CROSS CANADA ROUNDS

THE LONG CASE

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Dr. Wallace Wee, PGY-4

February 16, 2018

INTRODUCTION

Objectives

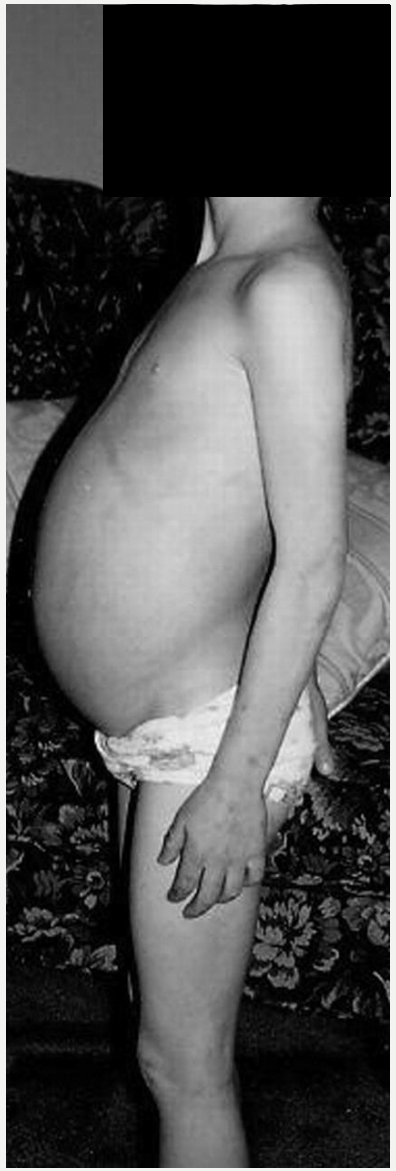
- Exposure to an interesting clinical case
- Understand the management of this disease

Outline

- Case presentation
- Background about disease and pulmonary sequelae

CASE: REFERRAL

- 12 year old M had recurrent pneumonia and was referred to respirology for PFT
- Unable to complete PFT
- Looks very fragile so CXR was ordered



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WHAT DOES THIS CXR SHOW?

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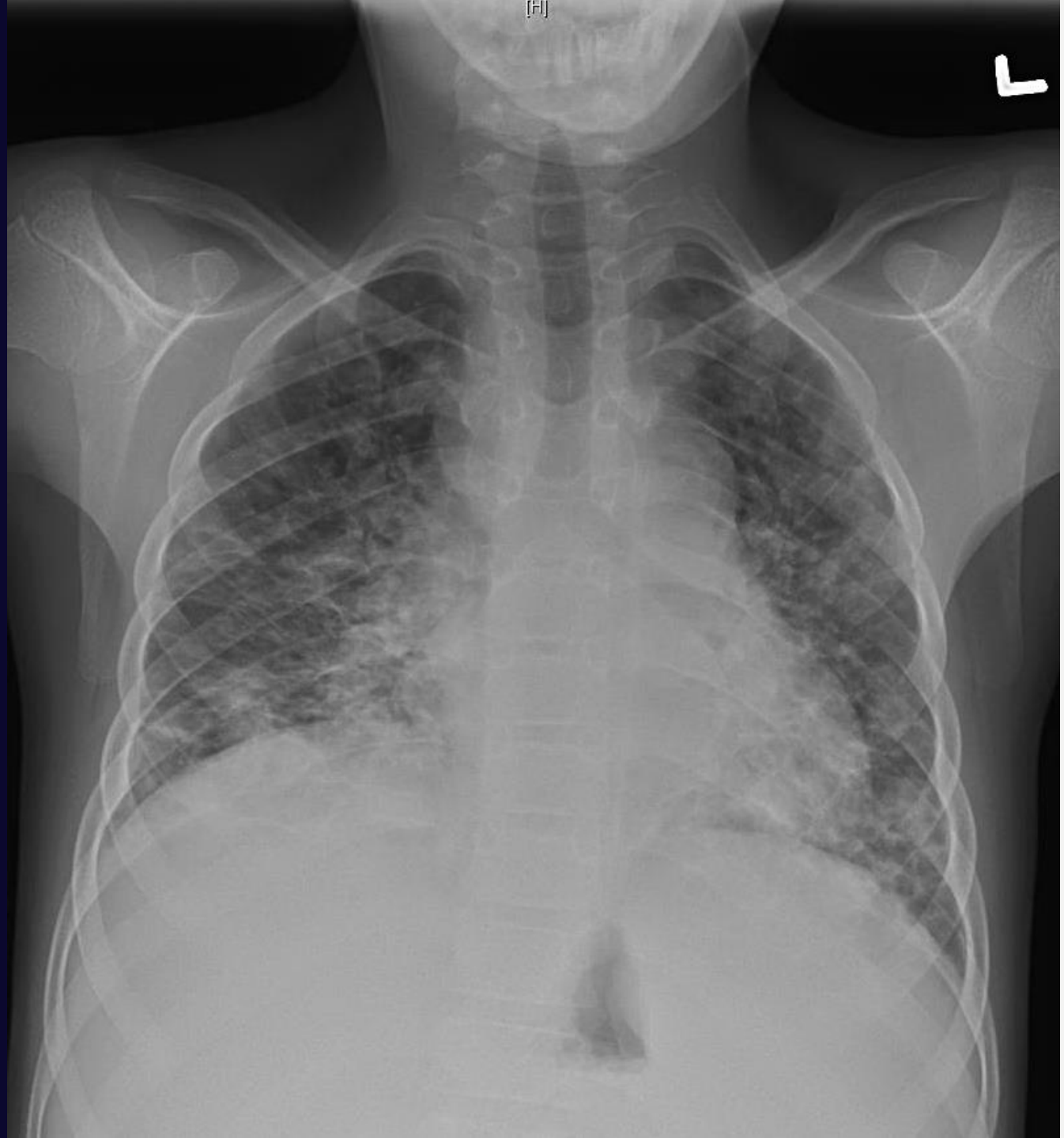
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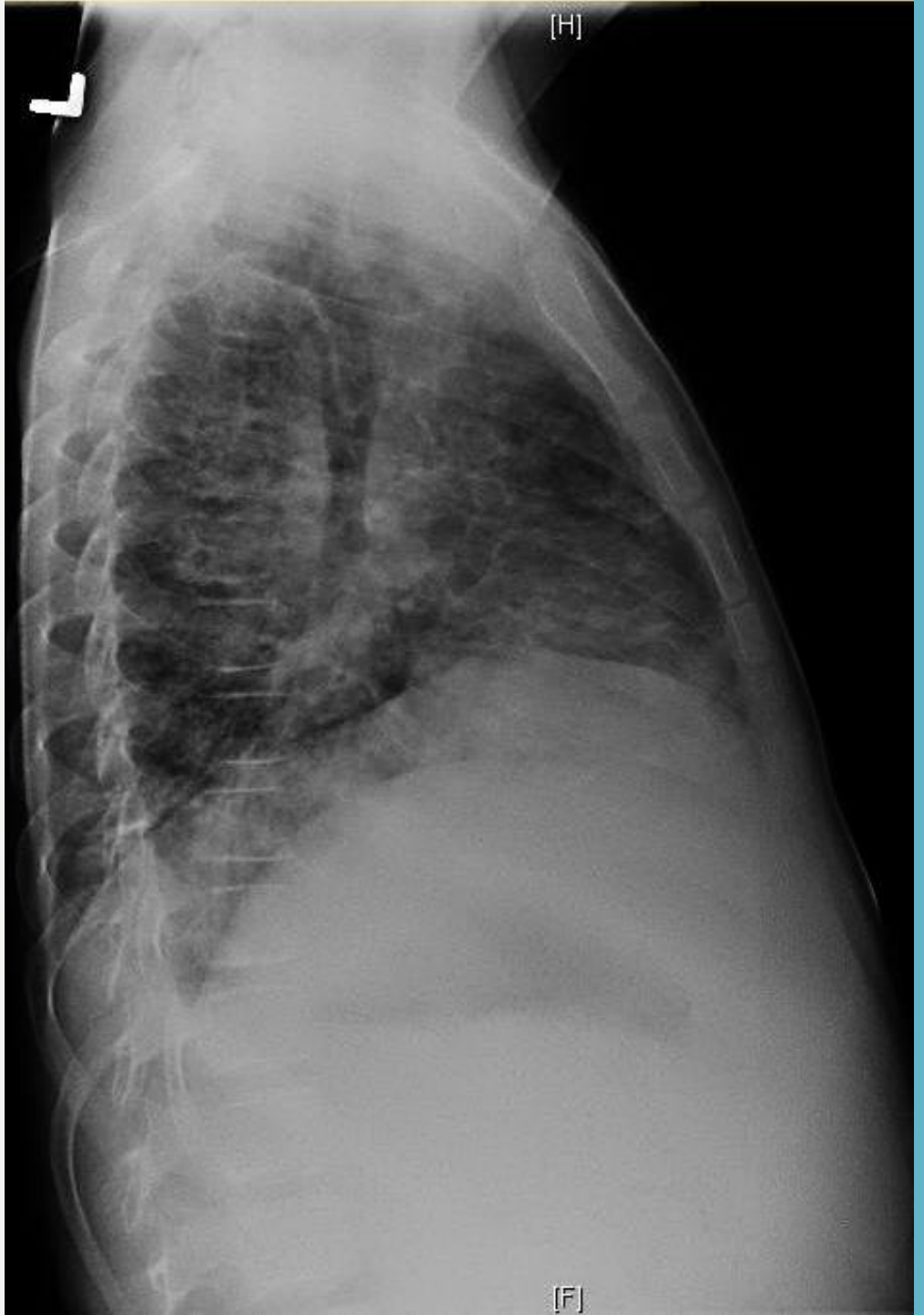
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ANY ADD'N INFO YOU WANT TO KNOW?

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CASE: BACKGROUND

Past Medical History

- **CNS**: HIE, CP, Global developmental delay, Strabismus S/P 2008
- **Resp**: ?sinus infection, Recurrent pneumonias, 2-3x per year sometimes requiring antibiotics
- **CVS**: pulmonary HTN, resolved PFO
- **GI**: Mild Hepatomegaly
- **Heme**: Pancytopenia, Splenomegaly
- **Immunology**: Hypogammaglobulinemia, ?CMPA resolved, ?Prev Contact dermatitis of cheeks – unclear history, no other eczema
- **MSK**: Bilateral club feet S/P 2007

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Pregnancy/Birth History

- GA 38+6, BW 2 kg
- C/S: breech, placental abruption
- APGAR: 2, 6, 8
- Req'd resus for resp. distress
- Had HIE, noted PTx (conservative)
- NICU 5/52; NGT Feeds 4/52, CPAP but no surfactant

CASE: BACKGROUND

- **Medications**
  - occasionally flovent and ventolin
- **Allergies**: NKDA
- **Immunizations**: UTD

CASE: BACKGROUND

- **Medications**
  - occasionally flovent and ventolin
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Family History

- Mother has history of asthma.
- Maternal FHx: asthma in grandma and aunty, great uncle has immunodeficiency NYD (who died of pancreatic cancer
- Dad has history of hypertension and hyperlipidemia.
- Brother has history of environmental allergies.

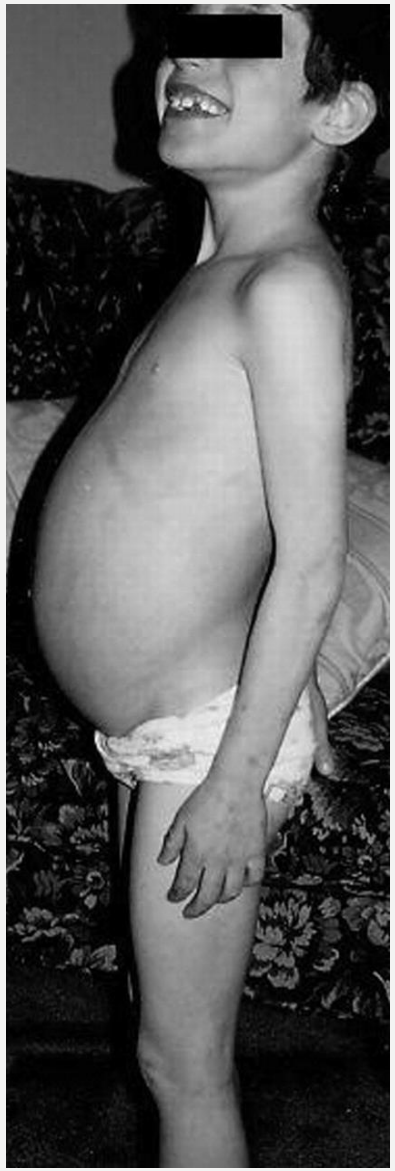
CASE: HISTORY

- History of RTI 2-3 per year
- Req'd antibiotics for >1 RTI
- ?Sinusitis
- ?History of constitutional symptoms

- **Recent History**
  - May/2016: LTRI Sx, Abx, 2/52
  - July/2016: Similar
  - Nov/2016: RTI Sx, CXR, Abx
  - April/2017: Same
  - May/2017: IVIG for Hypogam
  - Aug/2017: RTI, same CXR
  - Sept/2017: Presented to HSC

CASE: PHYSICAL EXAM

- Cooperative but looks unwell, somewhat cachectic
- HR 90-110, RR 24, BP 100/70, O2Sat > 95%, Afebrile
- **H/N:** shoddy cerv LN, dysmorphic, very prominent jugular pulse
- **Resp:** BS ALL, decr. to bases, crackles to left anterior
- **Cardiac:** S1, S2 loud, Systolic grade 2 ejection murmur
- **Abdo:** ++ distension, ?fluid wave, splenic area is dull, NT
- **Skin:** No axillary LN, no clubbing



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DIFFERENTIAL DIAGNOSES?

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DIFFERENTIAL DIAGNOSIS

- Infectious
  - Organizing pneumonia
- Oncologic
  - Lymphoma
  - Pulmonary Metastases
- Inflammatory
  - Sarcoidosis
  - Vasculitis
- Immunodeficiency
- Metabolic
- ?Syndromic/Genetic

https://smokebear.files.wordpress.com/2011/08/not-lupus.png

WHAT ARE THE NEXT STEPS?

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CASE: ACUTE MANAGEMENT

Admitted to hospital

- Concern for lymphoma
- Managed as Tumor Lysis Syndrome
- Bloodwork completed

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Bloodwork

Hgb 80, MCV 74, Plt 80, WBC 1.9

ANC 0.9, Lymph 0.8

Na 138, K 4.5, Cl 100, Glc 5.2

Cr 47, BUN 5.4

Urate 434, LDH 508

iCa 1.24, PO4 1.3, Mg 0.73

INR 1.0, PTT 31

CASE: ACUTE MANAGEMENT

Admitted to hospital

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- CT Chest Ordered

CT CHEST FINDINGS?

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[2018-02-06] CT CHEST.AVI

CASE: ACUTE MANAGEMENT

Admitted to hospital

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- CT Chest Ordered
- CT and US Abdomen + Pelvis

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U/S Abdomen + Pelvis

- Mild hepatomegaly, marked splenomegaly

CT Abdomen + Pelvis

- Gross splenomegaly, LAD, small volume ascites
- Concerning for lymphoproliferative disorder

CASE: ACUTE MANAGEMENT

Admitted to hospital

- Concern for lymphoma
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- Bloodwork completed
- CT Chest Ordered
- CT and US Abdomen + Pelvis
- ECHO

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ECHO

- Significant pHTN, RVSP > 63 mmHg (SBP 92 mmHg)
- No VSD/PDA
- Good biventricular systolic function

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- ECHO
- Overnight oximetry

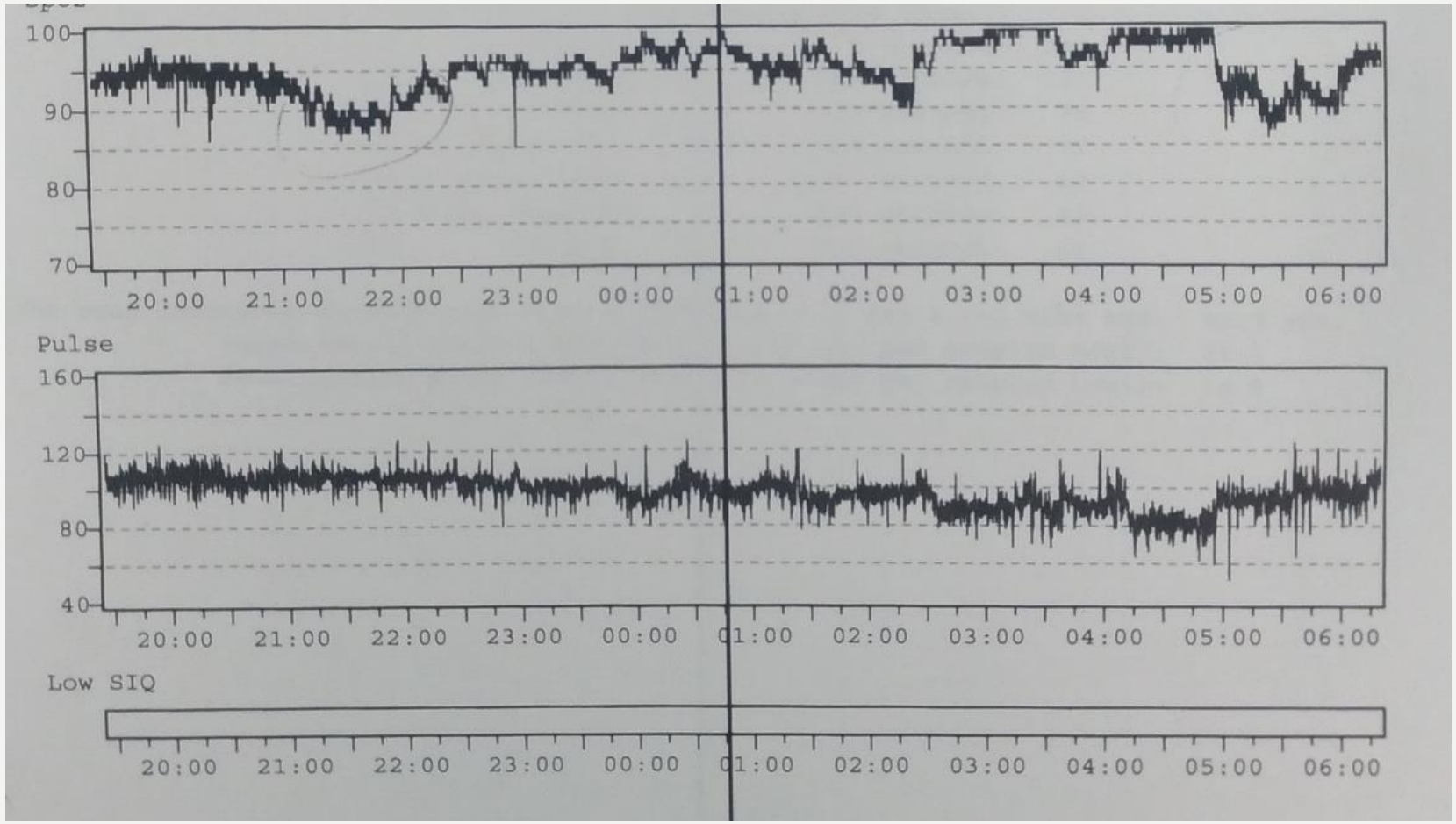
OVERNIGHT OXIMETRY?

Oximetry: Comprehensive Report

Comments: o/n oximetry started on room air. O2 applied per order.

Recording time:	10:53:58	Highest pulse:	126	Highest SpO2:	100%
Excluded sampling:	00:01:08	Lowest pulse:	52	Lowest SpO2:	85%
Total valid sampling:	10:52:50	Mean pulse:	98	Mean SpO2:	95.1%

Time with SpO2<90:	0:36:08,	5.5%	Time with SpO2 =>90:	10:16:42,	94.5%
Time with SpO2<80:	0:00:00,	0.0%	Time with SpO2=>80 & <90:	0:36:08,	5.5%
Time with SpO2<70:	0:00:00,	0.0%	Time with SpO2=>70 & <80:	0:00:00,	0.0%
Time with SpO2<60:	0:00:00,	0.0%	Time with SpO2=>60 & <70:	0:00:00,	0.0%



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- Bronchoscopy and BAL

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Fluid Type for Cell Count	Bronchial Alveolar Lavage	
WBC - fluids	658	[X 10^6/L]
RBC - fluids	2000	[X 10^6/L]
Neutrophils - fluids	2	[%]
Bands - fluids	1	[%]
Lymphocytes - fluids	25	[%]
Macrophages - fluids	72	[%]

- Flow cytometry shows majority of lymphocytes are mature T cells. No hemosiderin-laden macrophages, no malignancy. No fungal elements.
- Infectious panel negative

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- LN Biopsy, BMA, BM Biopsy

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LN Biopsy

- Right inguinal LN biopsy
- Benign/reactive LN, no malignancy

Bone Marrow Aspirate and Biopsy

- No clear morphological evidence of malignant infiltration

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Tumor Lysis Syndrome Ruled Out

REVISITING DIFFERENTIAL

- Infectious
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- Oncologic
  - Lymphoma
  - Pulmonary Metastases
- Inflammatory
  - Sarcoidosis
  - Vasculitis
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CASE: FURTHER W/U

- Ruled out
  - Malignancy and Tumor Lysis Syndrome
  - Infection
- Immunoglobulins

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Immunoglobulin Quantification

- Sept/2017 IgA <0.1, IgG 6.7, IgM 0.5, IgE <25
- Sept/2017 IgA <0.07, IgG 4.70, IgM 0.41
- Aug/2017 IgA <0.07, IgG 5.00, IgM 0.35
- July/2017 IgA <0.07, IgG 5.02, IgM 0.3
- June/2017 IgA <0.07, IgG 3.99, IgM 0.29
  - **IVIG started**
- May/2017 IgA <0.07, IgG 0.37, IgM 0.16
- April/2017 IgA <0.07, IgG 0.34, IgM 0.18, CH50 >60

CASE: FURTHER W/U

- Ruled out
  - Malignancy and Tumor Lysis Syndrome
  - Infection
- Immunoglobulins
- Lymphocyte Immunophenotyping

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LYMPHOCYTE IMMUNOPHENOTYPING	
CD2+	998
CD2+ %	93.2
CD19+	↓ 51
CD19+ %	↓ 4.8
CD20+	50
CD20+ %	4.7
CD3+/CD4+	763
CD3+/CD4+ %	↑ 71.3
CD3+/CD8+	↓ 135
CD3+/CD8+ %	12.6
HLA DRII+/CD3-	60
HLA DRII+/CD3- %	5.6
CD3+/HLA DRII+	124
CD3+/HLA DRII+ %	↑ 11.6
CD3+/TCR delta gamma +	10
CD3+/TCR delta gamma + %	0.9
CD3-/CD(16+56)+	↓ 64
CD3-/CD(16+56)+ %	6.0
CD3+/CD(16+56)+	2
CD3+/CD(16+56)+ %	0.2
Total CD (16+56)+	66
Total CD (16+56)+ %	6.2
Average CD3+	932
Average CD3+ %	↑ 87.1
CD4:CD8 Ratio	↑ 5.7
Lymph Immunophenotyping Cmt	Reduced I...

CASE: FURTHER W/U

- Ruled out
  - Malignancy and Tumor Lysis Syndrome
  - Infection
- Immunoglobulins
- Lymphocyte Immunophenotyping
- Neutrophil Oxidative Burst Index
- PHA Stimulation Test
- CD40/CD40L
- Metabolic workup
- Genetic workup

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Lung Biopsy

- Lymphocytes, majority are T cells with no significant antigen loss.
- Features of GLILD and BOOP

CASE: LUNG BIOPSY

Figure 1:
Interstitial lymphocytic infiltrate and pneumocyte hyperplasia

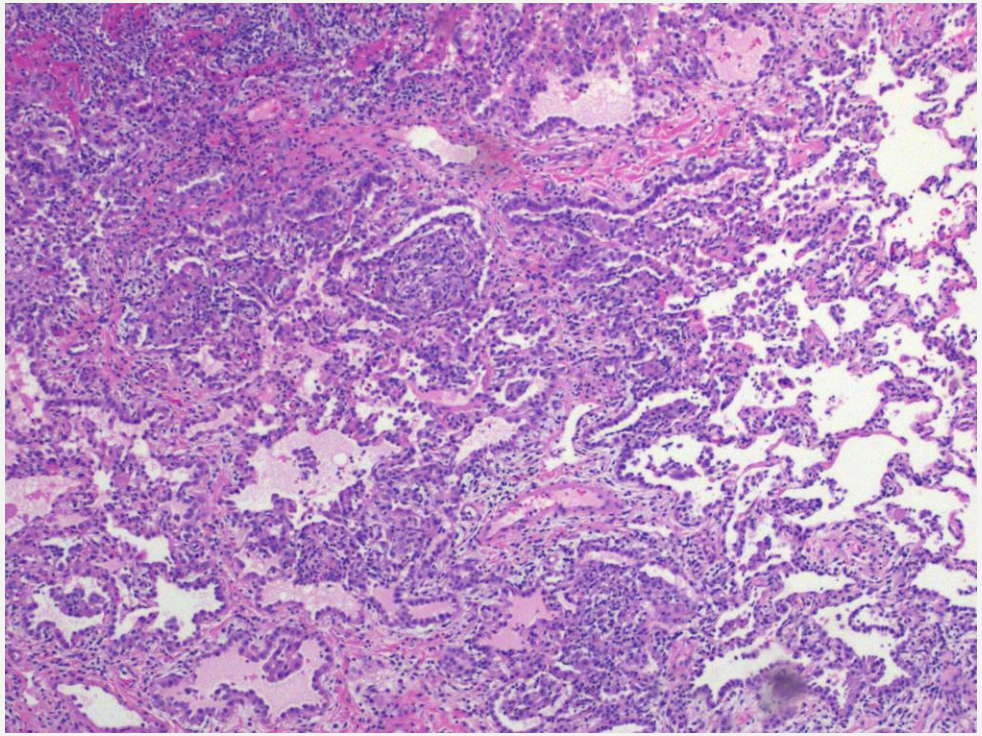
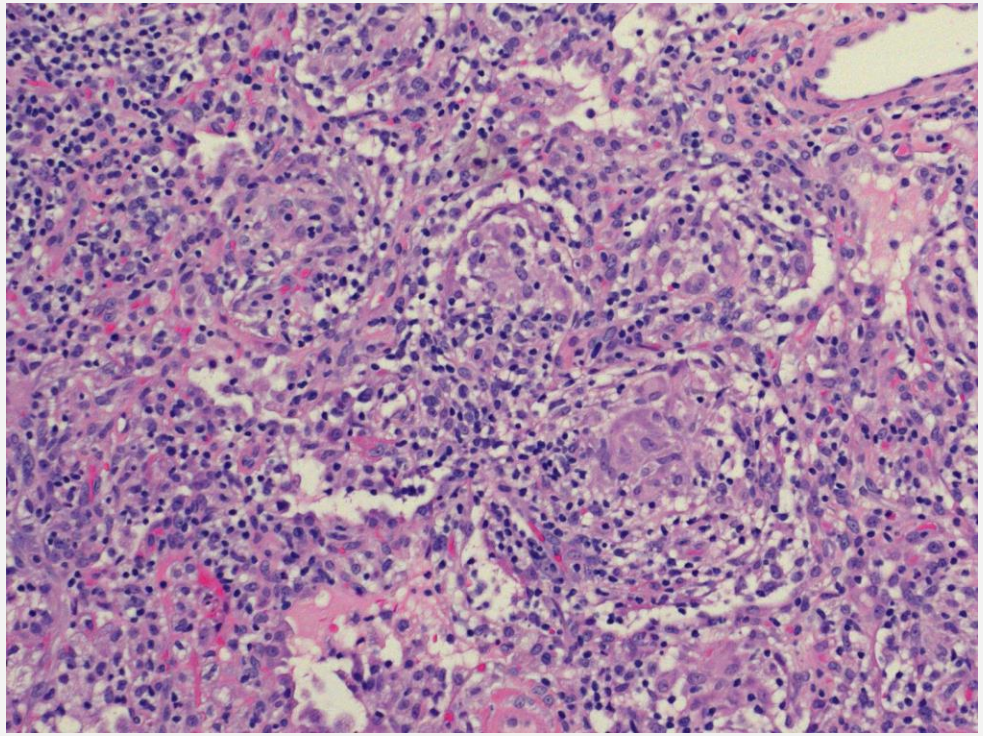


Figure 2:
Lymphocytic infiltrate and non-necrotizing granulomas



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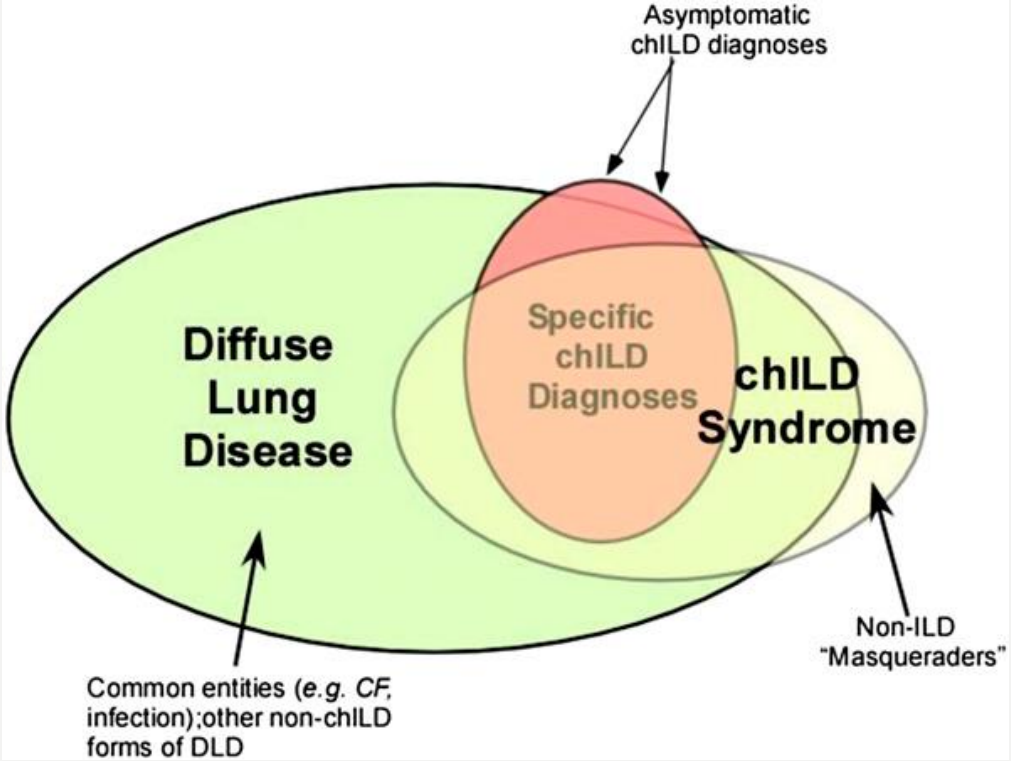
WHAT DOES IT ALL MEAN?

DIFFUSE LUNG DISEASE



Kurland, ATS, 2013

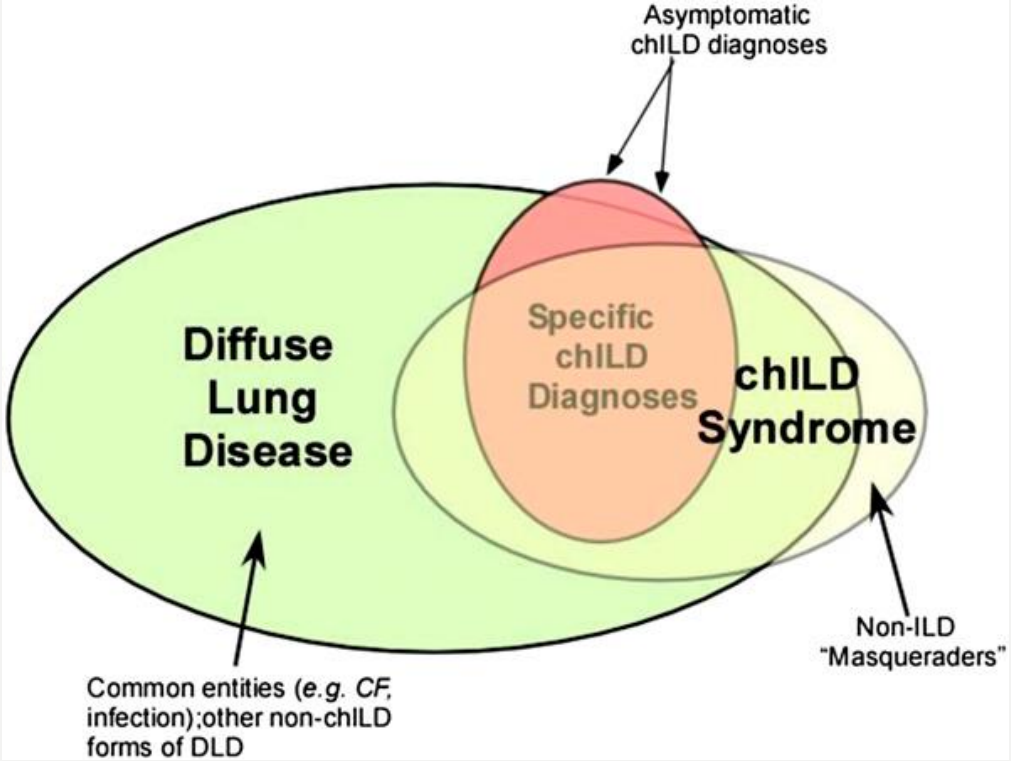
TABLE 2. PROPOSED CLASSIFICATION SCHEME FOR PEDIATRIC DIFFUSE LUNG DISEASE

I. Disorders more prevalent in infancy
- A. Diffuse developmental disorders
  - 1. Acinar dysplasia
  - 2. Congenital alveolar dysplasia
  - 3. Alveolar–capillary dysplasia with pulmonary vein misalignment
- B. Growth abnormalities
  - 1. Pulmonary hypoplasia
  - 2. Chronic neonatal lung disease
    - A. Prematurity-related chronic lung disease (bronchopulmonary dysplasia)
    - B. Acquired chronic lung disease in term infants
  - 3. Structural pulmonary changes with chromosomal abnormalities
    - A. Trisomy 21
    - B. Others
  - 4. Associated with congenital heart disease in chromosomally normal children
- C. Specific conditions of undefined etiology
  - 1. Pulmonary interstitial glycogenosis
  - 2. Neuroendocrine cell hyperplasia of infancy
- D. Surfactant dysfunction mutations and related disorders
  - 1. *SPFTB* genetic mutations—PAP and variant dominant histologic pattern
  - 2. *SPFTC* genetic mutations—CPI dominant histologic pattern; also DIP and NSIP
  - 3. *ABCA3* genetic mutations—PAP variant dominant pattern; also CPI, DIP, NSIP
  - 4. Others with histology consistent with surfactant dysfunction disorder without a yet recognized genetic disorder

II. Disorders not specific to infancy
- A. Disorders of the normal host
  - 1. Infectious and postinfectious processes
  - 2. Disorders related to environmental agents: hypersensitivity pneumonia, toxic inhalation.
  - 3. Aspiration syndromes
  - 4. Eosinophilic pneumonia
- B. Disorders related to systemic disease processes
  - 1. Immune-related disorders
  - 2. Storage disease
  - 3. Sarcoidosis
  - 4. Langerhans cell histiocytosis
  - 5. Malignant infiltrates
- C. Disorders of the immunocompromised host
  - 1. Opportunistic infection
  - 2. Disorders related to therapeutic intervention
  - 3. Disorders related to transplantation and rejection syndromes
  - 4. Diffuse alveolar damage of unknown etiology
- D. Disorders masquerading as interstitial disease
  - 1. Arterial hypertensive vasculopathy
  - 2. Congestive vasculopathy, including veno-occlusive disease
  - 3. Lymphatic disorders
  - 4. Congestive changes related to cardiac dysfunction

III. Unclassified—includes end-stage disease, nondiagnostic biopsies, and those with inadequate material

DIFFUSE LUNG DISEASE



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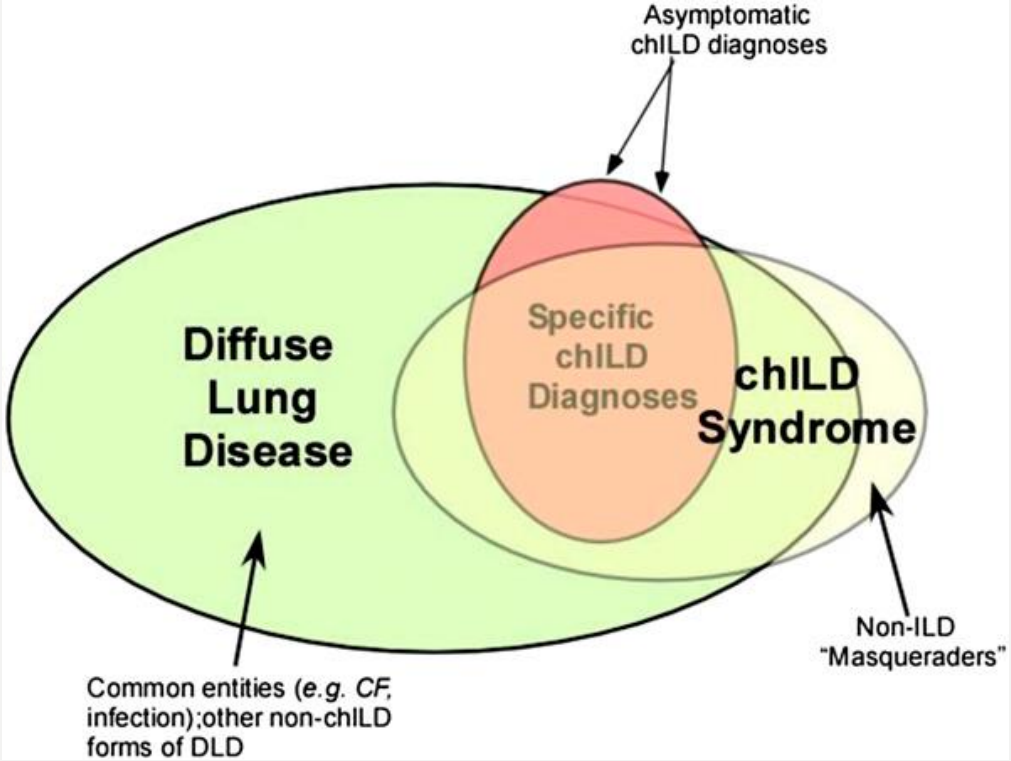

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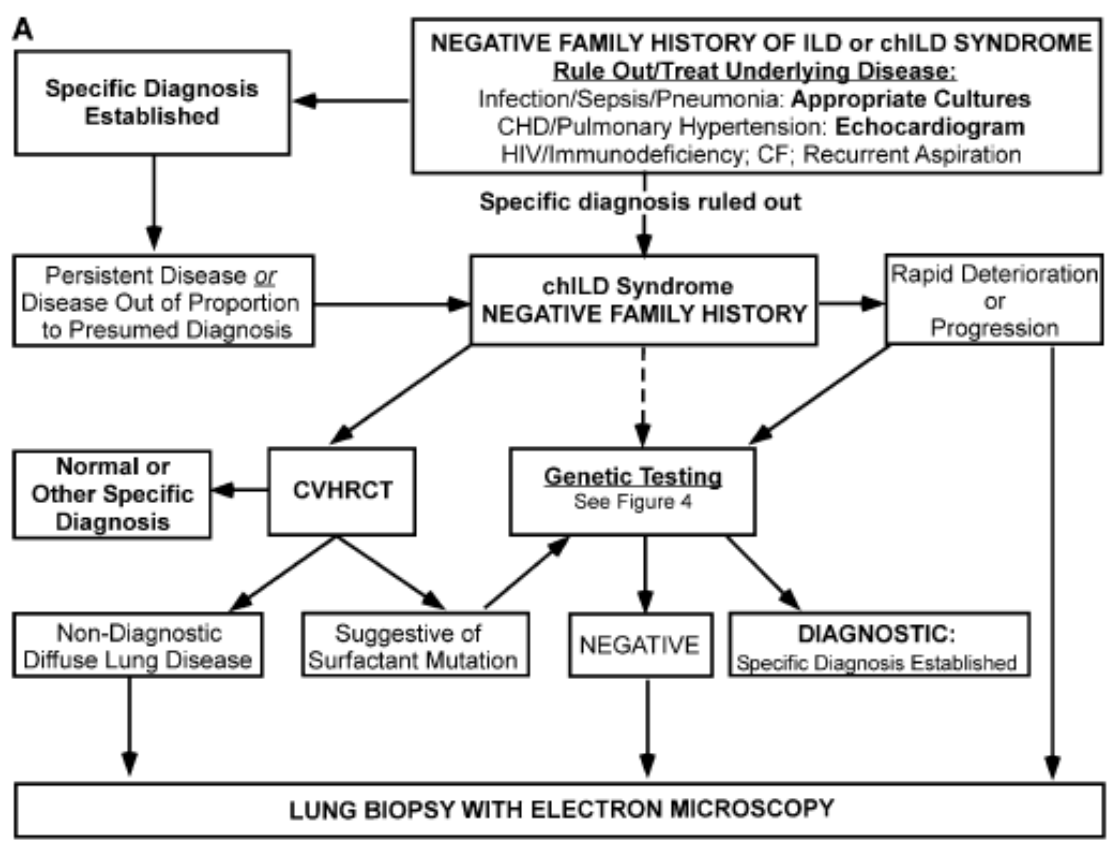

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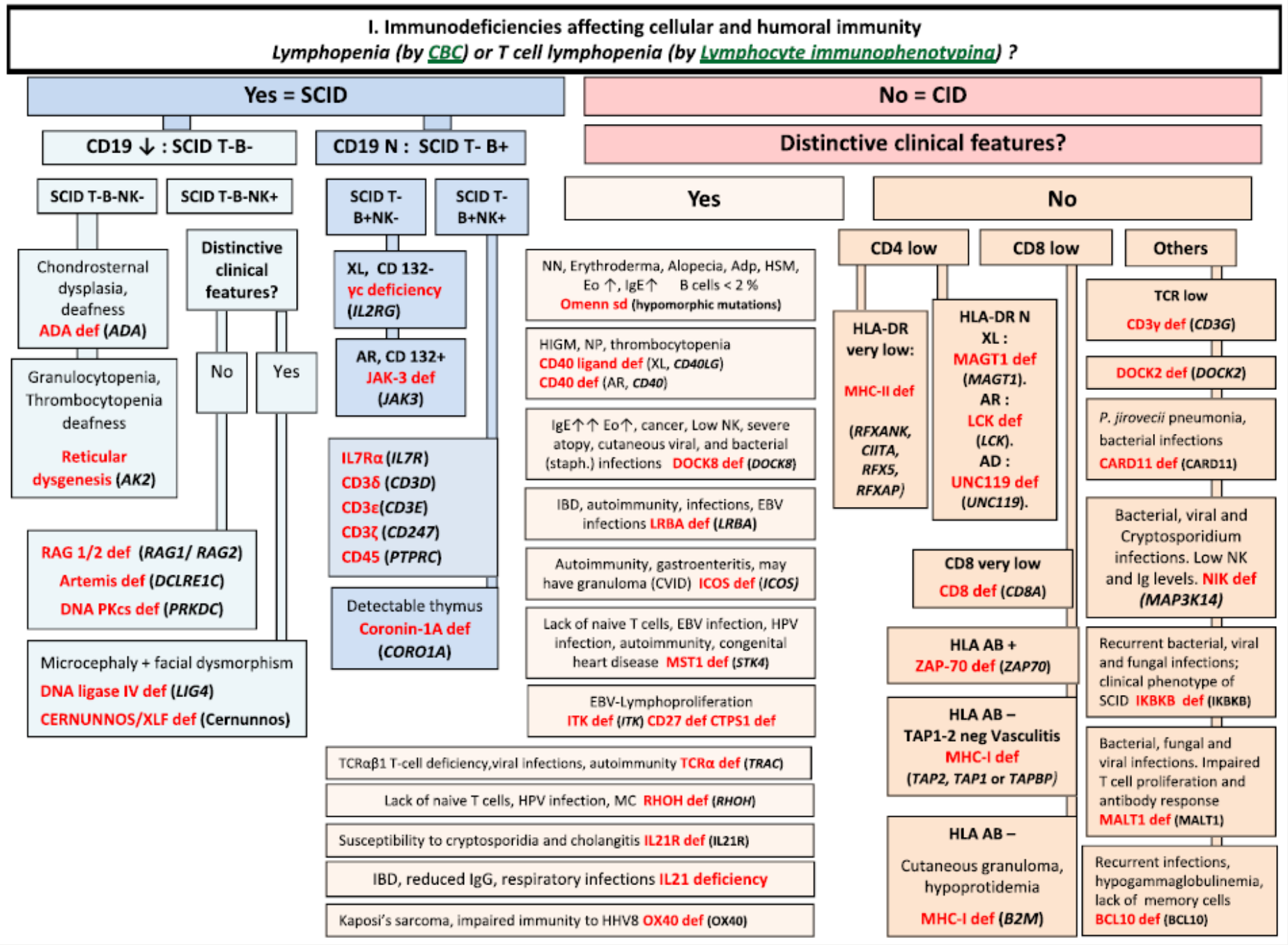
Kurland, ATS, 2013

DIFFUSE LUNG DISEASE: PID

- Primary immune deficiency (PID) from genetic abnormality in immunity
- Phenotype comprises of 1+ of:
  - Infection
  - Auto-immunity
  - Auto-inflammation
  - Allergy
  - Tumors
- Increase in PID detection due to whole exome sequencing
- Classification by the International Union of Immunological Societies (IUIS) Expert Committee for Primary Immunodeficiencies
- 2015, ~300 single-gene inborn errors of immunity have been identified

Slide courtesy of Dr. Schaballie



Boushifa, J Clin Immun, 2015

CVID

- Common Variable Immunodeficiency Disorders (CVID)
  - **Primary antibody deficiency**
  - Hypogammaglobinaemia
  - impaired production of specific antibodies after immunization
  - increased susceptibility to infections
- **Genetics**: Phenotypical and genetic heterogeneity

- **Epidemiology**:
  - Rarer in Children
  - Monogenic forms probably count for only 2-10% of patients with CVID
- **Pulmonary Sequelae:**
  - LIP
  - GLILD

Slide courtesy of Dr. Schaballie
Hurst, J Allergy Clin Immun Pract, 2017

LYMPHOID INTERSTITIAL PNEUMONIA

LIP: BACKGROUND

- Etiology: Unknown

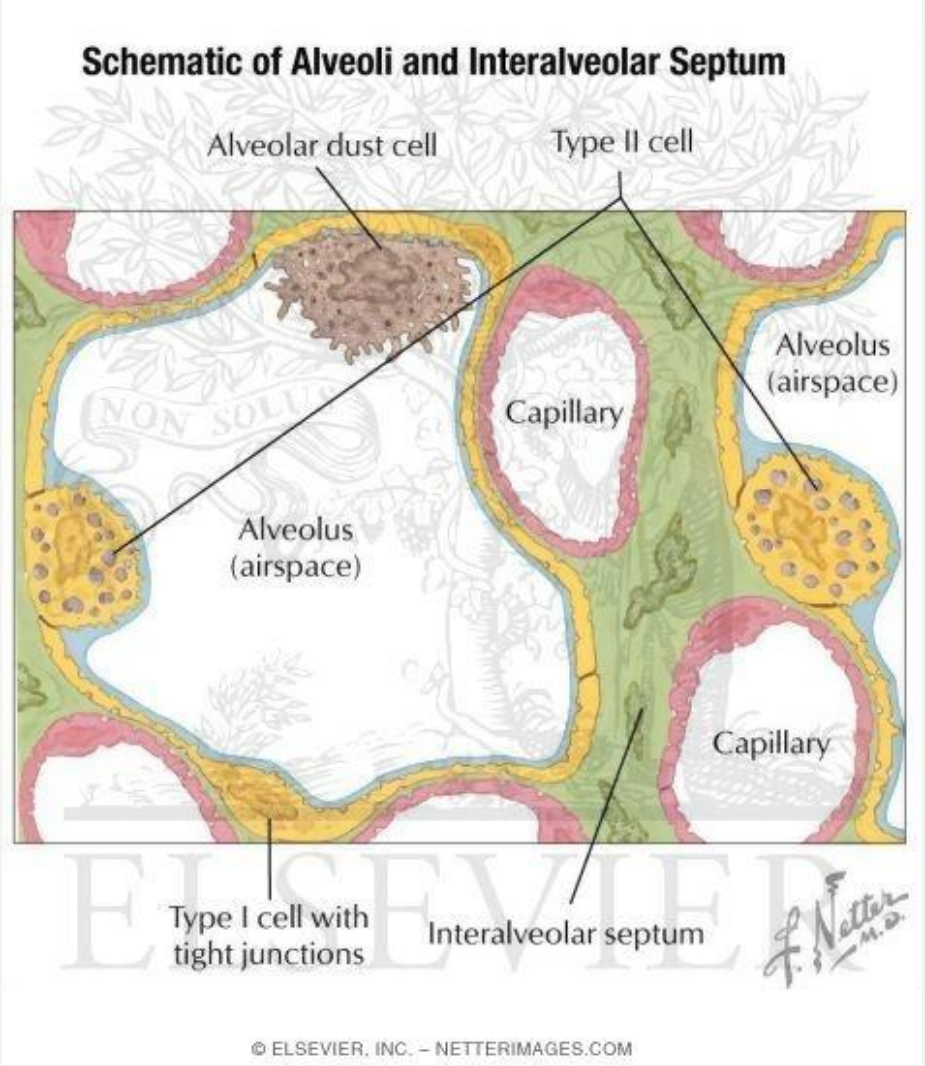
History

- 1973 – Liebow and Carrington describe LIP with hypogam.
- 1976 – Levinson et al, describe triad of CVID, pernicious anemia, LIP
- 1982 – Kohler et al. report a case of nodular LIP with CVID and intestinal nodular lymphoid hyperplasia

Up to date: Lymphocytic interstitial pneumonia in children
Deheinzelin, Am J Respir Crit Care Med, 1996

LIP: HISTOLOGY

- Histology:
  - Extensive interstitial (alveolar septa) infiltration of lymphocytes, plasma cells and histiocytes
  - Polyclonality of infiltrates (whereas lymphoma will have mono-clonal expansion)



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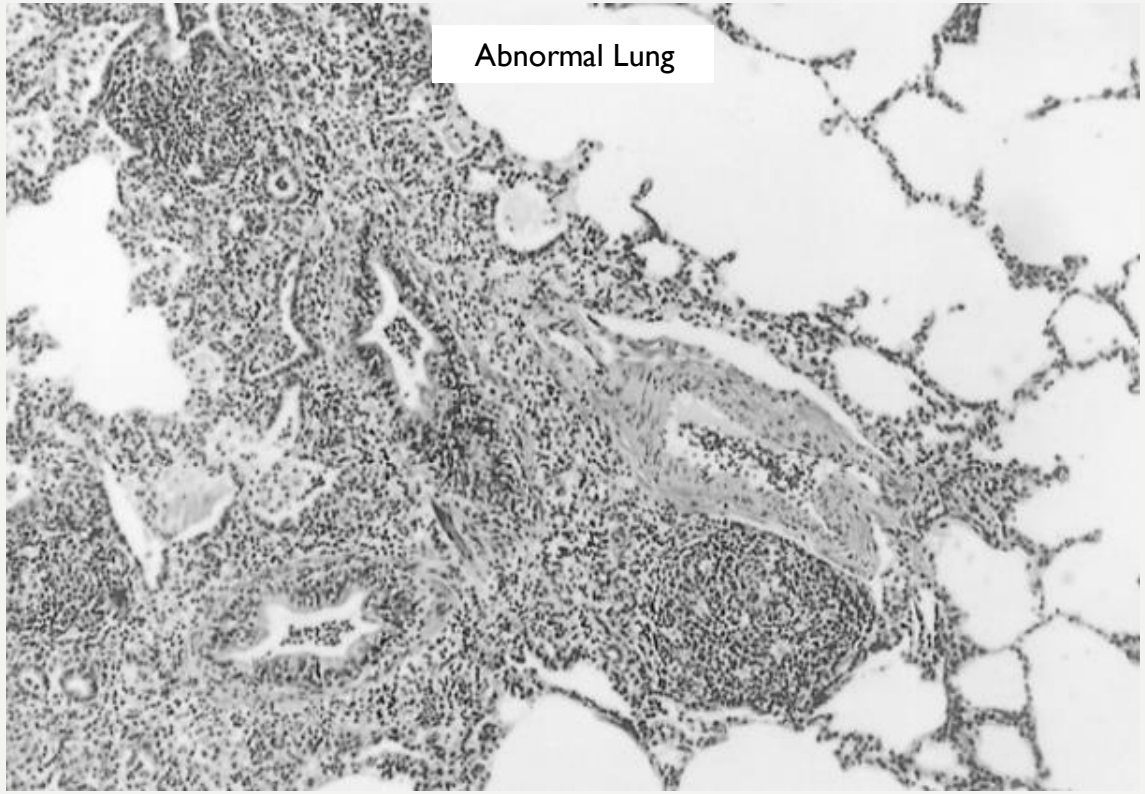
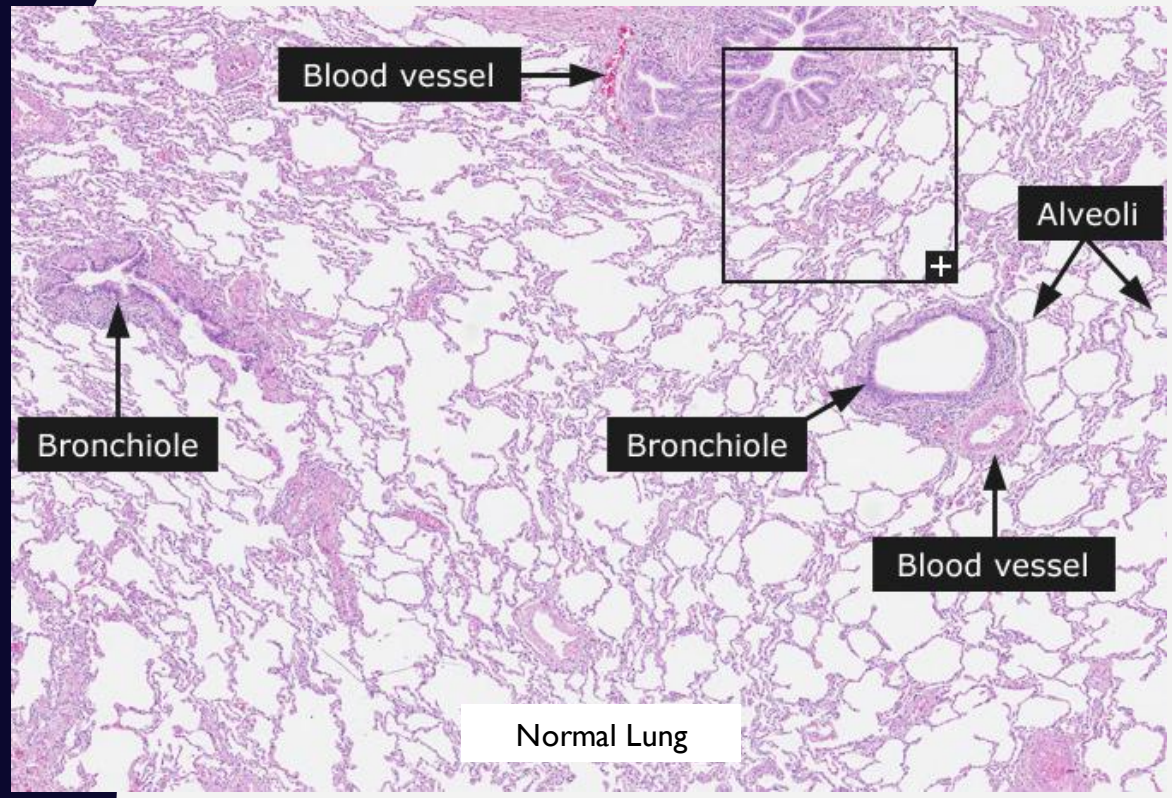
  - Extensive interstitial (alveolar septa) infiltration of lymphocytes, plasma cells and histiocytes
  - Polyclonality of infiltrates (whereas lymphoma will have mono-clonal expansion)

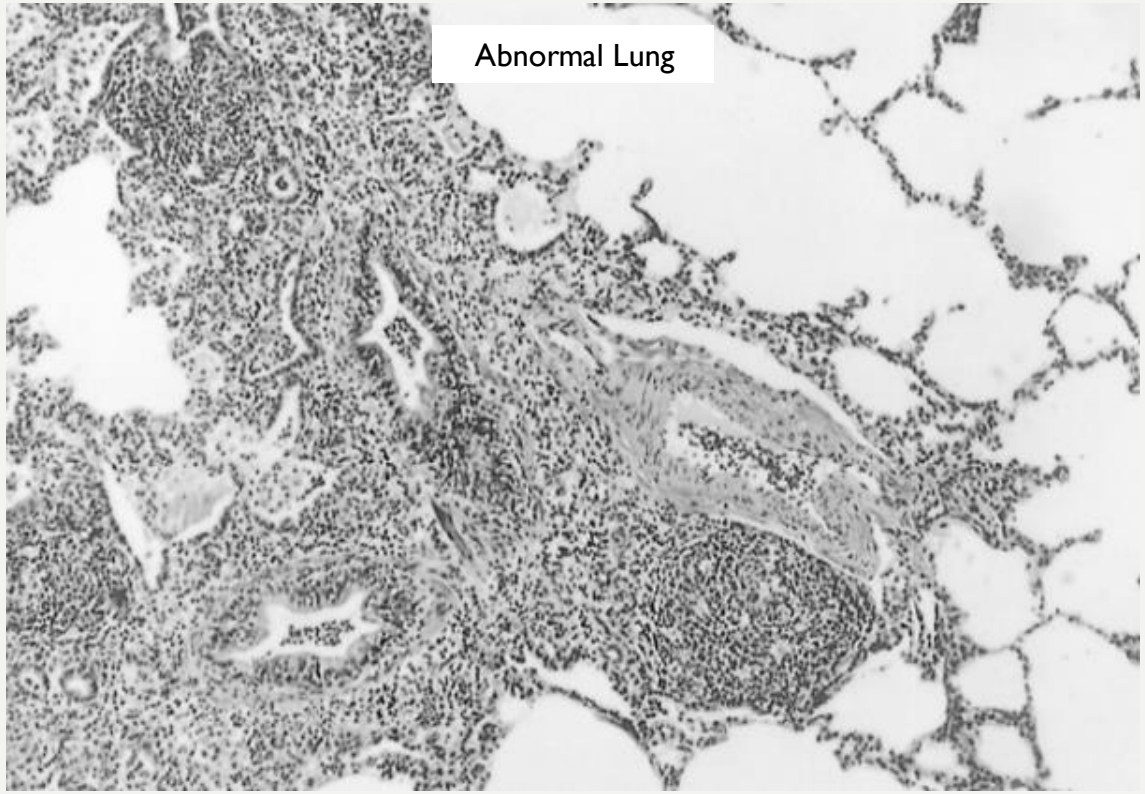


Kendig's, Figure 63-5

Up to date: Lymphocytic interstitial pneumonia in children

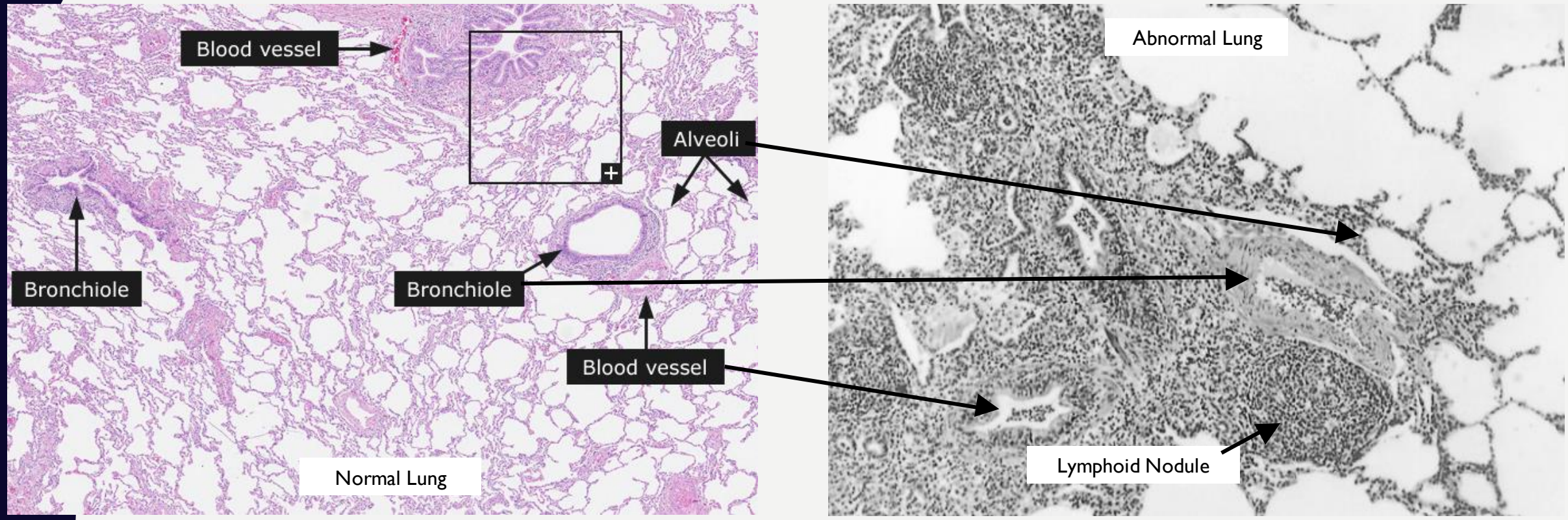
LIP: HISTOLOGY





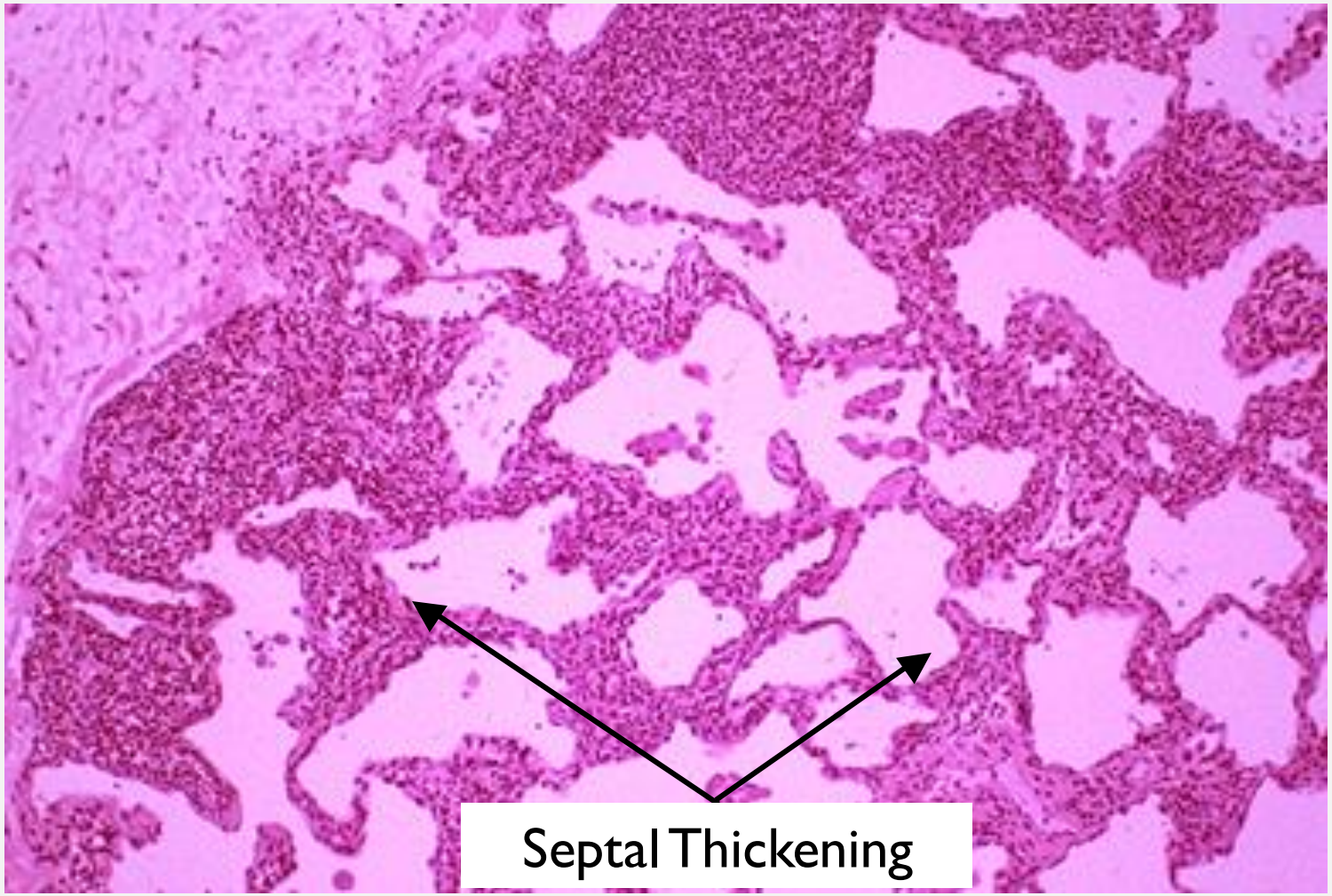
Kendig's, Figure 63-5

LIP: HISTOLOGY



Kendig's, Figure 63-5

LIP: HISTOLOGY



Up to date: Lymphocytic interstitial pneumonia in children

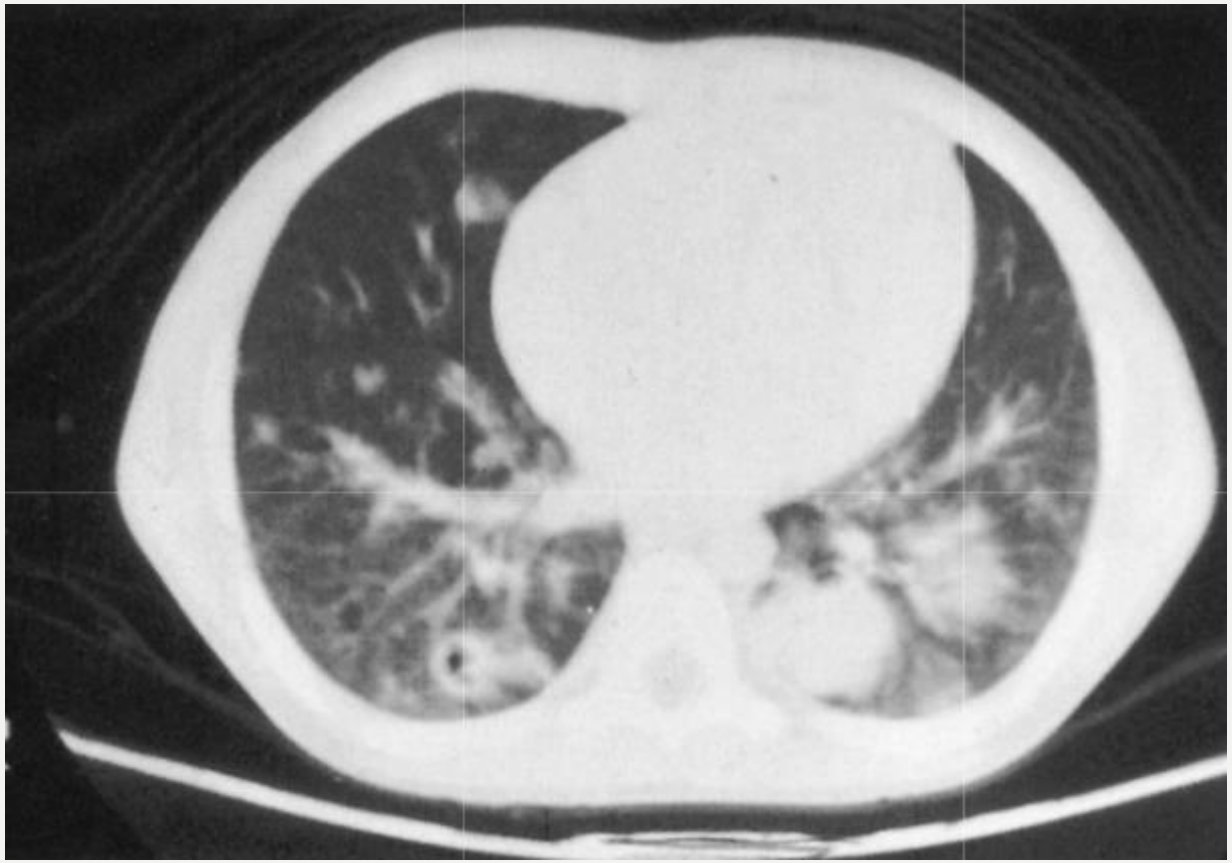
LIP: CLINICAL PRESENTATION

- Symptoms (slowly progressive)
  - Asymptomatic, cough, dyspnea, weight loss, fever, pleuritic CP, fatigue, arthralgias
- Physical Exam
  - Clubbing, HSM, LAD
  - Crackles, tachypnea

Park, Clin. Imm., 2010

LIP: INVESTIGATIONS

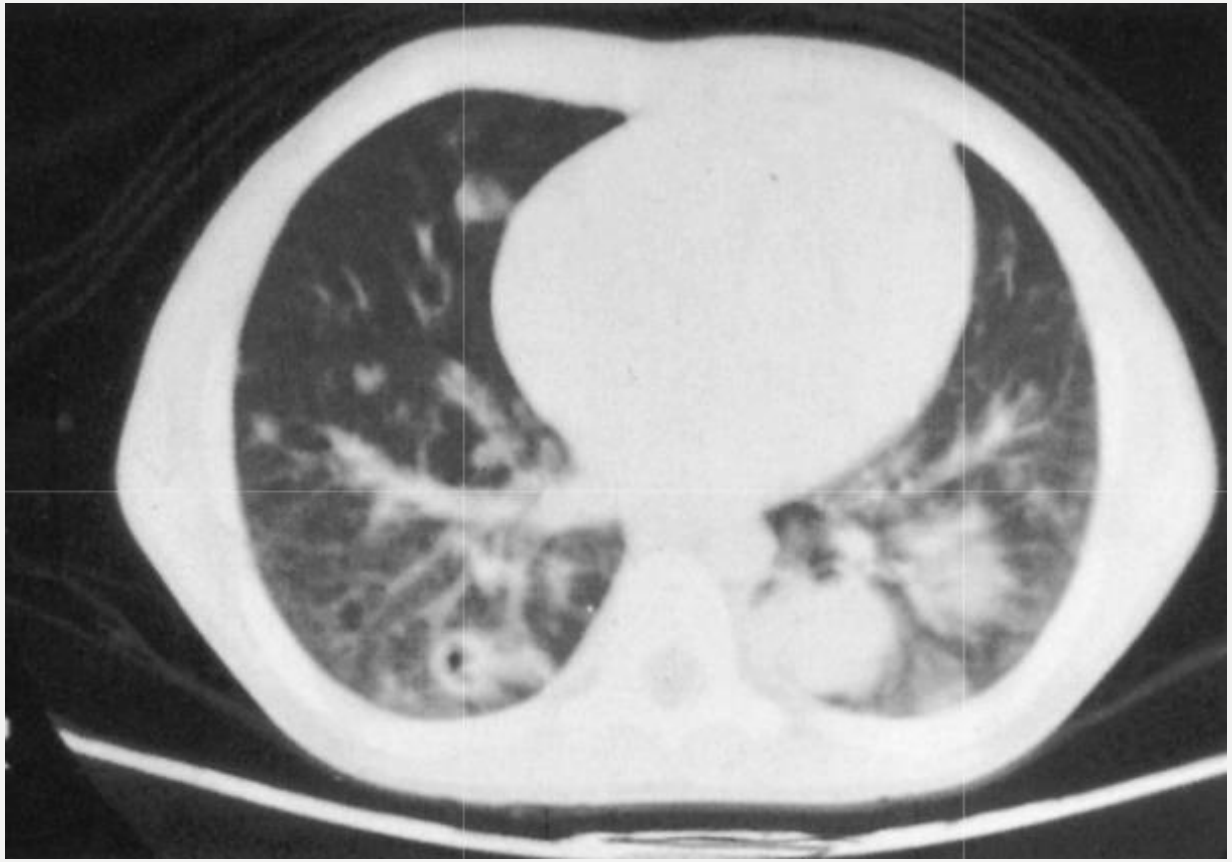
- CXR
- CT
- Immunoglobulin
- **Lung Biopsy**
- **Other: PFT**



Up to date: Lymphocytic interstitial pneumonia in children
Kendig's, Figure 63-6

LIP: PROGNOSIS

- Prognosis: unknown
- Treatment:
  - ?Steroids
  - ?Pneumocystis prophylaxis
  - ?azathioprine, cyclophosphamide, cyclosporine, rituximab
  - ?Bronchodilators
  - ?IVIG in CVID



Arish, Thorax, 2006
Park, Clin. Imm., 2010

GRANULOMATOUS LYMPHOCYTIC INTERSTITIAL LUNG DISEASE

GLILD

- **Definition**:
  - Non-infectious, diffuse lung disease complications that develop in CVID patient
  - Exhibit both granulomatous and lymphoproliferative histologic patterns consisting of LIP, follicular bronchiolitis, lymphoid hyperplasia
  - Granulomas are non-necrotizing and non-caseating
- **Pathogenesis**:
  - Not clearly understood
  - ?Impaired T-cell function leading to abnormal sequestration of antigen and formation of granulomas
- **Associated**: CVID, Infection (HHV-8, EBV, CMV), ?TNF-alpha
- **Prevalence**: 8-22% of CVID pts

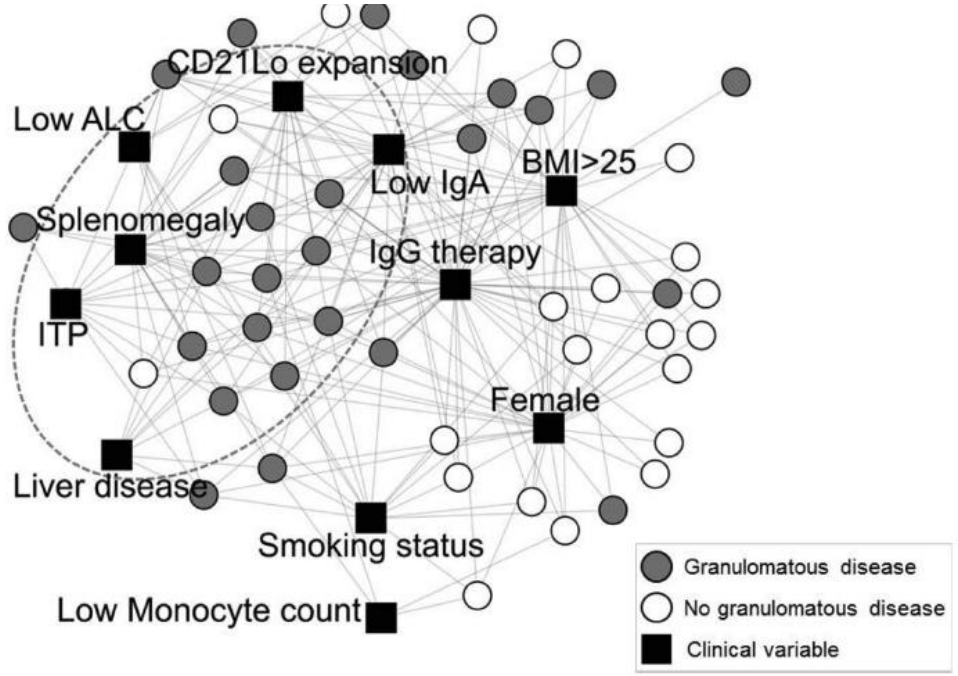
Jesenak, Frontiers in Peds, 2014
Park, Clinical Immunology, 2010

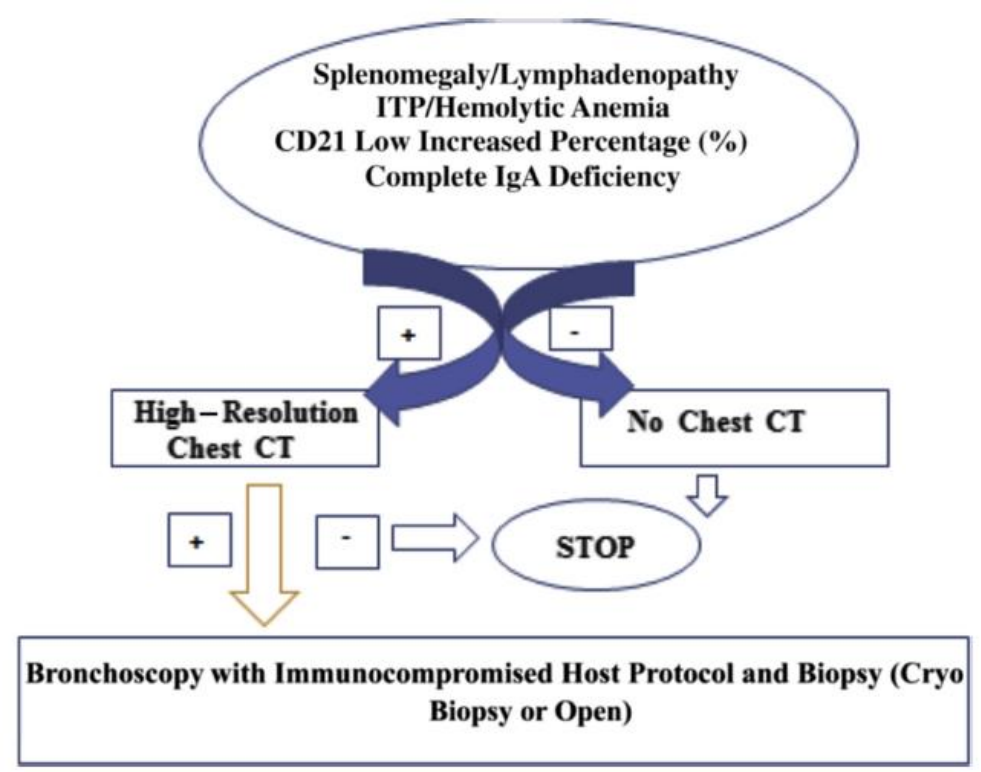
GLILD: PREDICTORS

Table 4
Univariate Analysis of Clinical Variables

Variable	OR (95% CI)	*P* value
Splenomegaly	17.3 (3.9–74.5)	<.001[a]
ITP or AIHA	4.8 (1.1–20.2)	.02[a]
IgA (<13 mg/dL)	3.6 (1.2–11.9)	.02[a]
CD21low >5%	5.8 (1.6–24.7)	.006[a]
Liver disease	9.2 (1.5–179.8)	.02[a]
Low ALC	3.3 (0.7–24.3)	.15

Abbreviations: AIHA, autoimmune hemolytic anemia; ALC, absolute lymphocyte count; ITP, immune thrombocytopenic purpura.
[a]Statistically significant.

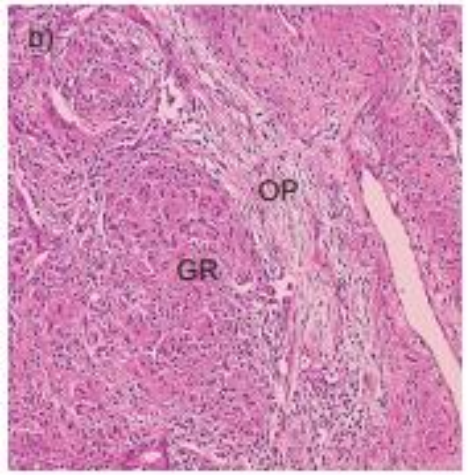


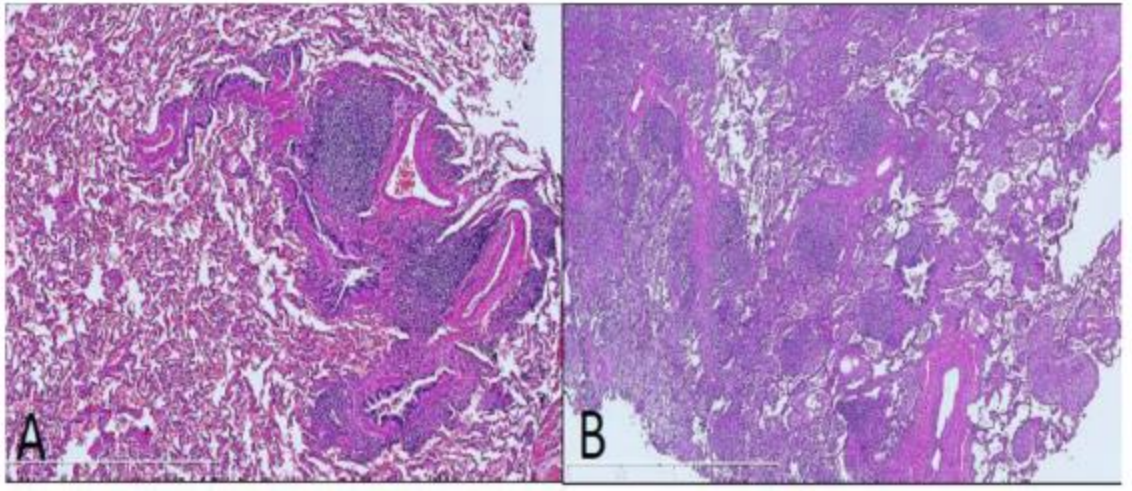


Hartono, et al., Ann Allergy Asthma Imm, 2017

GLILD: HISTOLOGY

	Microscopic features			
GLILD	Well, moderate or poorly circumscribed; May be cuffed by lymphocytes or associated with lymphoid infiltration; random distribution	Lymphocytic infiltration of variable density – peribronchiolar and interstitial	Consistently present; associated with interstitial inflammation	Present in a subset of patients; expansile and associated with interstitial inflammation
Lymphoid interstitial pneumonia	Granulomas are usually absent; isolated multinucleate giant cells with cholesterol clefts may be present	Diffuse interstitial chronic inflammatory infiltrate, with lymphoid aggregate formation	May be present focally (minor feature)	Usually absent

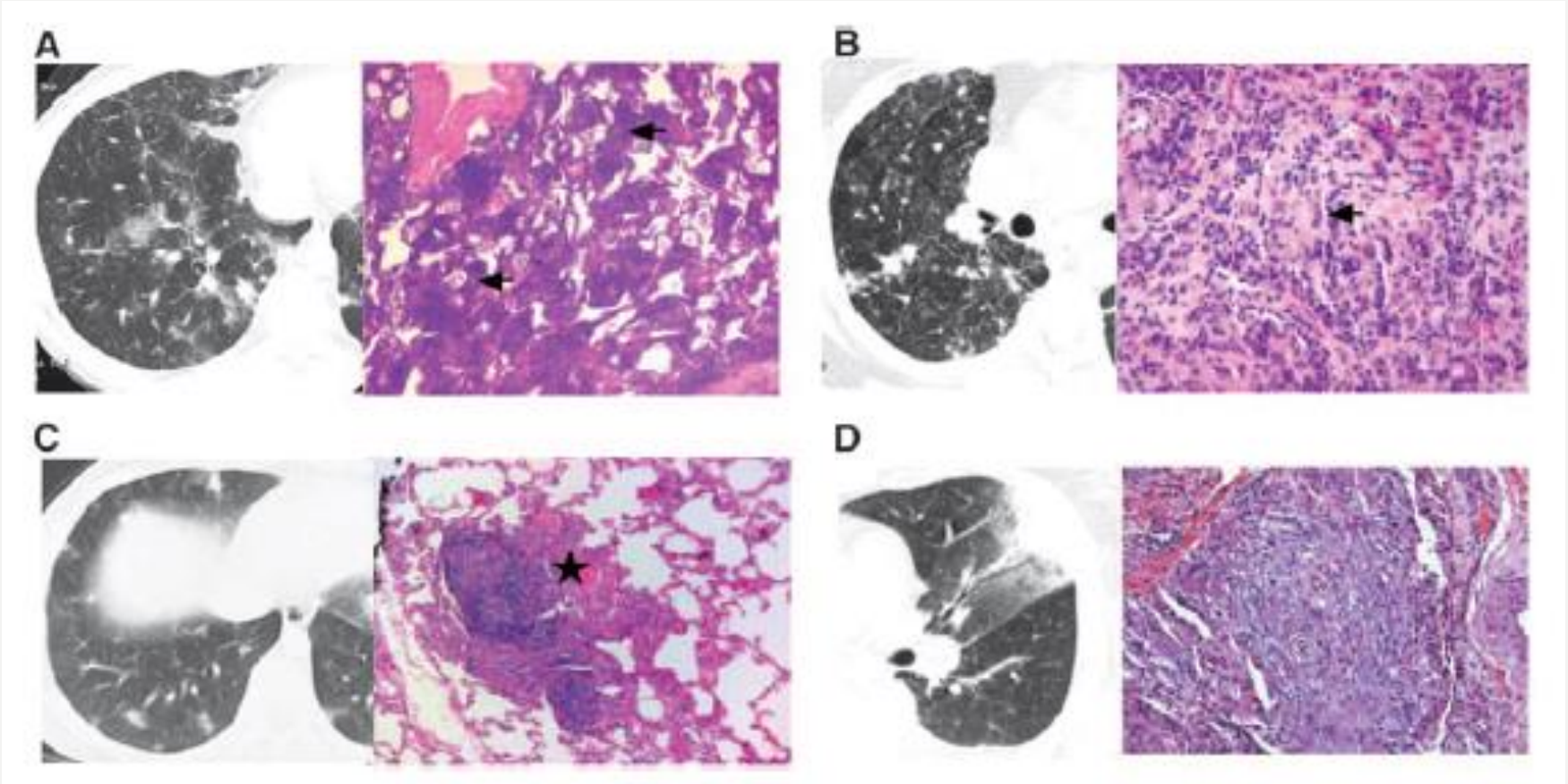




Jesenak, Frontiers in Peds, 2014
Rao, Hum Pathol, 2015

GLILD: IMAGING

- CXR
- **HRCT Chest**



Jesenak, Frontiers in Peds, 2014
Rao, Hum Pathol, 2015

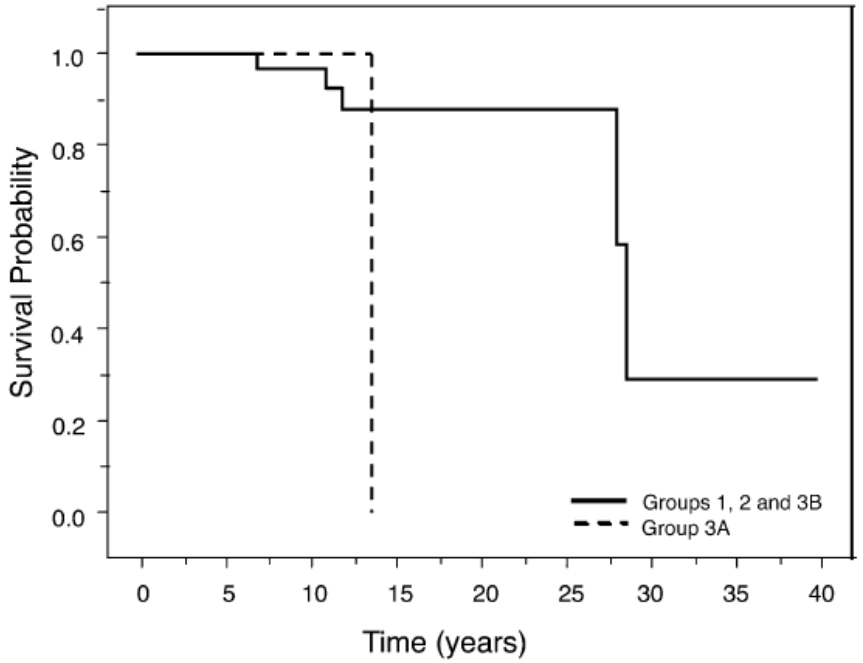
GLILD: PROGNOSIS

- **Population**
  - 69 patients with CVID > 16 years old; divided into 3 groups based on respiratory symptoms and radiographically
- **Intervention**
  - Retrospective study
- **Comparison** (See Table 1)
- **Outcome** (Median Survival)
  - Group 1, 2, 3B: 28.8 years
  - Group 3A: 13.7 years
  - P < 0.001

TABLE I. Noninfectious pulmonary disorders complicating CVID

Group 1	No pulmonary disease (n = 29)
Group 2	Bronchiectasis (n = 15)
	Asthma (n = 8)
Group 3A (GLILD)	Granulomatous disease (n = 5)
	LIP (n = 4)
	Lymphoid hyperplasia (n = 2)
	Follicular bronchiolitis (n = 1)
	B-cell lymphoma (n = 1)
Group 3B (other ILDs)	BOOP (n = 3)
	Hypersensitivity pneumonitis (n = 1)
	Metastatic gastric carcinoma (n = 1)

BOOP, Bronchiolitis obliterans organizing pneumonia.



Bates, J Allergy Clin Imm, 2004

GLILD: MANAGEMENT

British Lung Foundation and UK PID Network Consensus Statement

UKPIN
PRIMARY IMMUNODEFICIENCY NETWORK

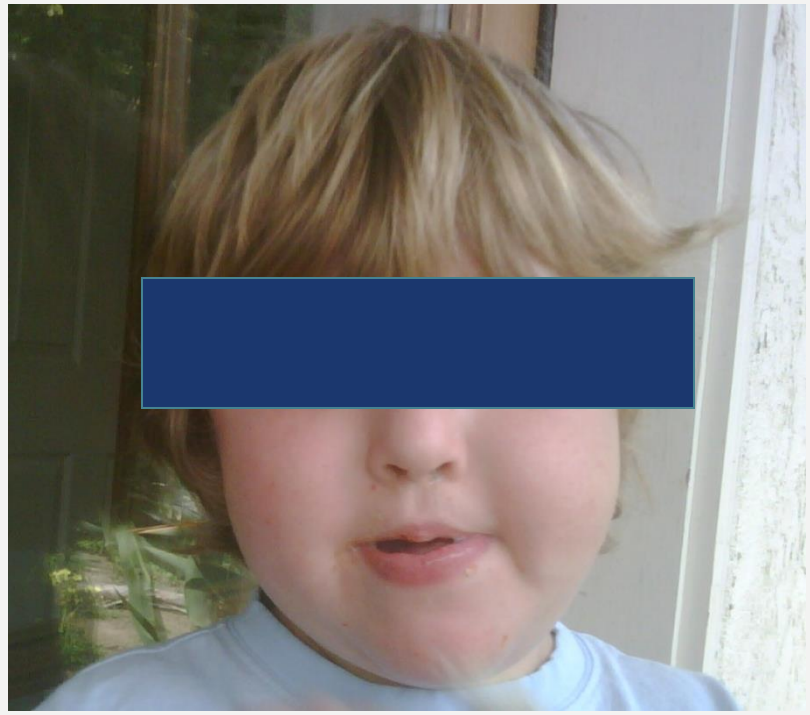
- Treatment
  - Prednisone PO minimum 10 to 20 mg/d, to a maximum of 1-2 mg/kg/d.
  - Commonly used second agent Azathioprine, Rituximab, MMF
  - Adjust based on symptoms, lung function, imaging
- No consensus for
  - Prophylactic antibiotics
  - Expectant management

Hurst, J Allergy Clin Imm Pract, 2017;5:4

BACK TO PATIENT

CURRENTLY…

- Currently on a prednisone wean
- Symptoms have resolved
- Follow up on CT Chest shows improvement to nodules
- WES still pending…



https://autismdad1966.files.wordpress.com/2011/12/img00044-20100313-1145.jpg

CONCLUSIONS

Objectives

- Exposure to an interesting clinical case
- Understand the management of this disease

Take Home Points

- GLILD mainly in adults but can occur in pediatrics
- Understand that GLILD is a pulmonary manifestation of CVID
- Recognize that it is associated with increased mortality
- Management is not yet well-defined

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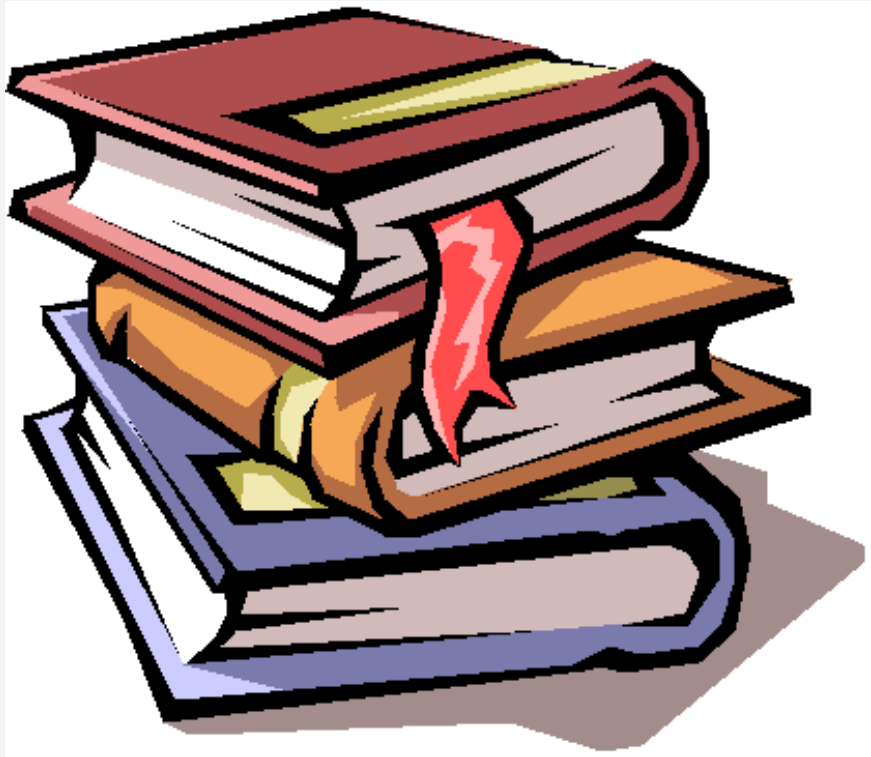

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Thank
you!!