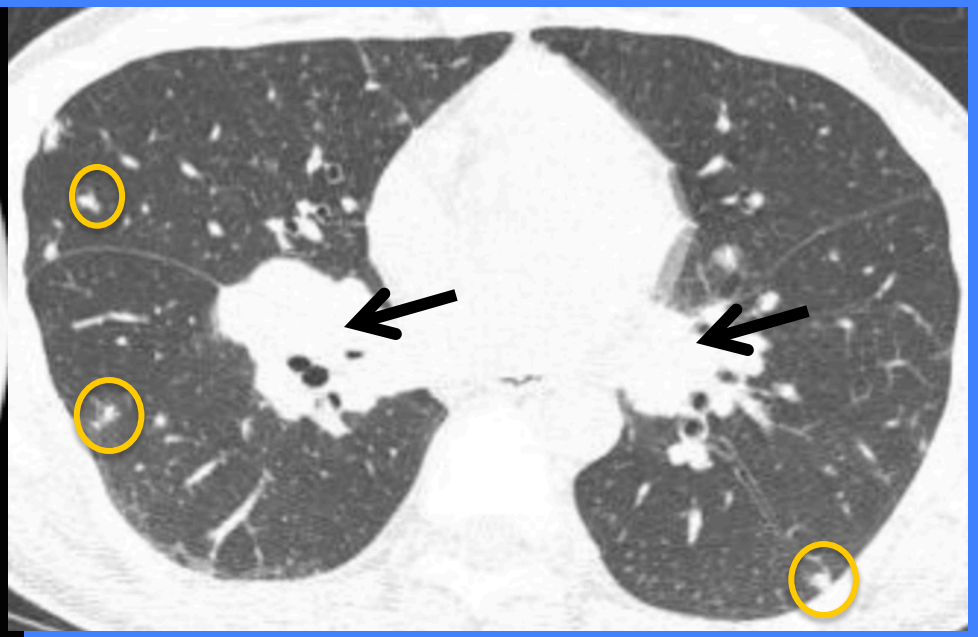
Granuloma



Organizing pneumonia

GLILD vs Sarcoidosis





GLILD

- Macronodular disease
- Hilar adenopathy less common
- Lower lung zone predominance
- Bronchiectasis in 20-40%

Sarcoid

- Micronodular disease and
- Marked hilar adenopathy
- Upper lung zone predominance
- Bronchiectasis uncommon

Semin Respir Crit Care Med. 2014 Jun;35(3):330-5

PMN Defects: CGD

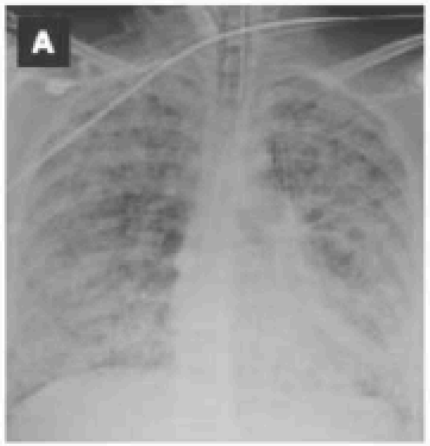
Chronic Granulomatous Disease (CGD)

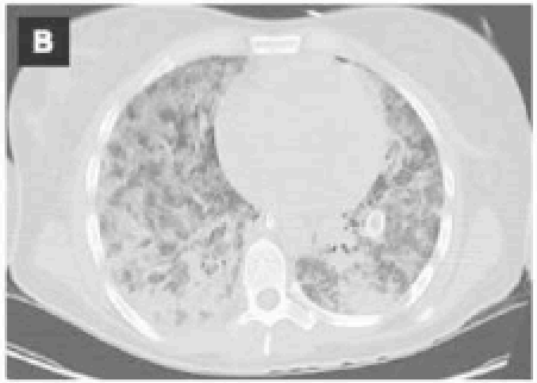
- Mutation in one of four subunits of NADPH oxidase: essential for respiratory burst: gp91phox (x-linked)-70%; others autosomal recessive; p47 phox (20%), p22 and p67phox (5% each)
- 5 organisms cause the bulk of the infections developed countries that do not use BCG: *Staphylcoccus aeures, Burkholeria cepacia, Serratia marcescens, Nocardia sp., Aspergillus sp.*,
    - BCG, TB and Salmonella in other parts of the world

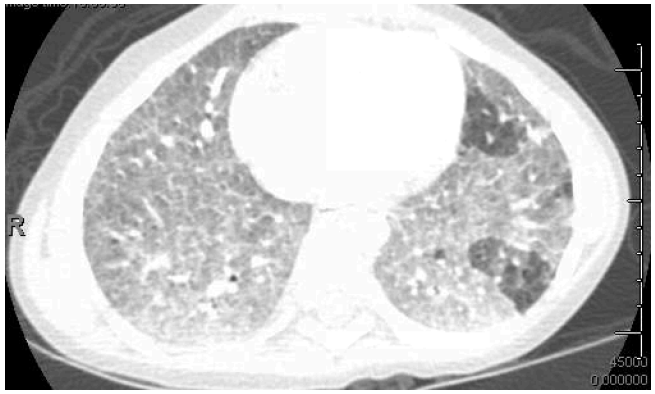
Chronic Granulomatous Disease (CGD)

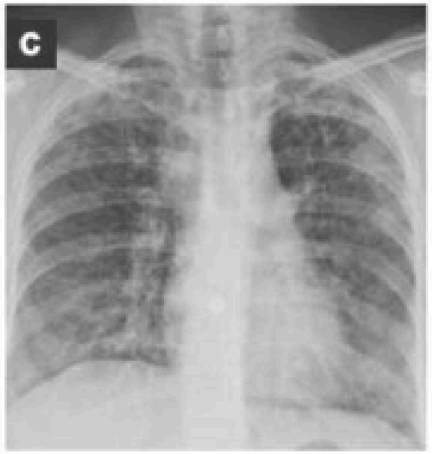
- Recurrent severe, complicated pneumonias
- Mulch pneumonitis-inhalation of decaying organic matter leads to fulminant pneumonitis: appropriate antimicrobial Rx AND corticosteroids needed
- Advise patients to avoid outside jobs with exposure to organic material (*e.g.* raking leaves, hay)
- Progressive interstitial lung disease (rare)

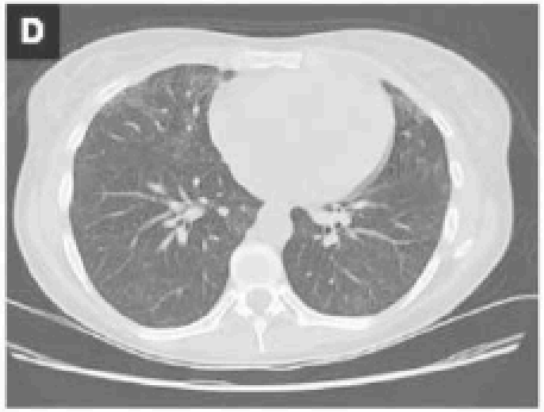
Chronic Granulomatous Disease

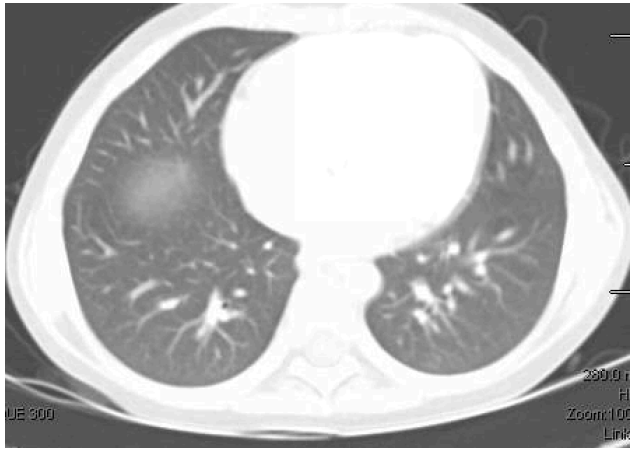












Mulch pneumonitis with aspergillus infection before and after Rx steroid and antifungal

Clinical Infectious Diseases 2007; 45:673–81

ILD in AR CGD (p47) before and 1 year post HSCT (JR paper in preparation)

Well Defined Syndromes w Immunodeficiency

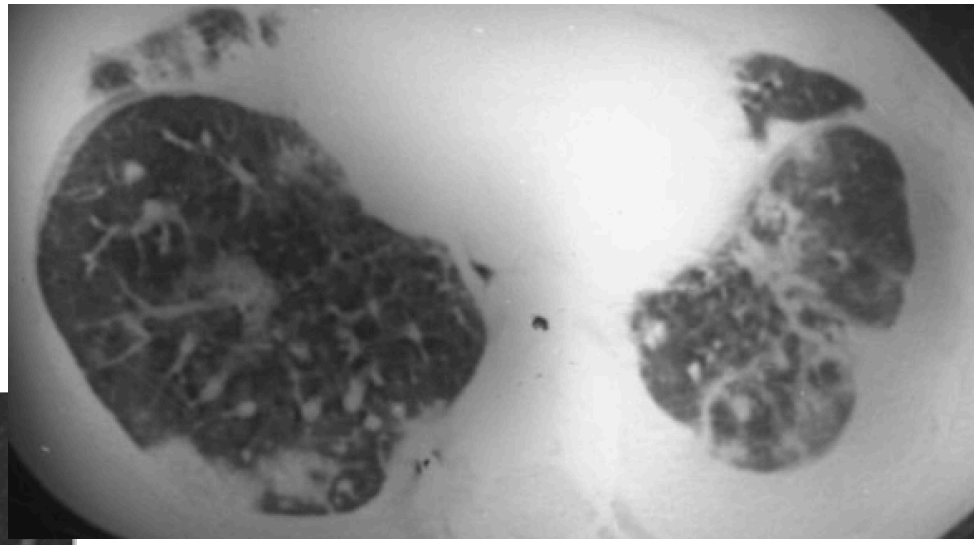
Ataxia Telangiectasia

- Mutation in ATM gene (DNA repair): immune deficiency, increased cancer, neurodegeneration, premature aging and telangiectasias
- T cell lymphopenia common, variable hypogammaglobulinemia and poor specific Ab response to PS antigens in some
- Recurrrent sinopulmonary infections: ommon pulmonary pathogens*: S. aureus*, *H. influenzae*, or *S. pneumoniae* (< 15 yrs old) and *P. aeruginosa* in older patients (Pediatr Pulmonol. 2014; 49:389–399). Mycoplasma sp, M.

Ataxia Telangiectasia

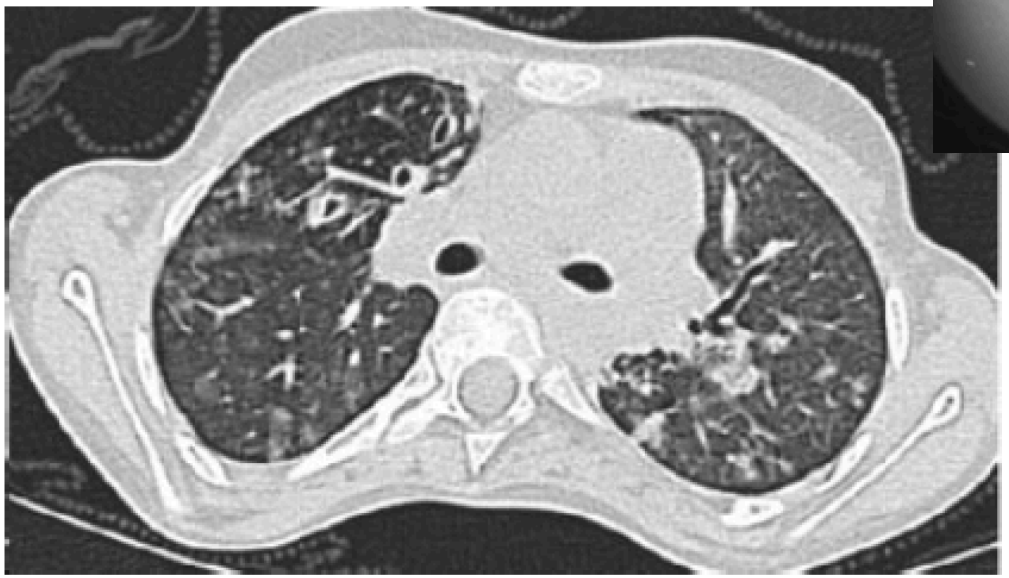
- Bronchiectasis due to recurrent infection, interstitial lung disease/ interstitial fibrosis and lung disease secondary to neurological sequela (weak cough and difficulty clearing secretions)
- ILD may be responsive to corticosteroids
- Radiation sensitivity limits and muscle weakness can limit pulmonary evaluation of patients
- Consider MRI in pulmonary evaluation of patients

Ataxia Telangiectasia



ILD and pulmonary fibrosis

Pediatr Pulmonol. 2005; 39:537–543



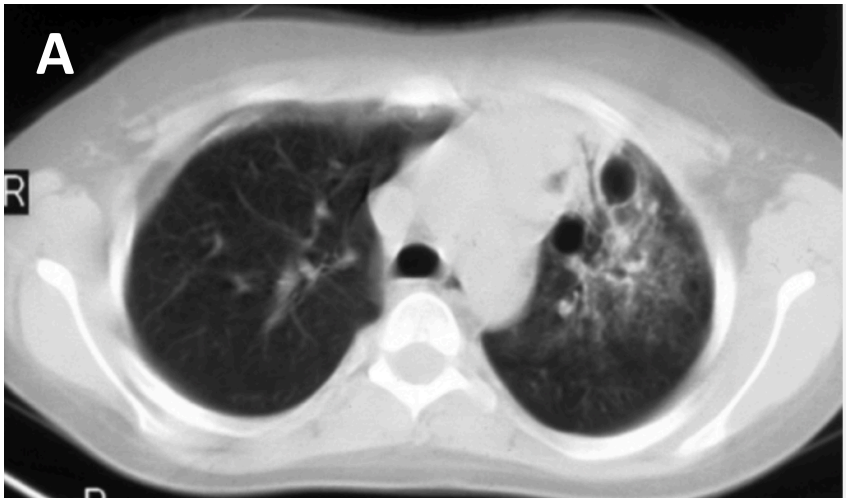
Severe bronchiectasis

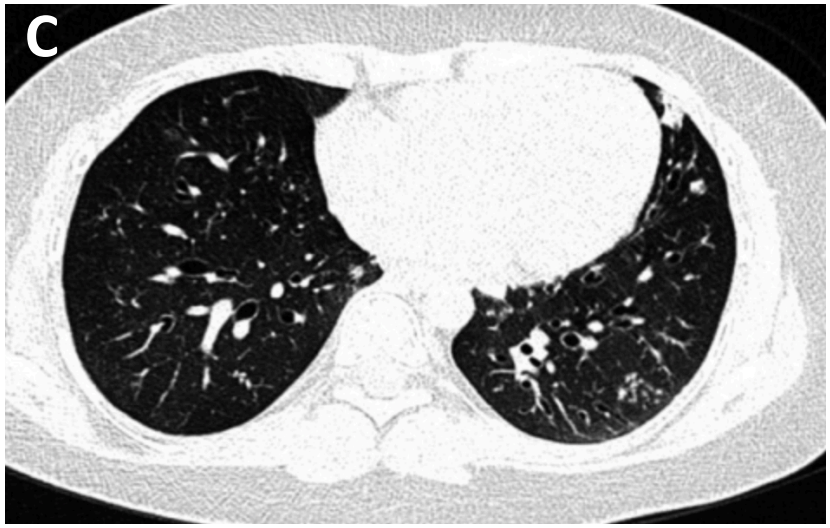
Pediatric Pulmonology 45:847–859 (2010)

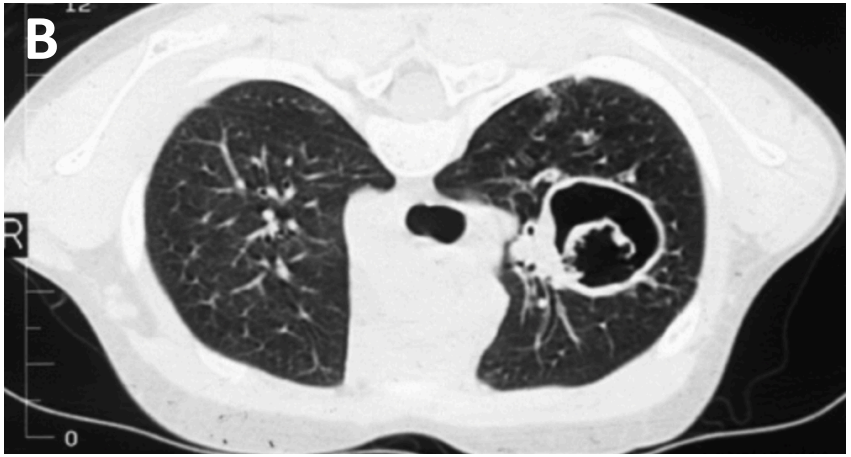
AD Hyper IgE Syndrome

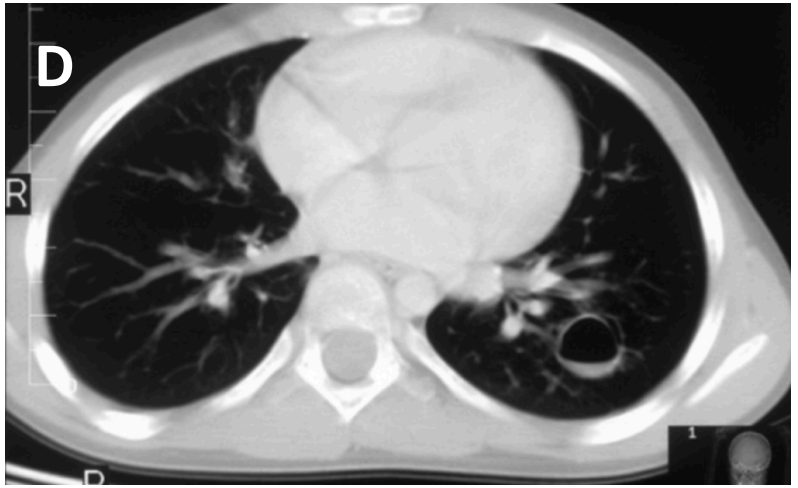
- DN mutation in STAT3: impaired TH17 response and dysregulated inflammatory response
- Eczema, cold abscesses, MCC, recurrent pneumonia with pneumotocoeles
- The most common pathogens of acute pneumonia are S . aureus , *H. influenzae* , and *S. pneumoniae*
- ~75% of AD-HIES pts: long-term pulmonary complications (pneumatoceles, bronchiectasis, cysts)-major cause of morbidity and mortality
- Chronic infection: non-tuberculous mycobacterium, GNR (Pseudomonas aeruginosa) and molds (Aspergillus fumigatus, Scedosporium sp)
- DOCK8 deficiency: Bronchiectasis common but pneumatocoeles are rare—more diverse pathogens (viral and bacterial, as well as PCP)

AD Hyper IgE Syndrome



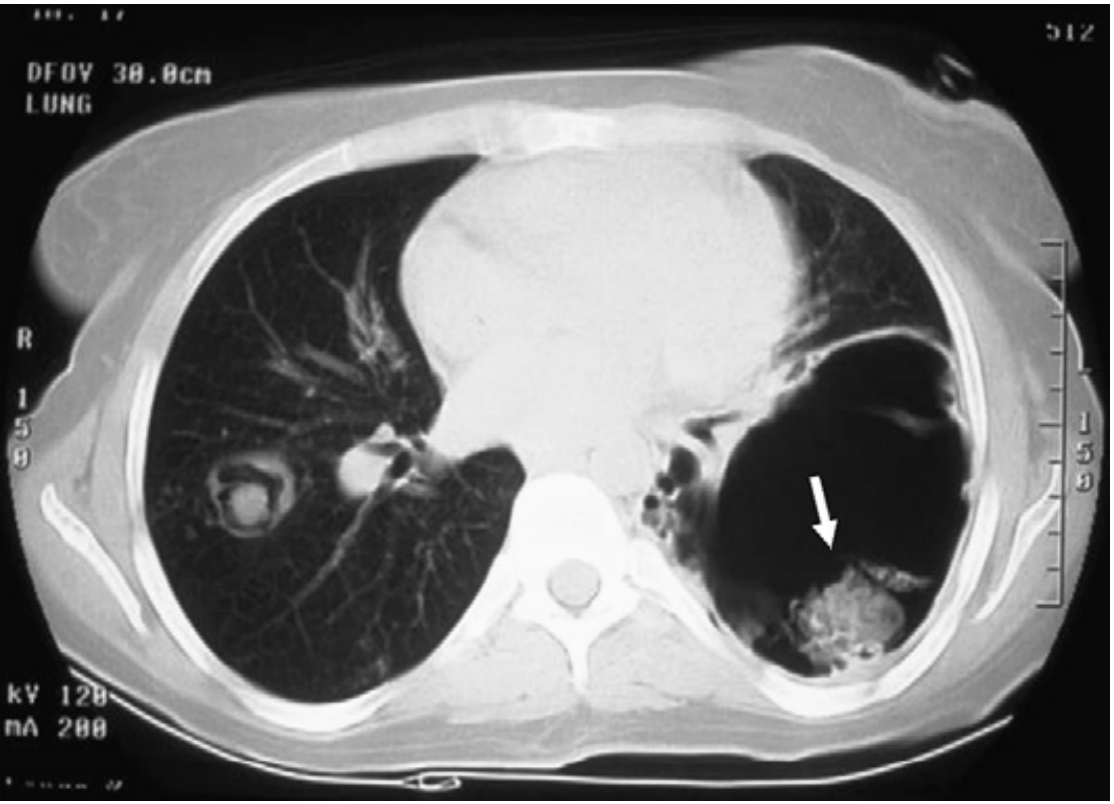






A. Cavities with areas of consolidation; B. Pneumatocoele complicated by aspergilloma; C. Diffuse bronchiectasis; D. Staphylcoccus abscess

AD Hyper IgE Syndrome



- Chest CT showing the characteristic pneumatoceles.
- The pneumatoceles are prone to infection with fungi and gram-negative bacteria. Arrow indicates an aspergilloma.

Immunol Allergy Clin N Am 28 : 277–291, 2008