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Common Variable Immune Deficiency & Granulomatous – Lymphocytic Interstitial Lung Disease

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Disclosures:

- I have been involved in pharmaceutical-sponsored trials and investigator initiated studies:
  - Boehringer Ingelheim
  - Genentech
  - NJH and CO advanced industry grant programs
- Non-FDA approved therapies will be discussed.

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Objectives:

- Describe the prevalence of ILD in patients with CVID.
- Describe the imaging findings and underlying pathologic patterns in GL-ILD.
- Describe (non-FDA approved) therapies that have been used for the treatment of GL-ILD.

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Case

- PS is a 34 y/o male h/o hand vitiligo
  - Age 15 dx with ITP
    - Treated with intermittently steroids
  - Age 30 through 34 dx with increasing number of infections
    - Treated with antimicrobials, sinus sx, tympanostomy
  - Age 34 seen by A/I for unifying diagnosis
- <u>He has no pulmonary complaints</u>

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Case

- Splenomegaly was noted on exam
- Laboratory studies
  - WBC = 4.1, HCT = 42.1, Plt = 112
  - Comprehensive panel was normal
  - IgG 293, IgM normal, IgA low
  - Abnormal response to vaccination with pneumoccocus
- HRCT imaging was abnormal …

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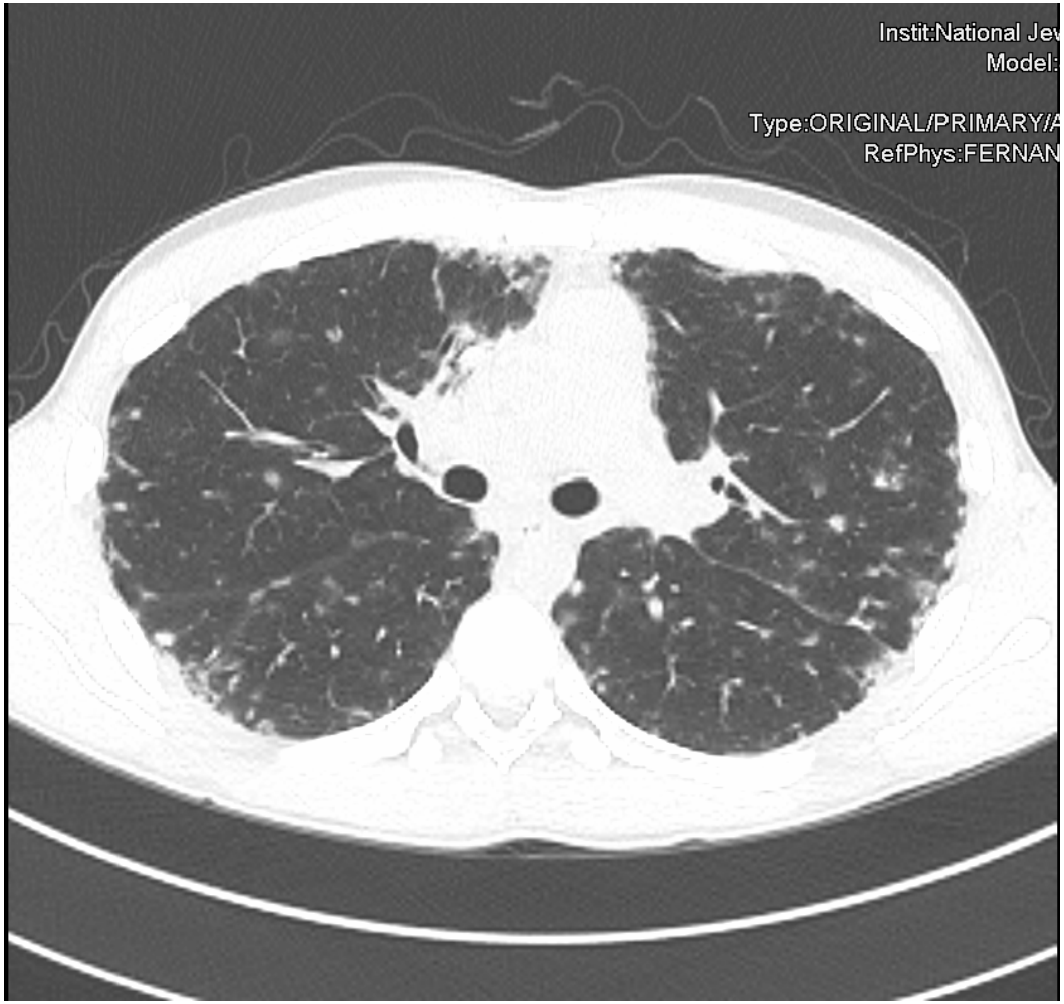
HRCT



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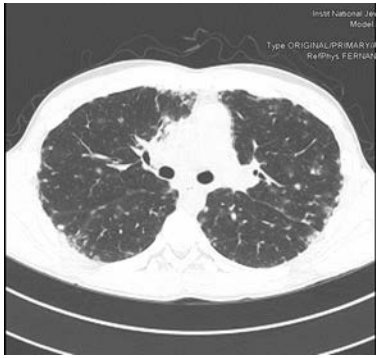
CVID

- The most common primary immune deficiency
  - 1:25,000 to 1:50,000
- Reduced serum immunoglobulin
  - IgG, IgA and/or IgM
  - Reduced or absent specific antibody response
- Diagnosed between 20 to 40 years of age
- Recurrent sinopulmonary infections …



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Pulmonary complications of CVID

- **Infectious disorders**
  - -Primary infections
  - -Recurrent or post-infectious (e.g. bronchitis)
- **Non-infectious disorders**
  - -ILD (e.g. GLILD)
  - -Neoplastic disorders
  - -Primary airway-centered disorders
  - -Benign local or diffuse lymphoproliferative disorders
- **Mixed infectious and non-infectious disorders**

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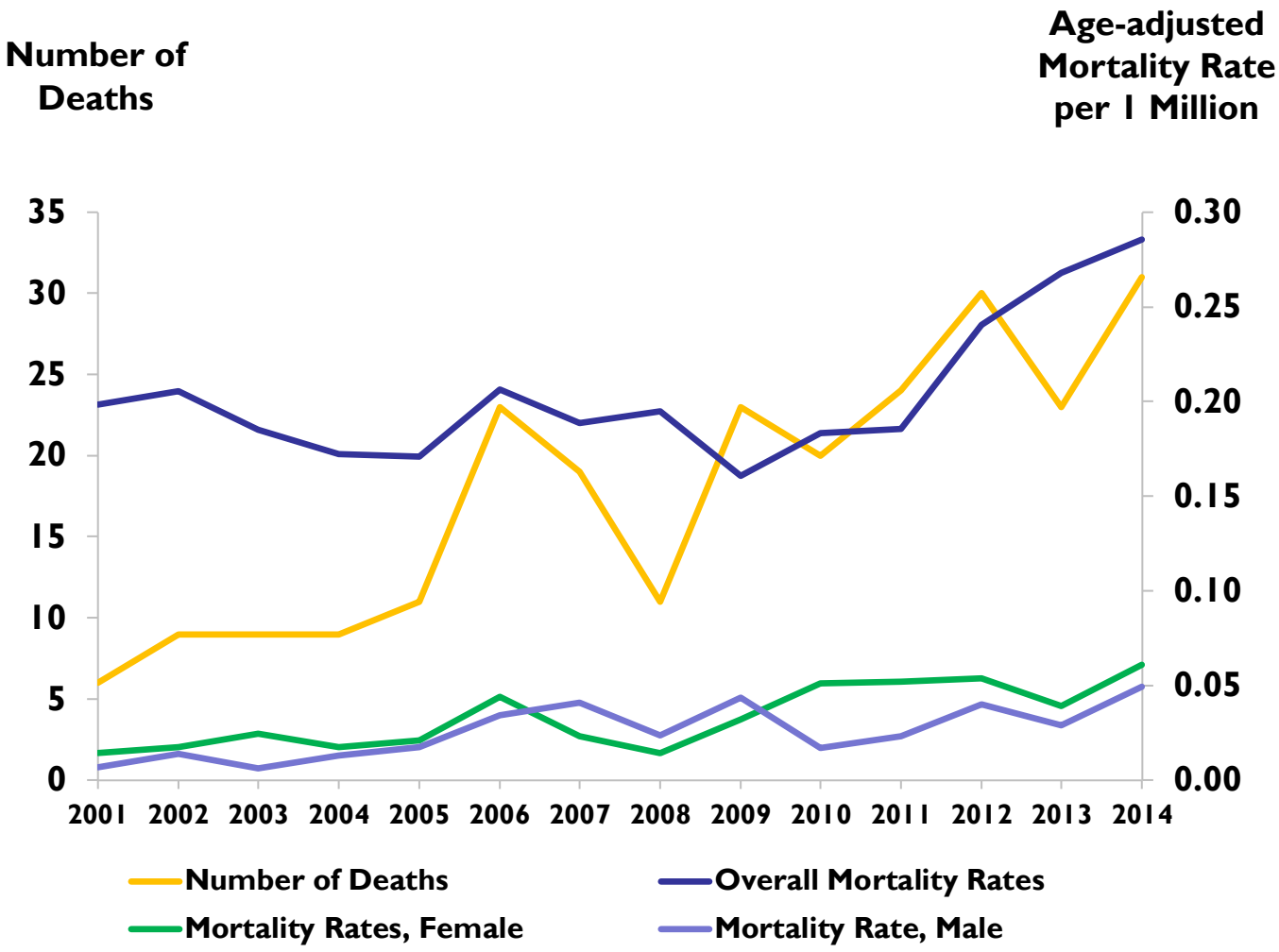
CVID Mortality in US: 2001-2014



N = 248

Race: W=235, B=9, H=4

Mean age: 49 yrs. (CI 47-51)

Mean crude : 1.4 per 100,000 (CI 1.1-1.8)

Mean rate: 0.20 (CI 0.18-0.22)

Mortality rate % change from 2001: 44%

Unpublished Data: ICD-10 D83.9 from NCHS.

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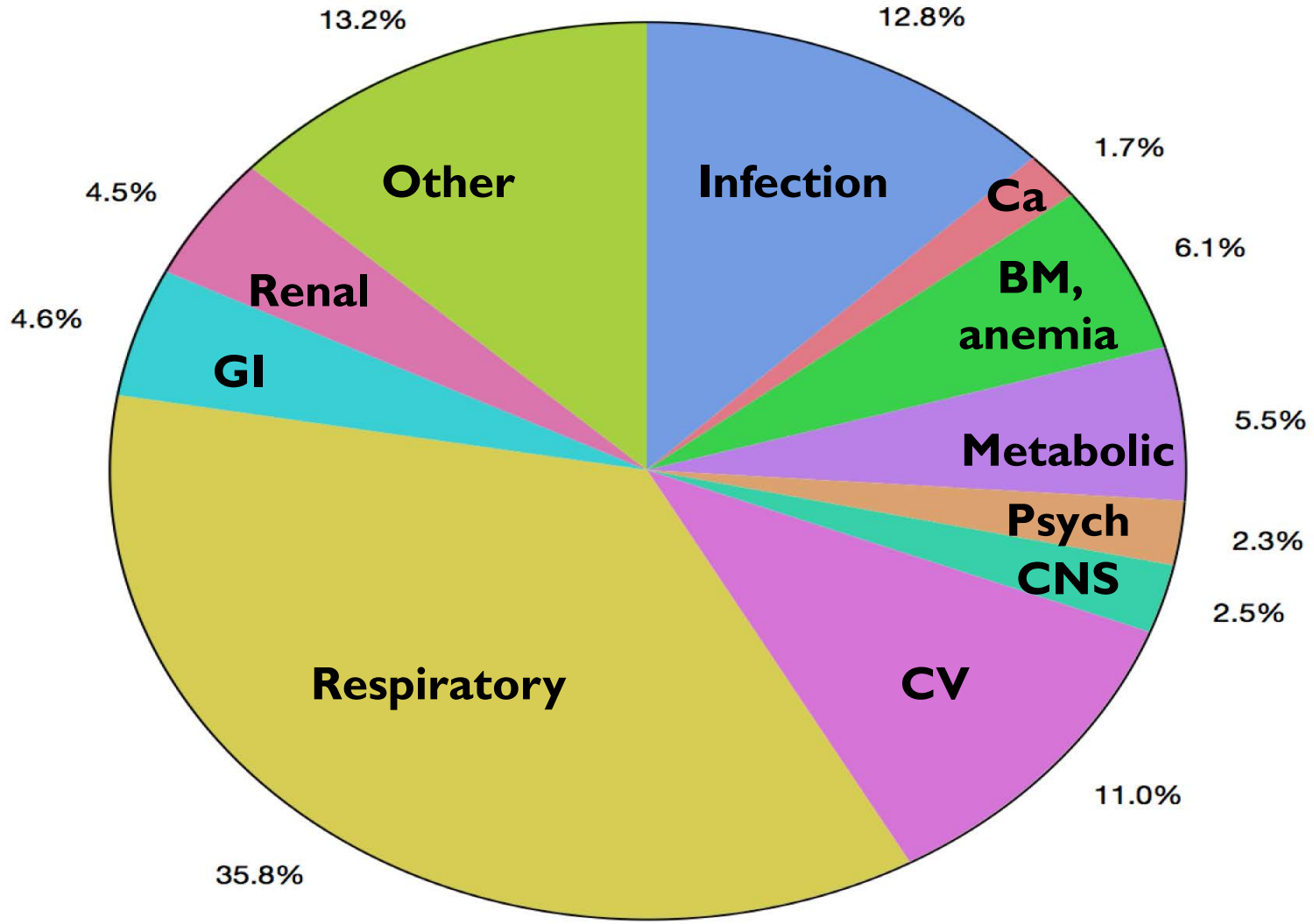
Contributing Causes of Death in CVID: 2001-2014



Unpublished Data: ICD-10 D83.9 from NCHS.

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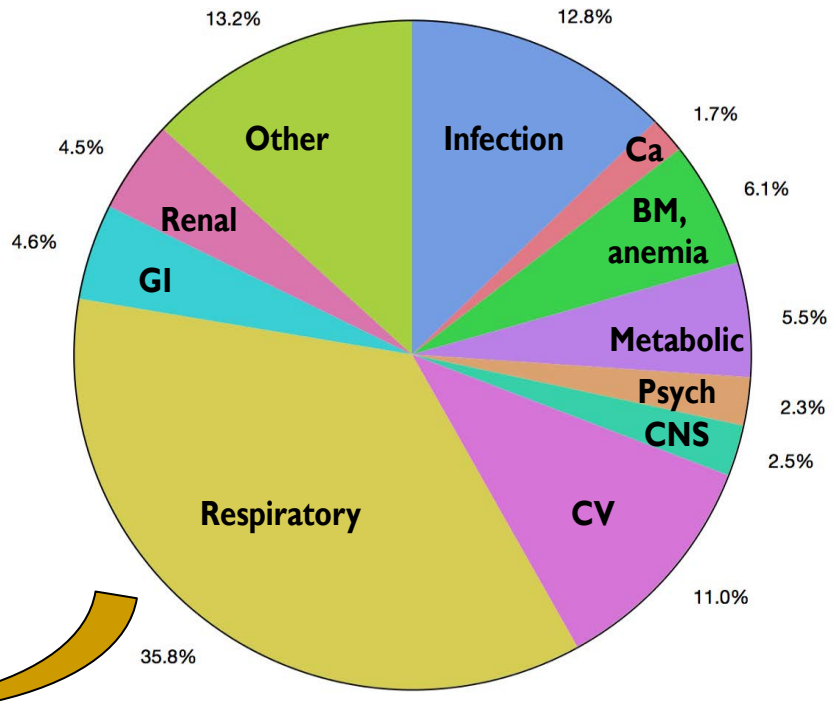
Contributing Causes of Death in CVID: 2001-2014

-Respiratory failure & ARDS	25%
-Bronchiectasis	15%
-PNA	14%
-COPD	13%
-ILD & Pulmonary fibrosis	7%

N = 248

Respiratory = 246



Unpublished Data: ICD-10 D83.9 from NCHS.

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What is the prevalence of ILD in CVID?

CLINICAL TRIALS AND OBSERVATIONS

Morbidity and mortality in common variable immune deficiency over 4 decades

Elena S. Resnick,[1,2] Erin L. Moshier,[3] James H. Godbold,[3] and Charlotte Cunningham-Rundles[1,2,4]

[1]Immunology Institute and Departments of [2]Medicine, [3]Preventative Medicine, and [4]Pediatrics, Mount Sinai School of Medicine, New York, NY

Resnick ES, et al. Blood 2012; 119:1650-1657.

Table 2. Selected complications

Associated condition	No.	% of cohort (n = 473)
Infections only (no complications)	151	31.9
Chronic lung disease (functional/structural)	135	28.5
Bronchiectasis	53	11.2
Autoimmunity	134	28.6
ITP	67	14.2
AIHA	33	7
Evans syndrome	20	4.2
Rheumatoid arthritis	15	3.2
Anti-IgA antibody	7	1.5
Alopecia	5	1.1
Neutropenia, pernicious anemia, anticardiolipin antibody, antiphospholipid syndrome, diabetes mellitus, juvenile rheumatoid arthritis, uveitis, multiple sclerosis, systemic lupus erythematosis, autoimmune thyroid disease, lichen planus, vasculitis, vitiligo, psoriasis	< 5	< 1
Gastrointestinal disease	73	15.4
Malabsorption	28	5.9
Inflammatory bowel disease (Crohn disease, ulcerative colitis, ulcerative proctitis)	20	4.2
Chronic diarrhea	9	1.9
Idiopathic mucosal inflammation	6	1.3
Nodular lymphoid hyperplasia	5	1.1
Gastrointestinal bleeding, irritable bowel syndrome, partial gastrectomy, diverticulitis, esophagitis	1	< 1
Liver disease/hepatitis	43	9.1
Hepatitis C	9	1.9
Liver granuloma	8	1.7
Idiopathic liver disease	8	1.7
Non-A, non-B hepatitis*	6	1.3
Chronic hepatitis of unknown origin	5	1.1
Primary biliary cirrhosis	3	< 1
Nodular regenerative hyperplasia	2	< 1
Hepatitis B, cirrhosis of unknown etiology	1	< 1

68% had one or more autoimmune/inflammatory complication from CVID

*** 473 patients, followed over 40 years**

Resnick ES, et al. Blood 2012; 119:1650-1657.

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Selected Complications

Associated Complication	No.	% of Cohort
Infections Only	151	31.9%
Pulmonary Complications		
Chronic Lung Disease	**135**	**28.5%**
Bronchiectasis	53	11.2%
Autoimmunity	**136**	**28.6%**
Gastrointestinal Disease	73	15.4%
Liver Disease	43	9.1%

* 473 patients, followed over 40 years

Resnick ES, et al. Blood 2012; 119:1650-1657.

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Granulomatous Disease (GD)

- Of those 473 patients, 46 (9.7%) had biopsy-proven GD.
- Of those with GD, > 50% had lung involvement.

Location	No. (n = 46)
Lung	**20**
Multiple sites (ie, liver, lung, spleen)	7
Lymph node	6
Liver	4
Skin	3
Spleen	2
Bone marrow	1
Brain	1
Neck tissue	1
Operative site	1

Resnick ES, et al. Blood 2012; 119:1650-1657.

Prognosis:

- Of 411 patients followed over 4 decades, 93 died (19.6%)
- The most common cause of death was pulmonary-related (36.6%)
- Chronic lung disease was associated with reduced survival
  - (HR = 2.06, p =0.022)

Table 7. Causes of death

Cause of death	No. (n = 93)	Comments
Lung failure	34	14 of these from respiratory failure, 3 after lung transplant
Lymphoma	17	2 cases with coexistent lung disease and 1 with coexistent liver disease contributing to death
Cancers	10	2 lung, 2 stomach, 1 ovarian, 1 esophageal, 1 carcinoid, 1 oral, 1 breast, 1 colon
Liver disease	8	1 after liver transplant, 4 infectious hepatitis
Other infections	5	Pneumocystis pneumonia, measles, nocardia brain abscess, multiple anaerobes, meningitis
Heart disease	4	1 with coexisting lung disease
Aplastic anemia	4	1 with coexisting neurodegenerative disease
Unknown cause of death	4	
Progressive multifocal leukoencephalopathy	2	
Vasculitis	1	
Neurodegenerative disease	1	
Autonomic amyloidosis	1	
Accidental death	1	
Suicide	1	

Resnick ES, et al. Blood 2012; 119:1650-1657.

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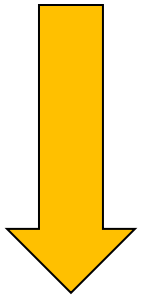
CVID & ILD

- In CVID, "chronic lung disease" is common occurring in ~ 25% of patients
- Granulomatous disease occurs in ~ 10% of patients, > 50% of the time involves the lung.



What is this form of interstitial lung disease?

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CVID & ILD History

- In patients with low immunoglobulins:
  - Lymphoid Interstitial Pneumonia (LIP) had been long recognized.
    - Granulomas in this setting had also been identified.
  - "Sarcoidosis" (granulomatous lung disease) had also been recognized.

Liebow AA, Carrington CB. Med Clin North Am 1973;136:809-843.

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CVID & ILD, 2004

Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency

Christopher A. Bates, MD,[a] Misoo C. Ellison, PhD,[a,e] David A. Lynch, MD,[a,f]
Carlyne D. Cool, MD,[a,d] Kevin K. Brown, MD,[a] and John M. Routes, MD[a,b,c] *Denver, Colo*

Bates et al. J Allergy Clin Immunol **2004**;114:415-421.

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CVID & ILD

Retrospective analysis of 69 patients from National Jewish Health; ~ 25% ILD.

Group 1	Group 2 Airways Dz	Group 3A GL-ILD	Group 3B Other ILD/ Malignancy
No pulmonary disease	Bronchiectasis Asthma	**Granulomatous Disease** **LIP** **Follicular Bronchiolitis** **Lymphoid Hyperplasia** MALT-lymphoma	Organizing Pneumonia Hypersensitivity Pneumonitis Metastatic Gastric CA
29/69 (42%)	23/69 (33%)	13/69 (19%)	5/69 (7%)

Bates CA et al. J Allergy Clinic Immunol 2004;114:415-421.

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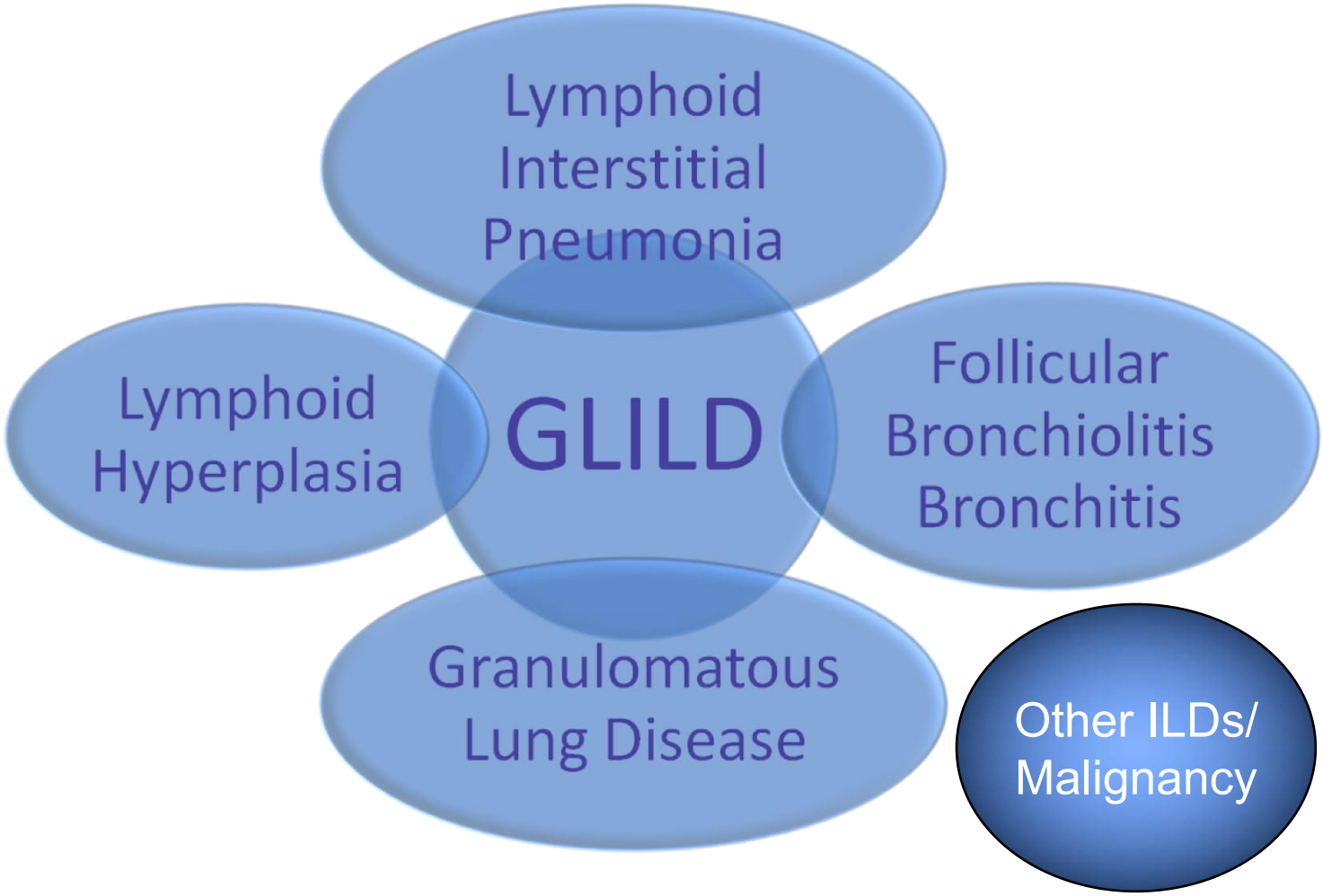
ILD in CVID: GLILD and others



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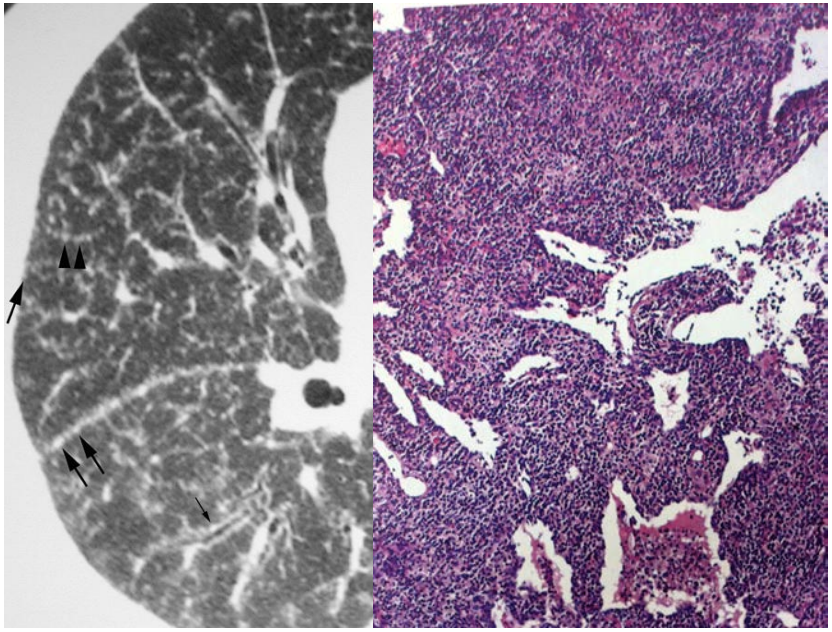
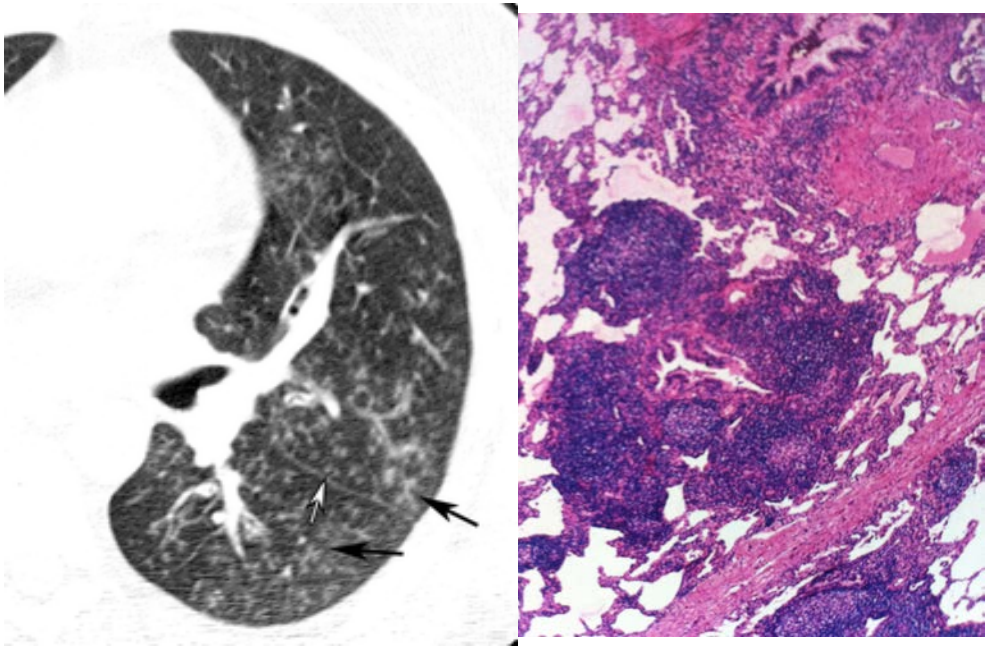
Pathologic features GLILD

- Benign Lymphoproliferative patterns

LIP **Follicular bronchiolitis**





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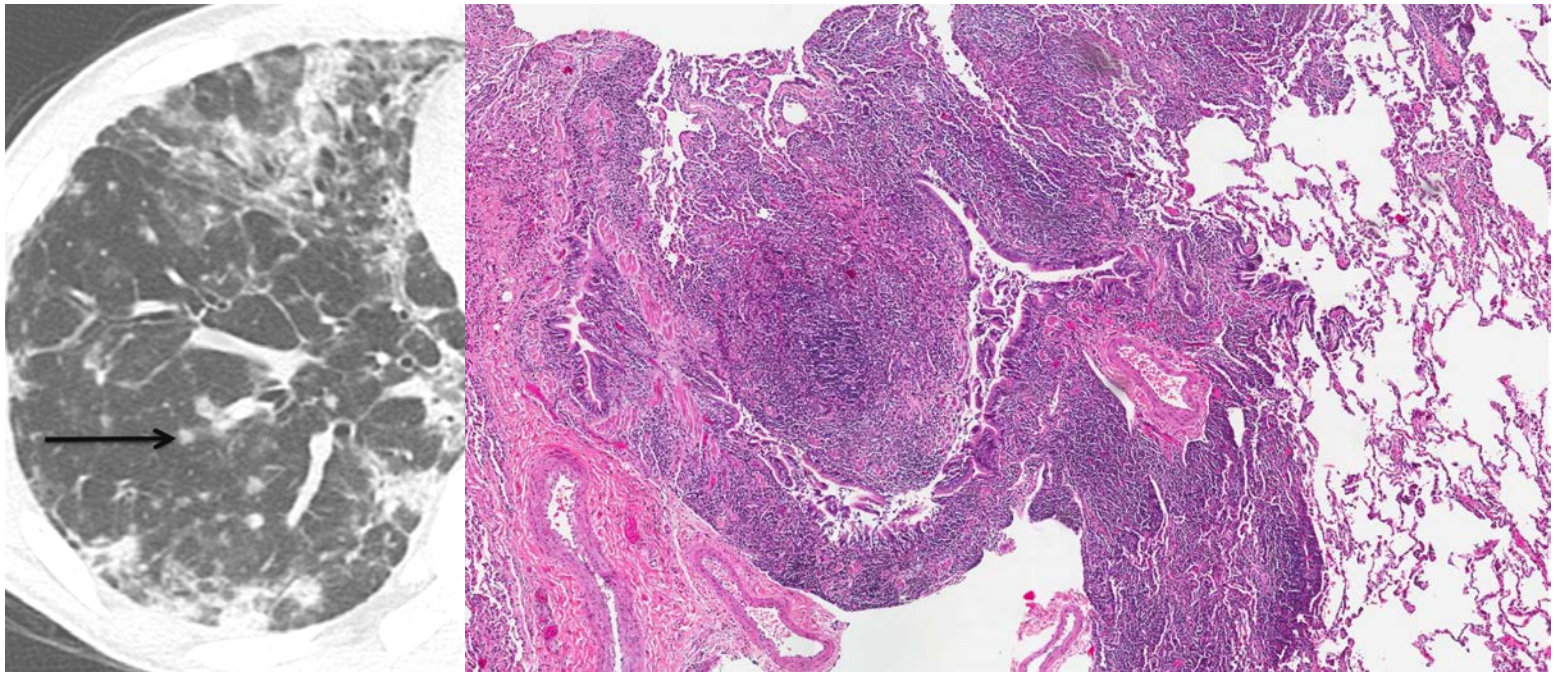
Pathologic features GLILD

- Benign Lymphoproliferative patterns

Lymphoid hyperplasia



Fernández Pérez ER. Immunol Allergy Clin N Am 2012;32:621-632.

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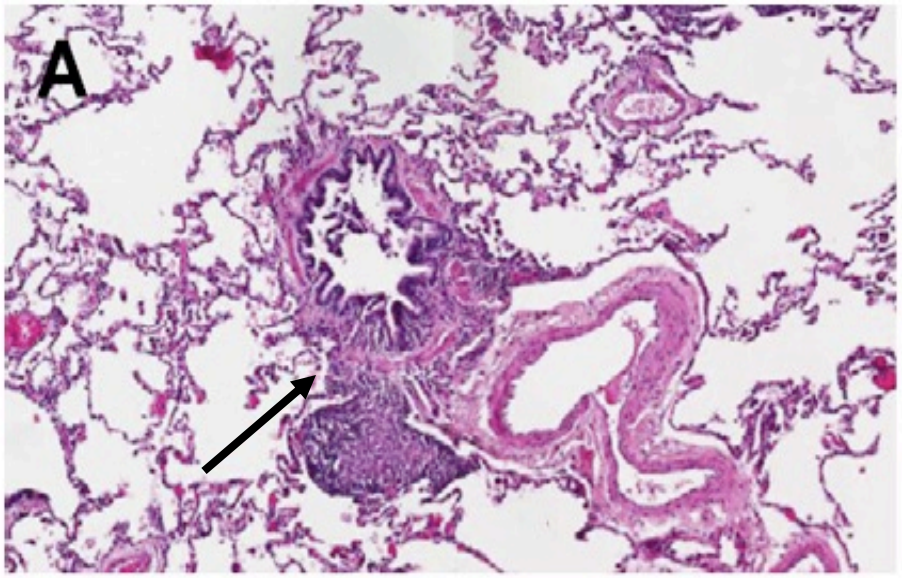
Pathologic features GLILD

- **Granulomas**
  - Giant cells, histiocytes, and lymphocytes
  - Non-necrotizing
  - "Sarcoid-like"
    - Loose vs. well defined granulomas of sarcoid
  - Alone or with LP features



Fernández Pérez ER. Immunol Allergy Clin N Am 2012;32:621-632.

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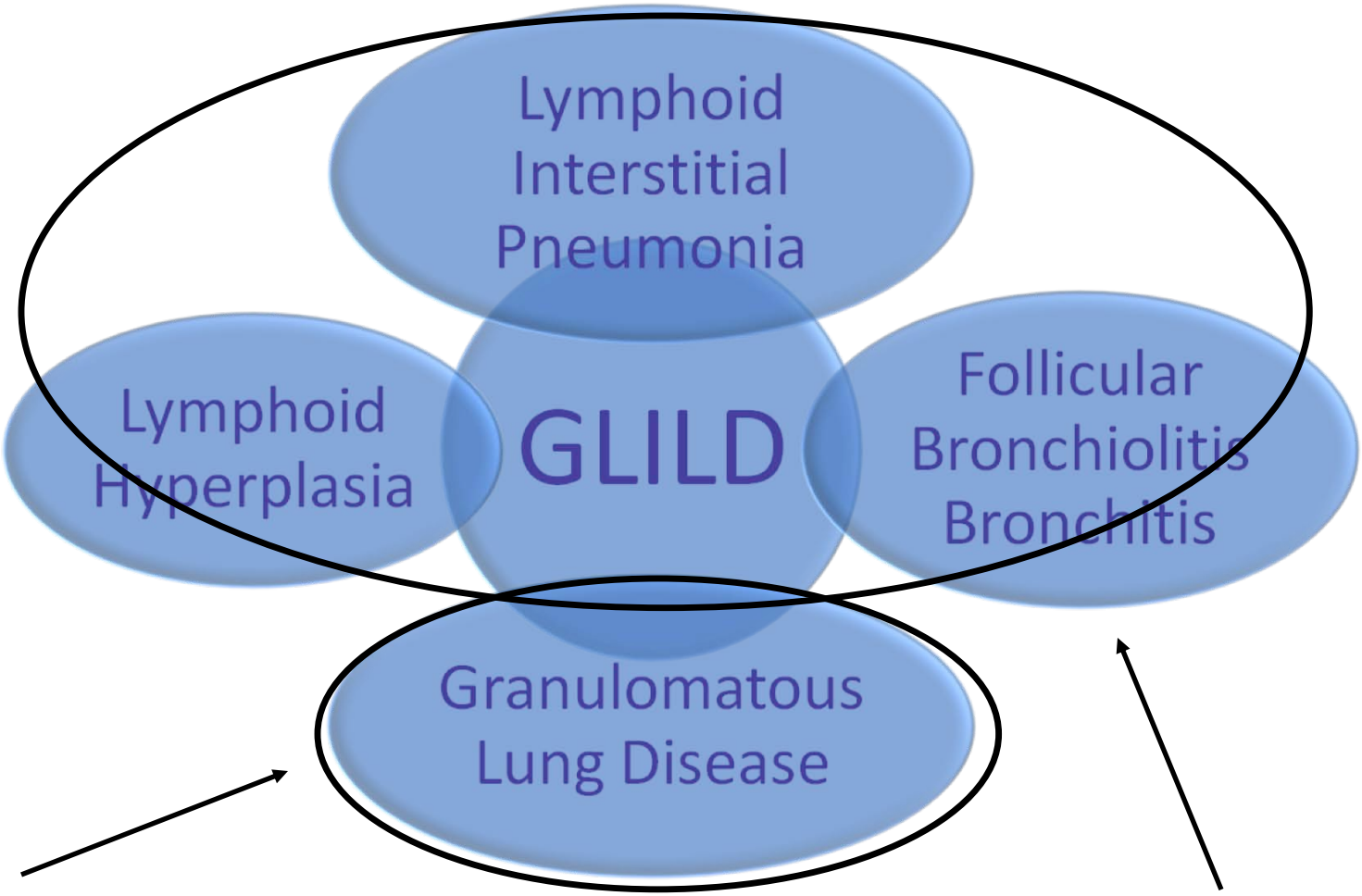
Pathogenesis?



Impaired T-cell function

Disregulated lymphoproliferation

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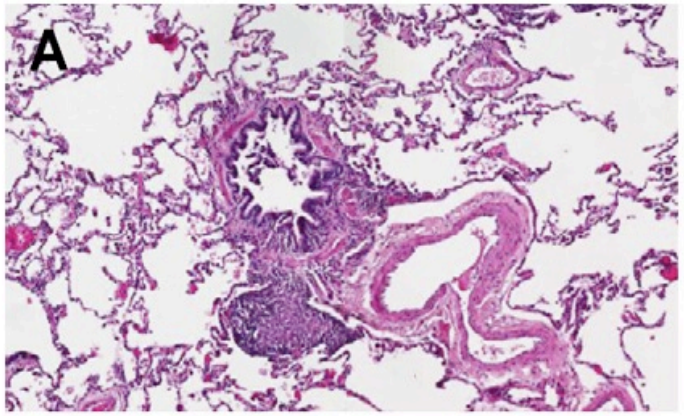
Increased Risk for Granulomas

- Dysregulated T-cell function/cytokine production:
  - ↓ T-cell proliferation to mitogens[1]
  - ↓ CD4+ CD45RA+ naïve T cells[2,3]
  - ↓ CD4+ CD127 low regulatory T cells[3]
  - ↑ CD8+ CD57+ activated T cells[2,3]
  - Associated with TNF +488A allele[2]
  - Associated with autoimmunity[1], splenomegaly, and LAD [2,3,4]
- B-cells
  - Low memory (switched) B-cells



1. Mechanic LJ et al. Ann Intern Med 1997;127:613-617.
2. Mulligan CG et al. J Immunol 1997;159:6236-6241.
3. Boursiquot JN et al. J Clin Immunol 2013;33:84-95.
4. Wehr C, et al. Blood 2008;111:77-85.

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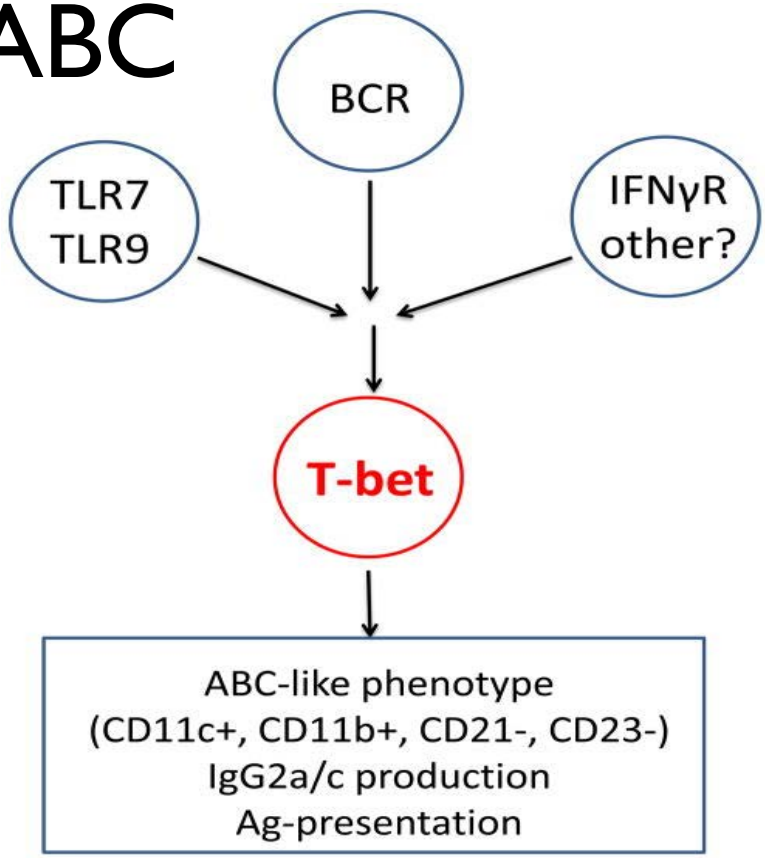
GLILD Lymphoproliferation

- Lymphoproliferation
  - HHV8+
  - B-cell role
    - Case report of tx with rituximab alone → ↑ T-regs
  - Age associated B cells?



ABC



Rutsova K et al. J Imm 2015; 195(5) 1933-37
Wheat WH et al. J Exp Med 2005;202:479-84.
Detkova D et al. Chest 2007;131:1883-89.

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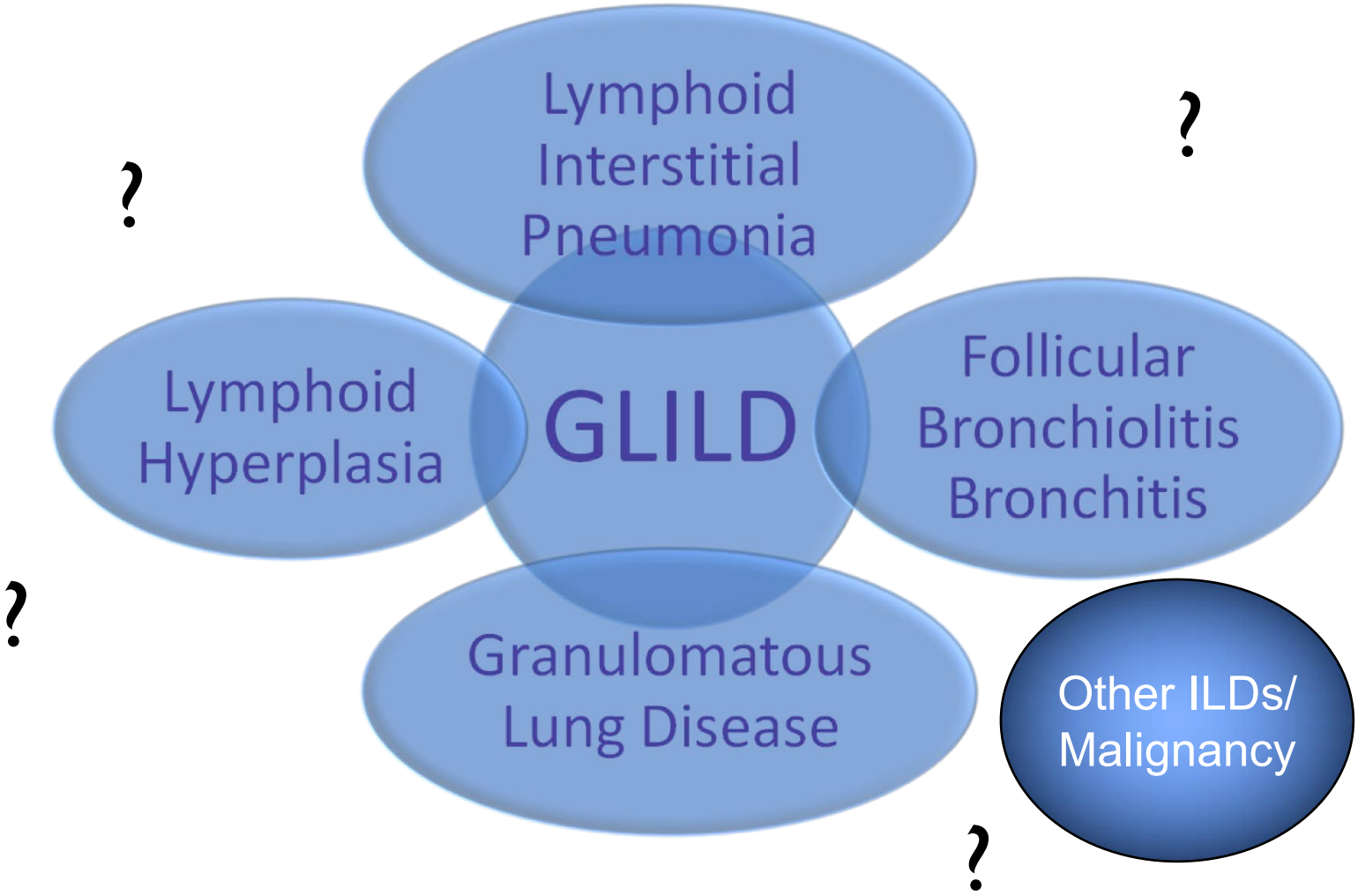
What is our evaluation for presence these diseases?



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ILD

150+ ILDs

Many ILDs share similar symptoms, physiology and radiologic findings

Idiopathic | **Known causes** | **Other forms**

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Making the diagnosis in GLILD, requires that you become a detective:

- History
- Physical Exam
- Pulmonary physiology
- Radiography
- +/- Surgical lung biopsy



Image from: google.com

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Our Evaluation:

- History
  - Symptoms
    - Constitutional/Infectious (malignancy, active infection)
    - Pulmonary (airways disease, ILD)
      - Cough & Dyspnea
    - Gastrointestinal (malabsorption, IBD, infection)
    - Musculoskeletal (polyarthritis)
    - Hematologic (cytopenias)
    - Reticular (LAD/splenomegaly)
  - Medications
  - Occupational & Environmental Exposures
    - Hypersensitivity Pneumonitis

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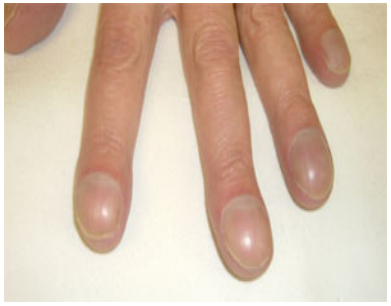
Our Evaluation:

– Physical examination
  - VS: Oxygen saturation (at rest and w/ambulation)
  - SKIN and FINGERS
  - LYMPH: **LAD**
  - PULM: **Crackles**
  - ABD: **Splenomegaly**
  - EXT: **Synovitis, clubbing**



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Our Evaluation:

- Laboratory Testing
  - Immunology:
    - Immunoglobulins
    - Lymphocyte enumeration: T & B cell numbers/subsets and NK cells
    - Post-vaccination antibody response
  - Other:
    - CBC, comprehensive metabolic panel
  - Microbiologic:
    - Evidence of infection?
    - Microbiologic testing w/possible bronchoscopy

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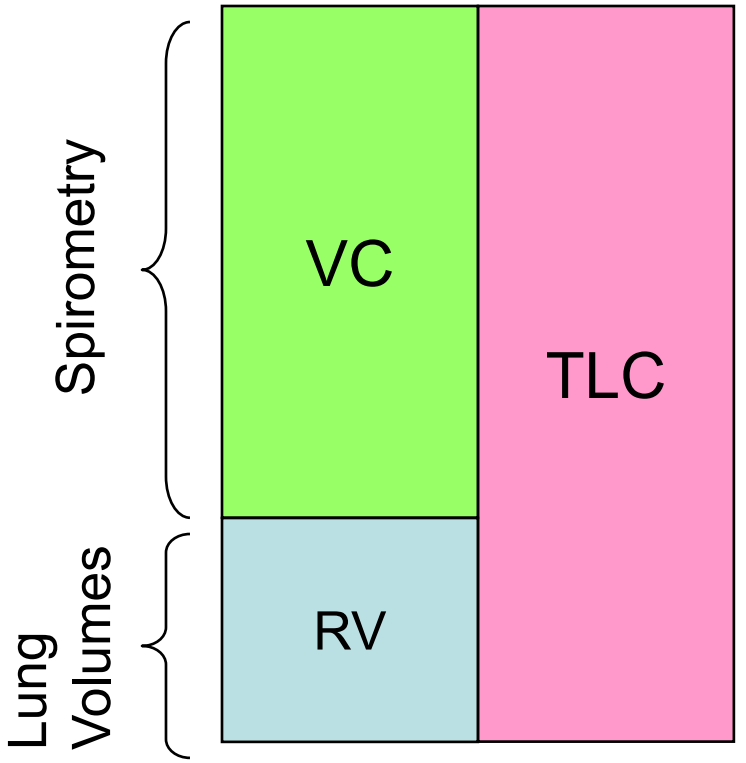
Pulmonary Function Tests

- Lung Volumes & Spirometry
  - **Typically restrictive**
  - Obstructive
  - Mixed patterns
  - Normal
- Diffusion (DLCO)
  - **Typically reduced**
  - Normal
- Normal PFTs do not rule out disease



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Our Evaluation: Pulmonary Evaluation

- Physiology
  - Pulmonary Function Testing
- Gas Exchange
  - ABG and Walk Oximetry
  - Cardiopulmonary Exercise Testing
- Imaging
  - Chest radiographs are not sensitive
  - High-resolution Computed Tomography

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Clinical History …

ORIGINAL RESEARCH

Clinical Predictors of a Diagnosis of Common Variable Immunodeficiency-related Granulomatous-Lymphocytic Interstitial Lung Disease

Amar Mannina[1], Jonathan H. Chung[2], Jeffrey J. Swigris[1], Joshua J. Solomon[1], Tristan J. Huie[1], Zulma X. Yunt[1], Tho Q. Truong[3], Kevin K. Brown[1], Rosane Duarte Achcar[4], Amy L. Olson[1], Christian W. Cox[5], Seth J. Kligerman[6], Douglas Curran-Everett[7], and Evans R. Fernández Pérez[1]

Annals ATS 2016 (7):1042-9.

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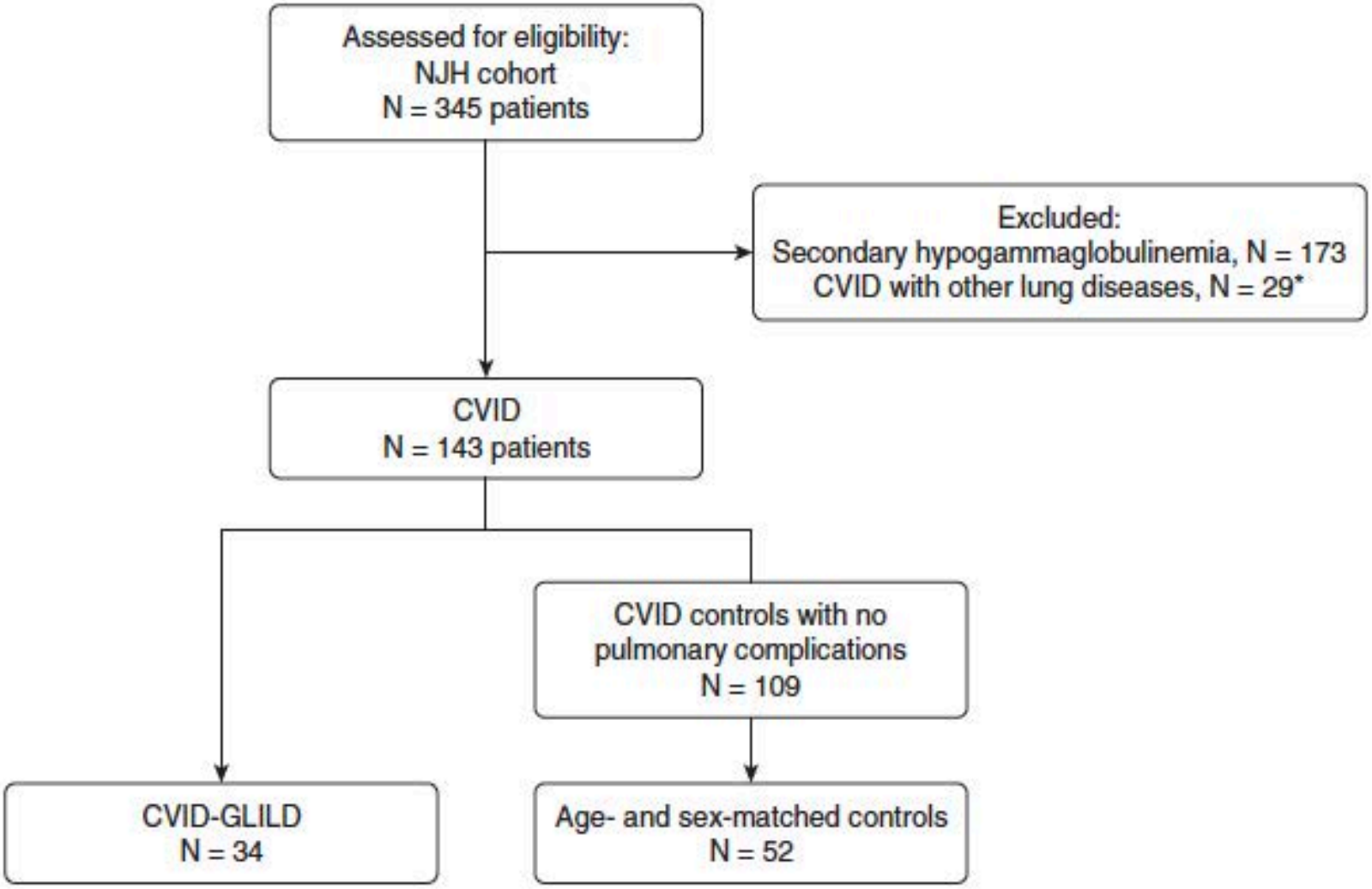
Clinical History …



Annals ATS 2016 (7):1042-9.

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Clinical History …

Variables	Odds Ratio	95% CI	*P* Value
Cytopenia	26.62	6.63–181.40	<0.01
Hypersplenism	31.91	10.05–120.87	<0.01
Polyarthritis	4.91	1.43–19.75	0.01
Dyspnea score*	1.77	1.31–2.55	<0.01
Dosage MIG†	1.01	1.01–1.07	0.01
IgA‡	0.95	0.89–0.98	0.01
IgE	0.99	0.96–1.00	0.09
IgG‡	0.99	0.98–0.99	<0.01
IgM	0.99	0.97–1.00	0.09
IgD^+CD27^+ B cells,§ %	0.95	0.90–0.99	0.02
IgD^-CD27^+ B cells,§ %	0.91	0.82–0.99	0.02
FVC % predicted‖	0.96	0.93–0.98	<0.01
FEV_1, % predicted‖	0.96	0.94–0.99	<0.01
D_{LCO} % predicted‖	0.92	0.88–0.95	<0.01

Mannina et al. Annals ATS 2016 (7):1042-9

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Clinical History …

Variables	Odds Ratio	95% CI	*P* Value
Hypersplenism	23.9	4.5–179.10	<0.01
Polyarthritis	18.7	2.3–206.86	0.01
FVC, % predicted	0.93	0.87–0.98	0.01

Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio
84.5 (68.1–94.8)	90.2 (78.6–96.7)	84.8 (68.1–94.8)	90.2 (78.6–96.7)	8.7 (3.7–20.1)

Mannina et al. Annals ATS 2016 (7):1042-9.

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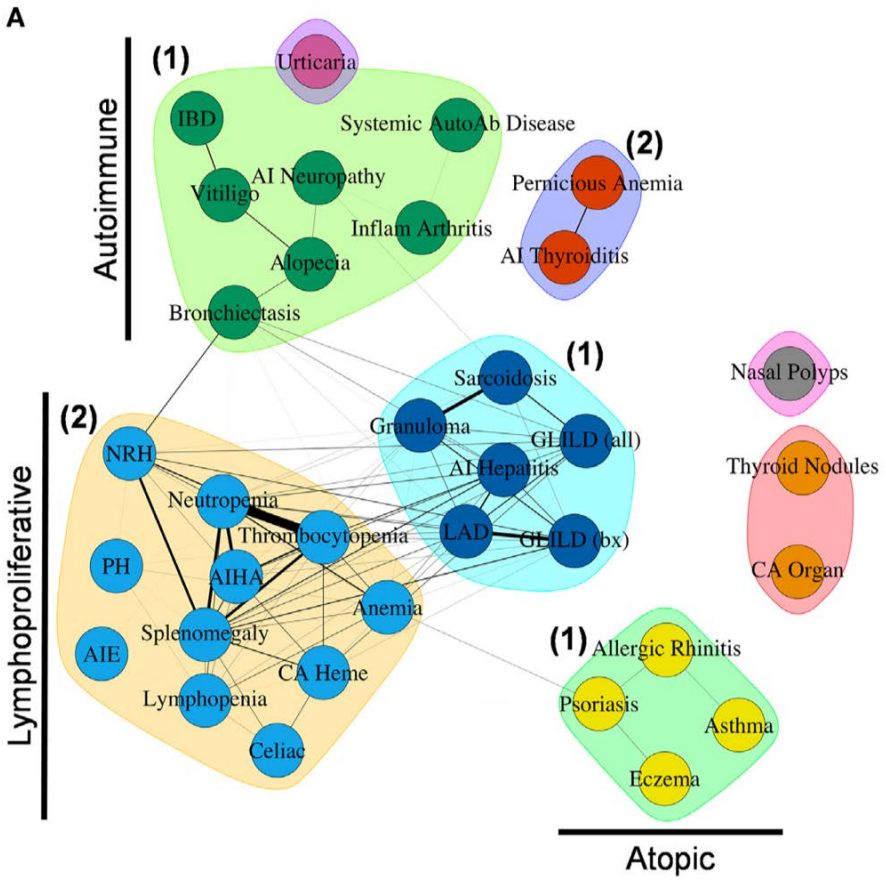
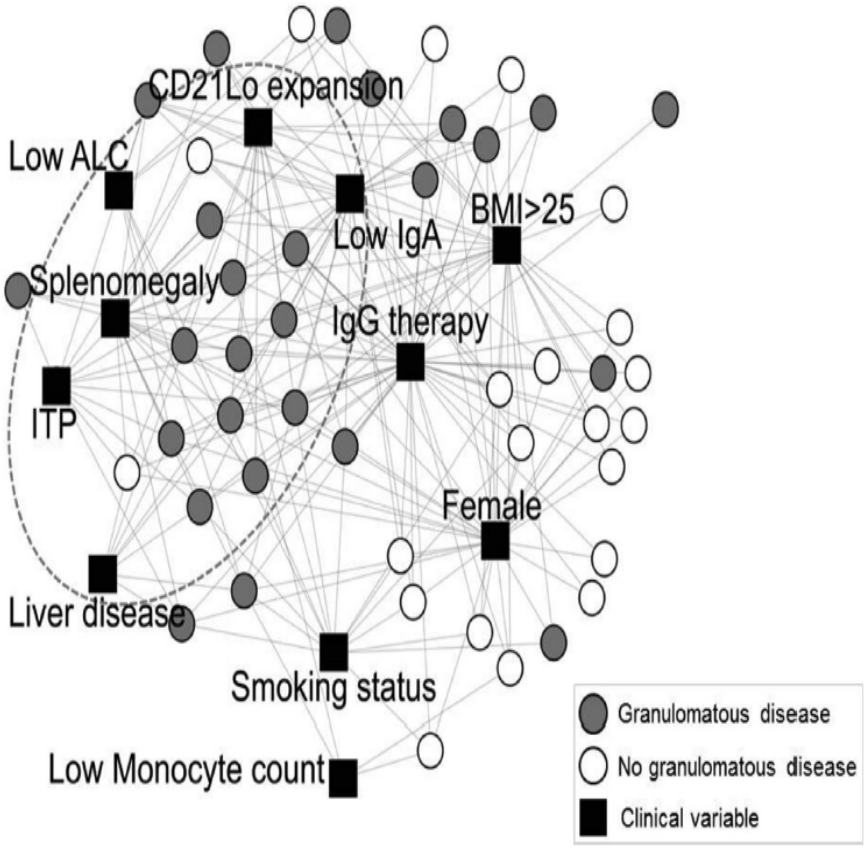
Clinical History …





Farmer J et al. Front Imm 2018 (8):1-15.

Hartono et al. AAAI 2017 (118):614-20.

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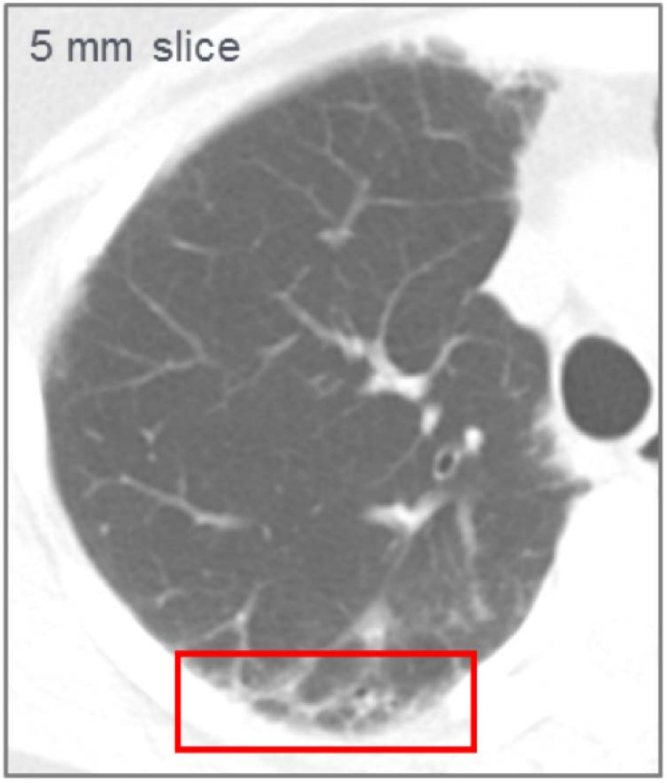
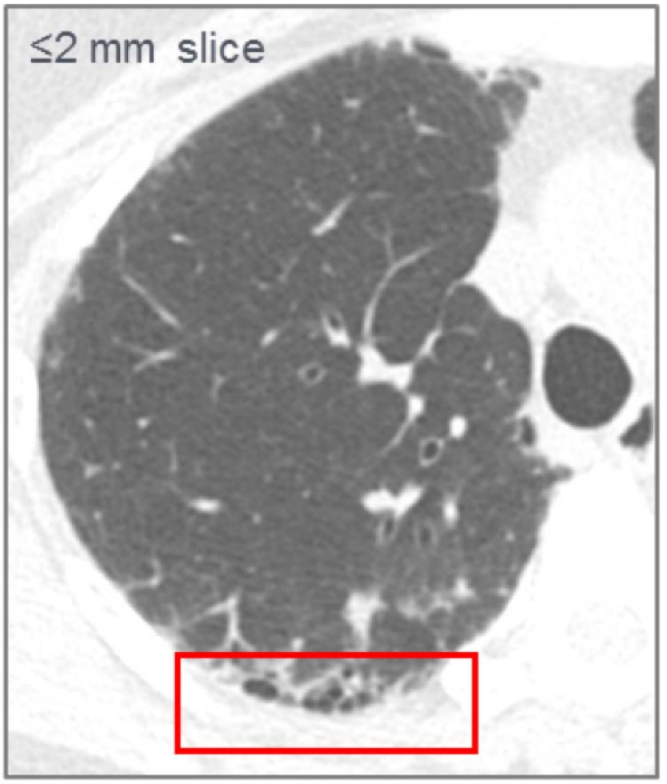
HRCT

- For Quality Imaging: slice thickness ≤ 2 mm, non-contrast, full inspiration, expiration, prone





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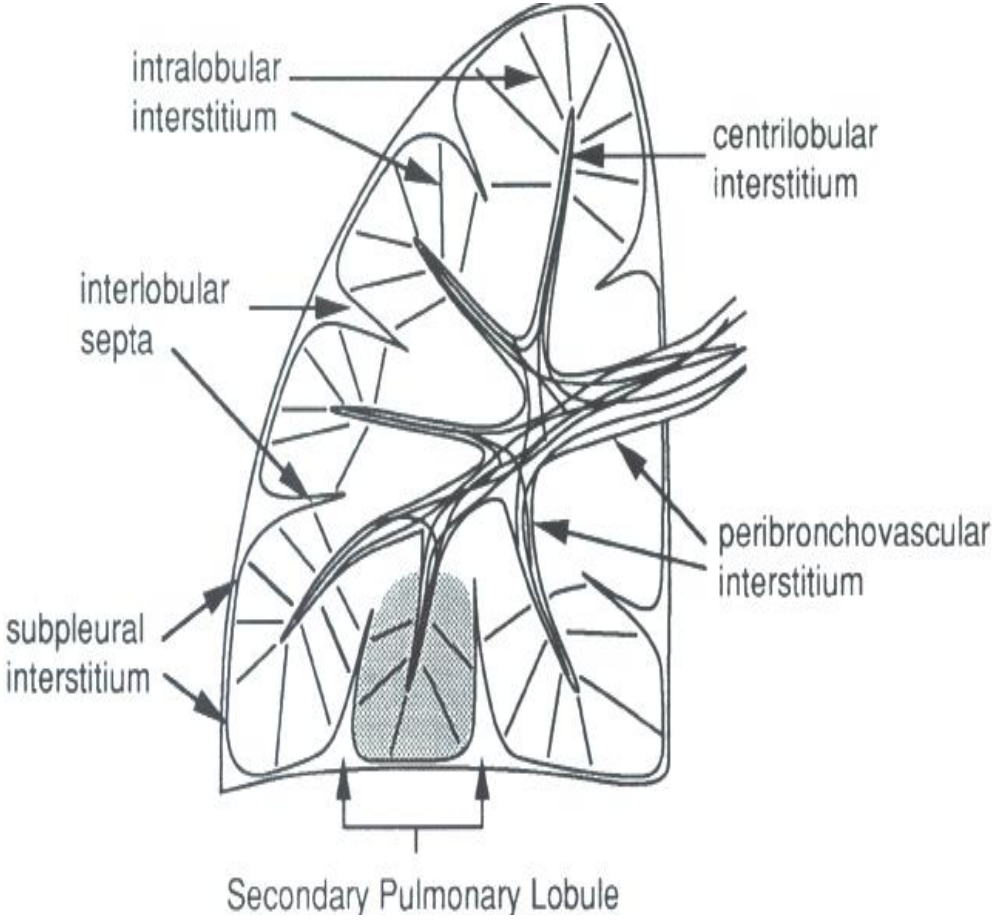
HRCT imaging in GL-ILD

- Micronodules & nodules, randomly distributed
- Patchy ground glass opacities & consolidation
- Interlobular septal thickening
- Mid-lower lung zone predominant



http://www.ufrgs.br/imunovet/molecular_immunology/lungs.html

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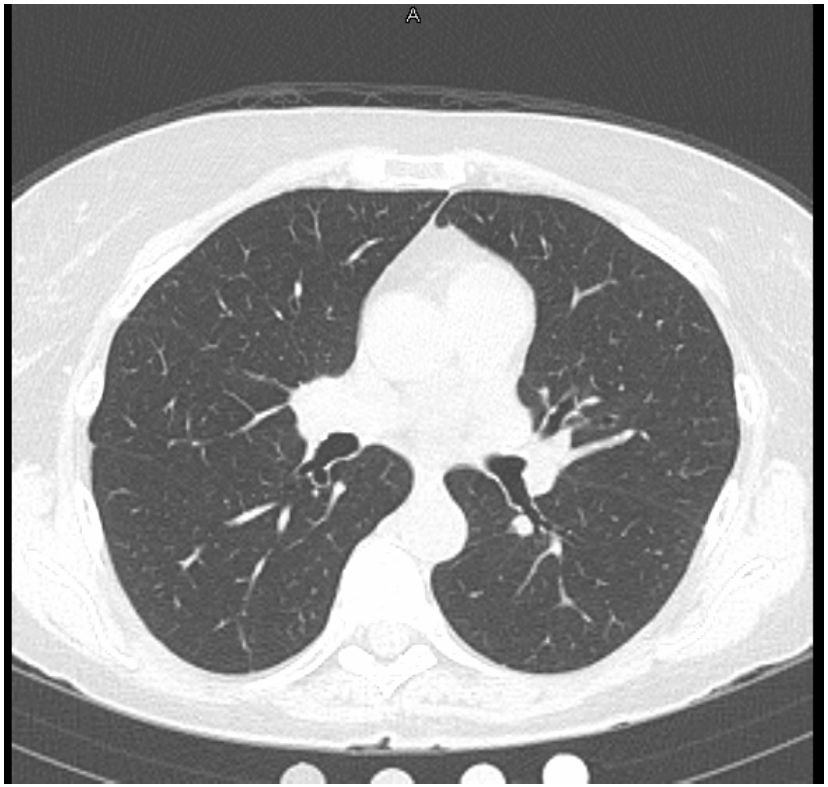
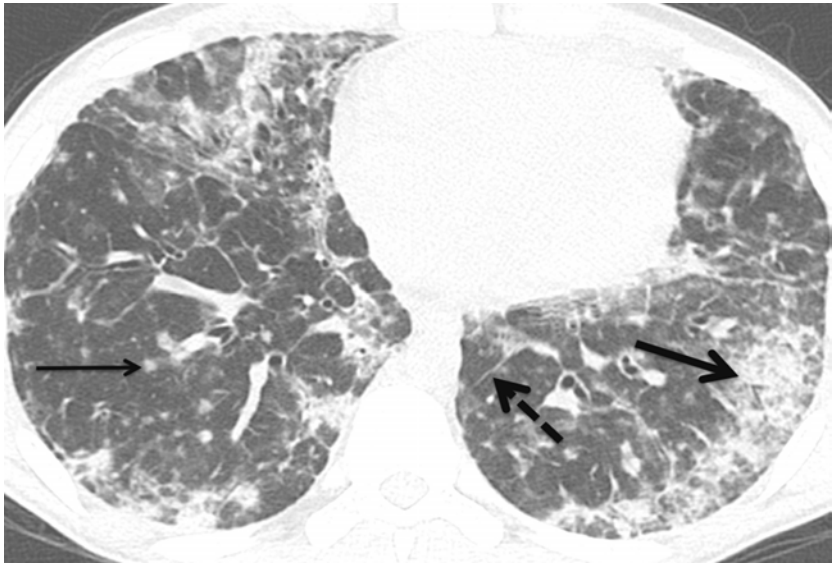
GLILD HRCT Findings

Pattern







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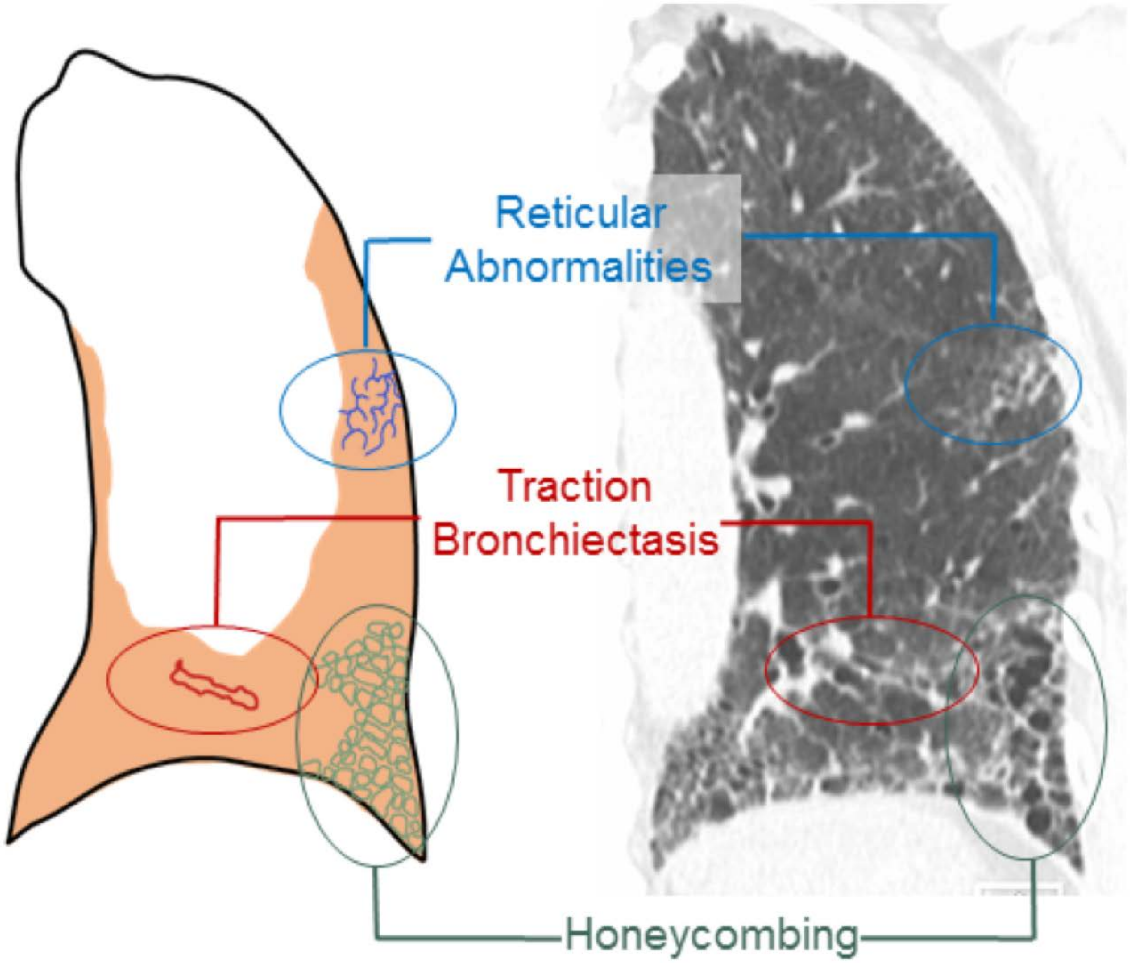
HRCT Findings
Advanced disease



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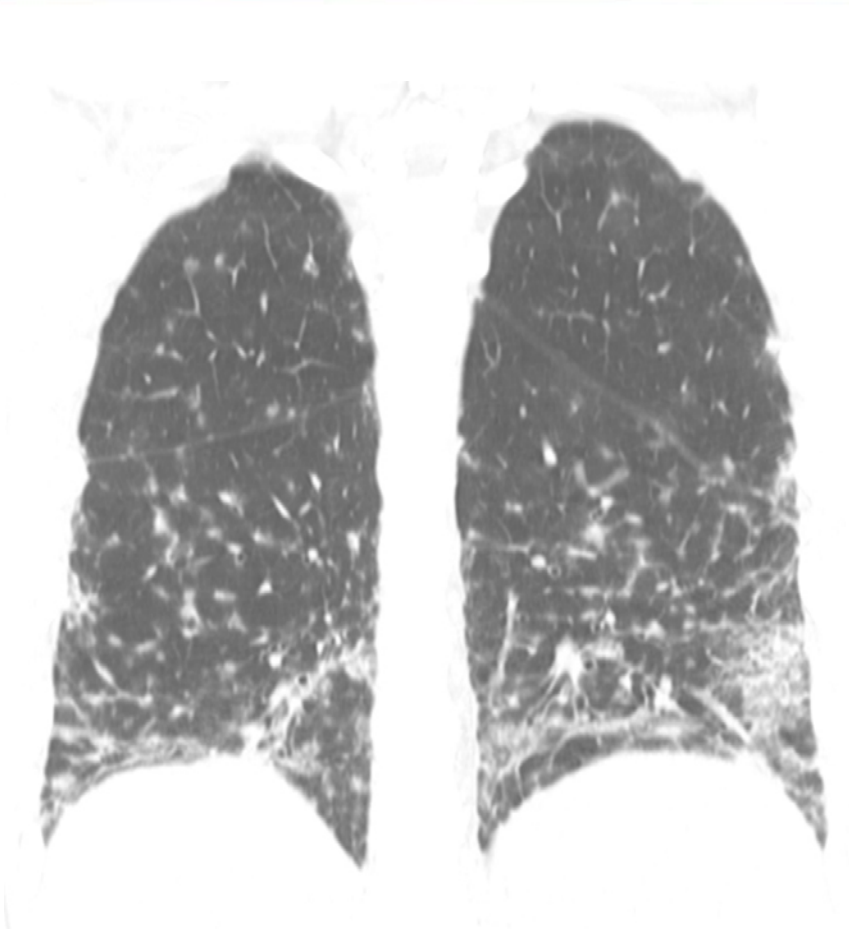
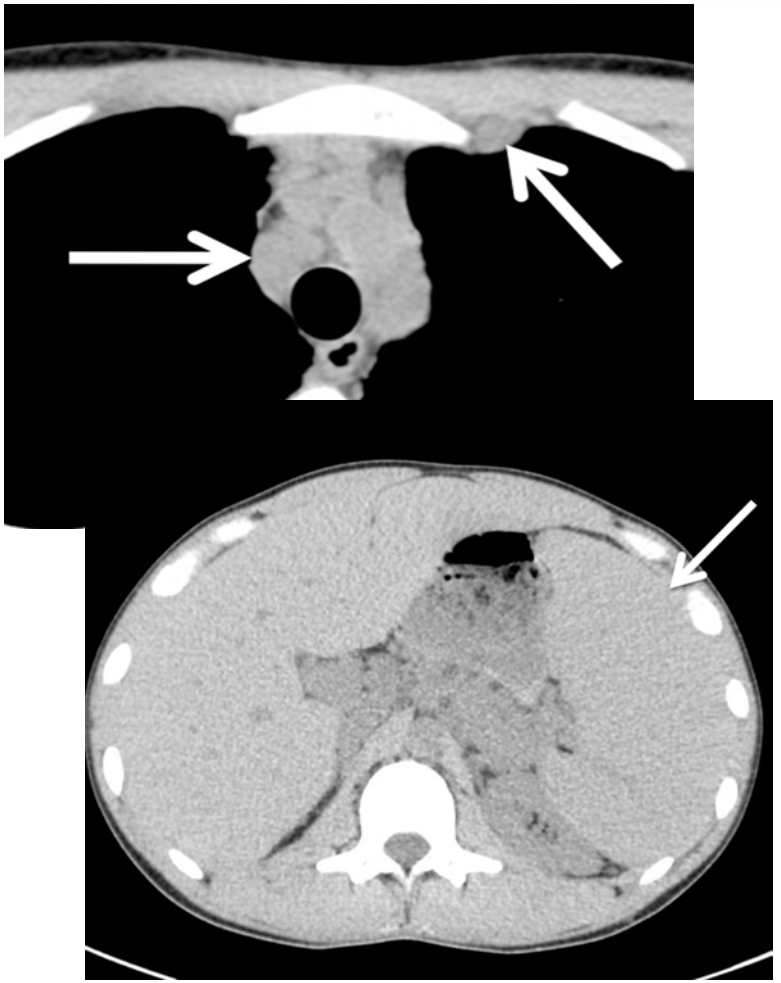
GLILD HRCT
Findings



Distribution



Associated findings

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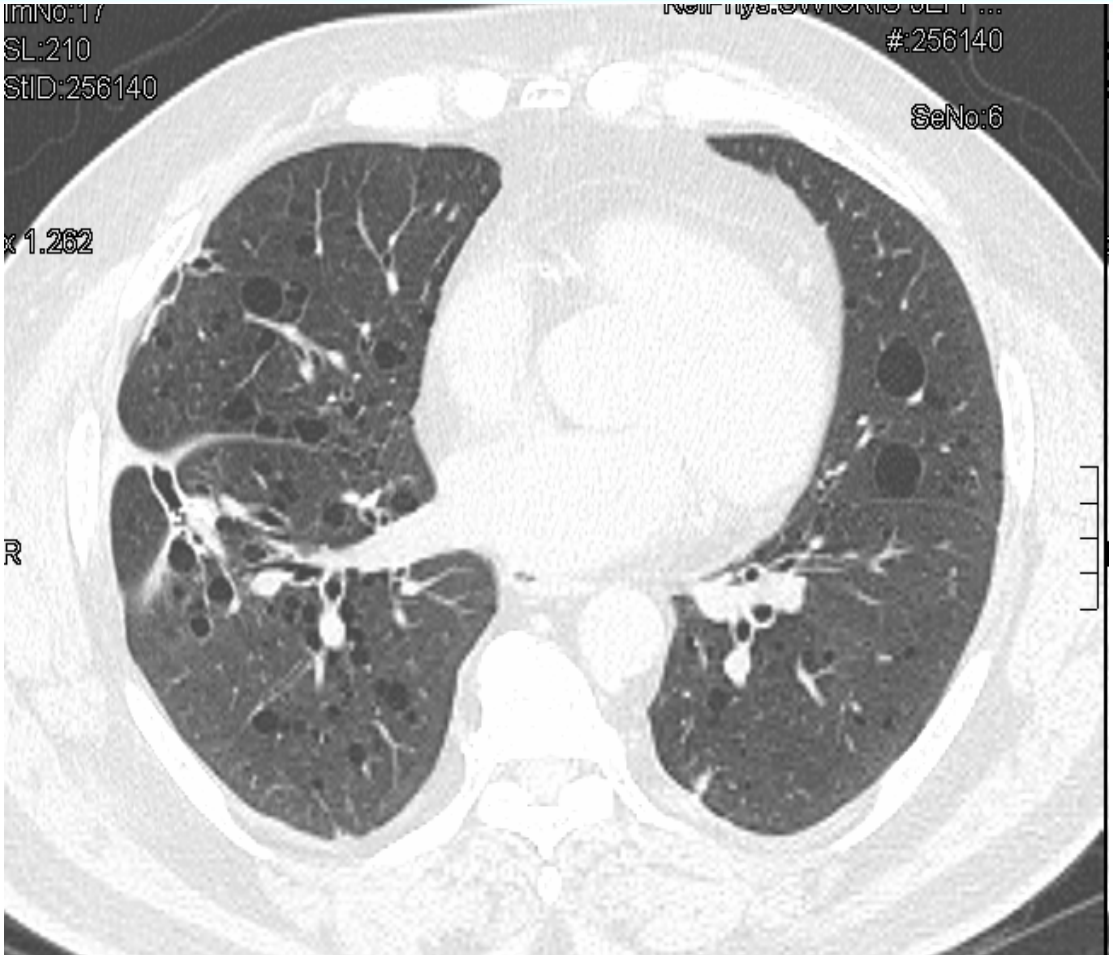
Lymphoid Interstitial Pneumonia HRCT

- Thin cysts
- Bronchovascular and diffuse



Occasionally, we see these cysts in GL-ILD.
More common in autoimmune-associated ILD.

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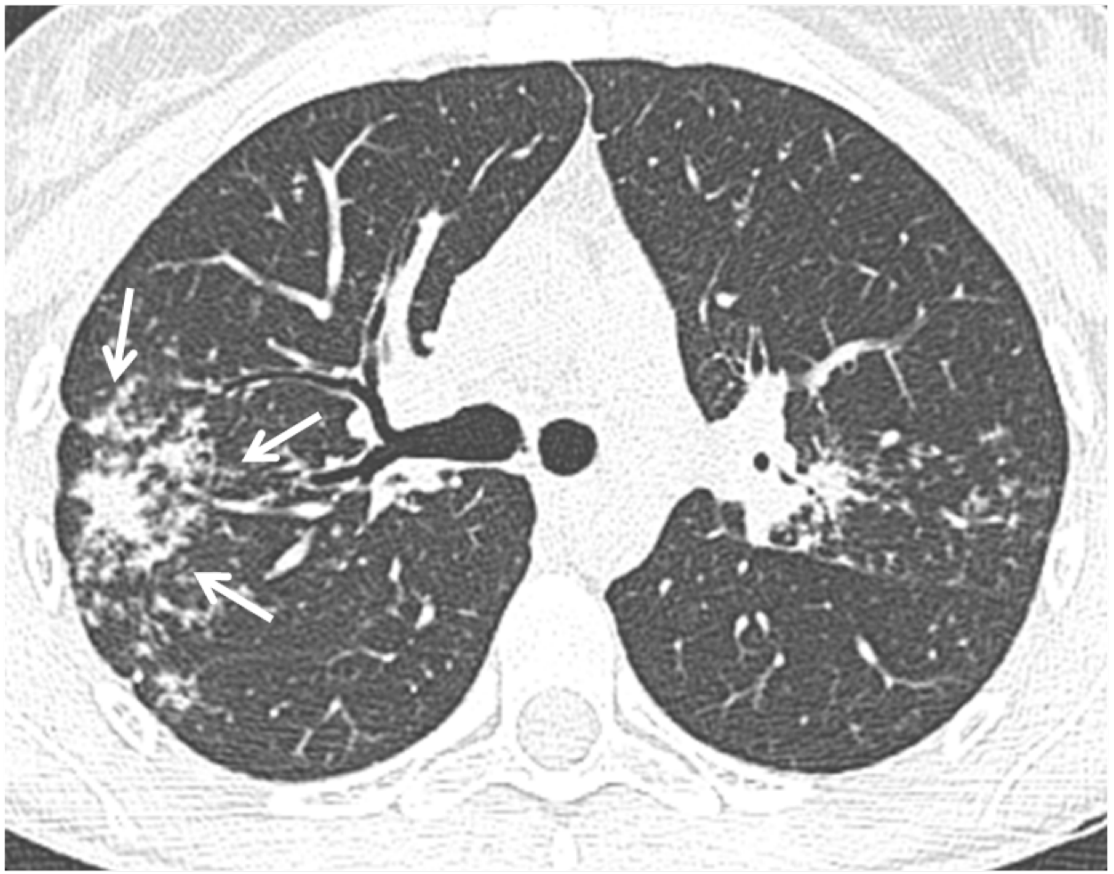
Sarcoidosis HRCT

- Nodules
- Upper lung
- Bronchovascular and perilymphatic





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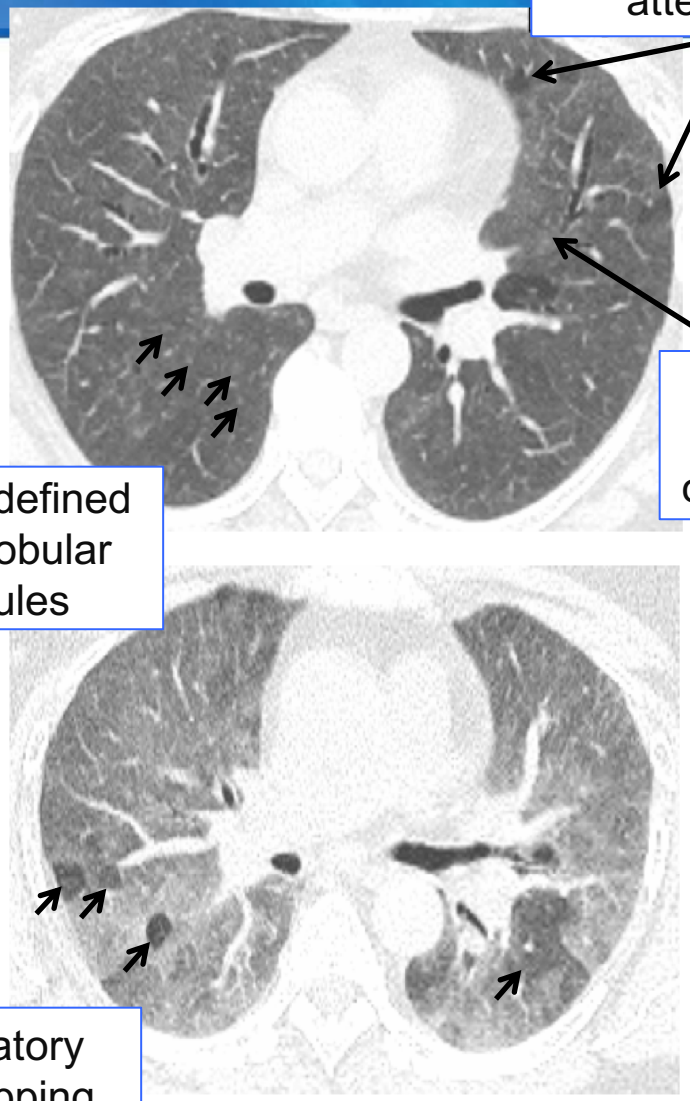
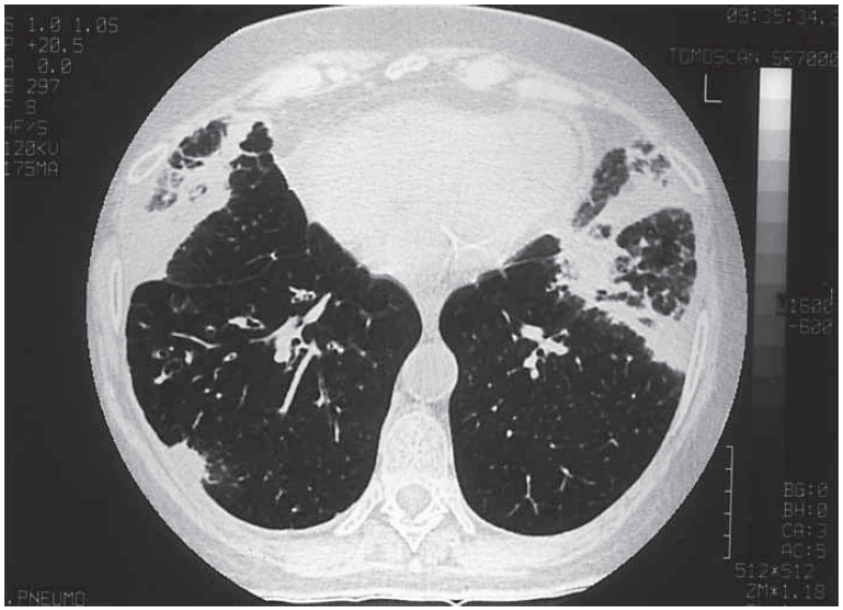
Hypersensitivity Pneumonitis HRCT

- Centrilobular nodules
- Ground glass
- **Mosiacism/Air trapping**
- Rarely reported
- Overlap between
  - CTD & HP
  - CVID & HP



Organizing Pneumonia

- OP looks like PNA
  - Consolidation
  - Air bronchograms
- Injury pattern →



Wislez M et al. Respiration 2000;67:467.
Drakopanagiotakis F, et al. *Am J Med Sci*. 2008;335:34-39.

Table 1. Causes of SOP

- Associated with connective tissue disorders
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Sjogren syndrome
  - Polymyositis-dermatomyositis
  - Polymyalgia rheumatica
  - Systemic sclerosis
  - Behcet's disease
  - Ankylosing spondylitis
  - Mixed connective tissue disease
- Associated with immunological disorders
  - Common variable immunodeficiency syndrome
  - Essential mixed cryoglobulinemia
- Associated with infectious disease
  - Bacterial
    - Streptococcus pneumoniae
    - Legionella pneumophila
    - Mycoplasma pneumoniae
    - Coxiella burnetti
    - Nocardia asteroides
    - Chlamydia pneumoniae
    - Staphylococcus aureus
  - Viral
    - Adenovirus
    - Cytomegalovirus
    - Influenza and parainfluenza
    - Human immunodeficiency virus
    - Herpes virus
  - Fungal
    - Cryptococcus neoformans
    - Pneumocystis jiroveci
  - Parasites
    - Plasmodium vivax
- Associated with aspiration pneumonia
- Associated with radiation therapy for breast cancer
- Associated with organ transplantation
  - Bone marrow
  - Lung
  - Renal
  - Liver
- Drug-related (see Table 2)
- Miscellaneous
  - Inflammatory bowel disease
  - Primary biliary cirrhosis
  - Polyarteritis nodosa
  - Chronic thyroiditis
  - Hematological malignancies (myelodysplastic syndrome, T-cell leukemia, lymphoma)
  - Coronary artery bypass graft surgery
  - Environmental exposure (textile printing dye, house fire, cocaine abuse)
  - Sweet's syndrome

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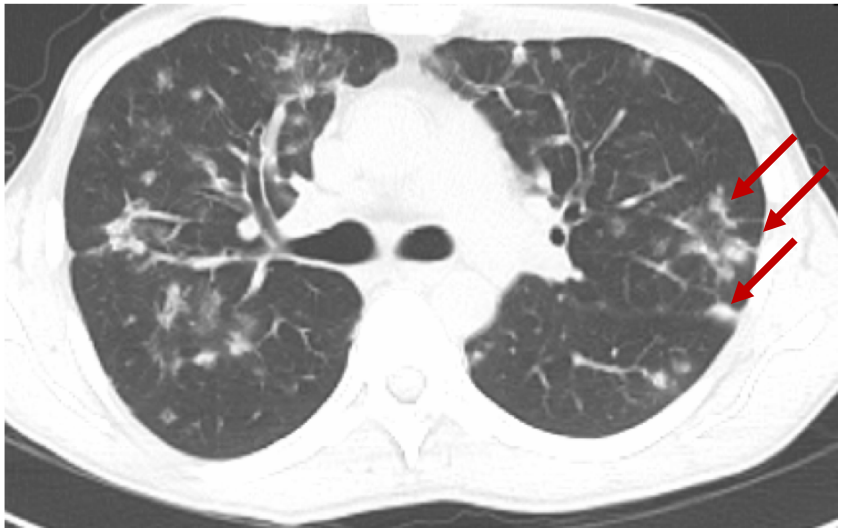
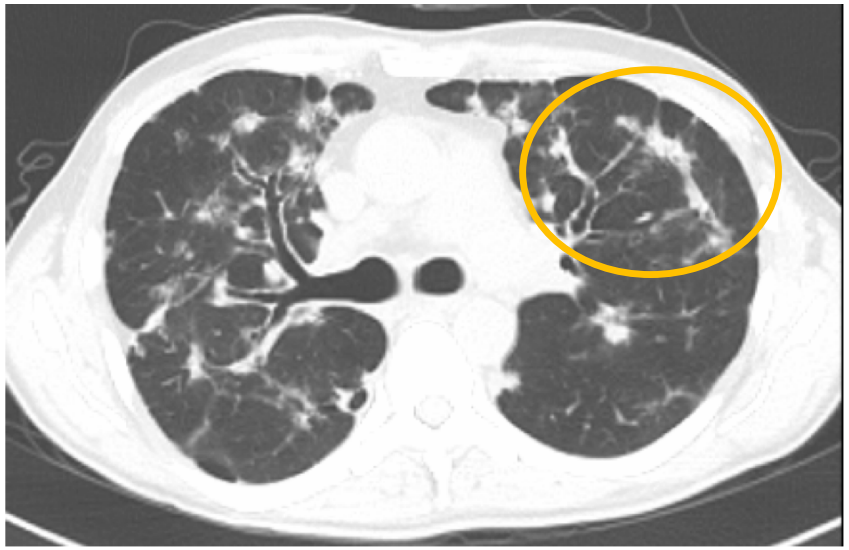
Pulmonary nodules in GLILD





- Mucus plugging
- Organizing pneumonia
- Granulomas
- Benign Lymphoproliferation

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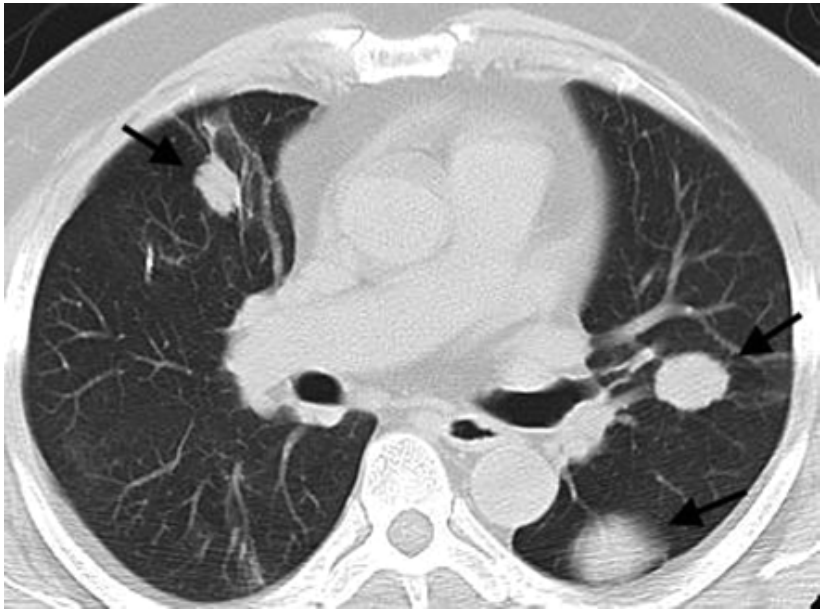
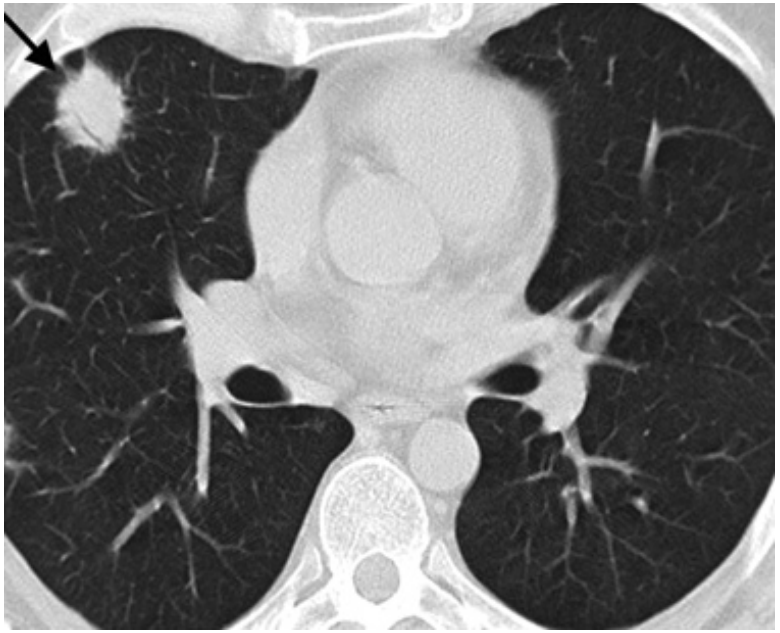
Which is benign vs. malignant?

MALT Lymphoma



Nodular Lymphoid Hyperplasia



Hare SS et al. Br J Radiol 2012;85:848-864.

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Treatment?

- *At present, there is no established standard of care for the treatment of patients with CVID & GLILD*
- Not all patients need to be treated
  - Severity of symptoms/physiologic impairment
  - Pace of disease
  - Comorbid conditions
- If you are going to treat, pre-define what you want to make better
  - Imaging changes ≠ clinical changes

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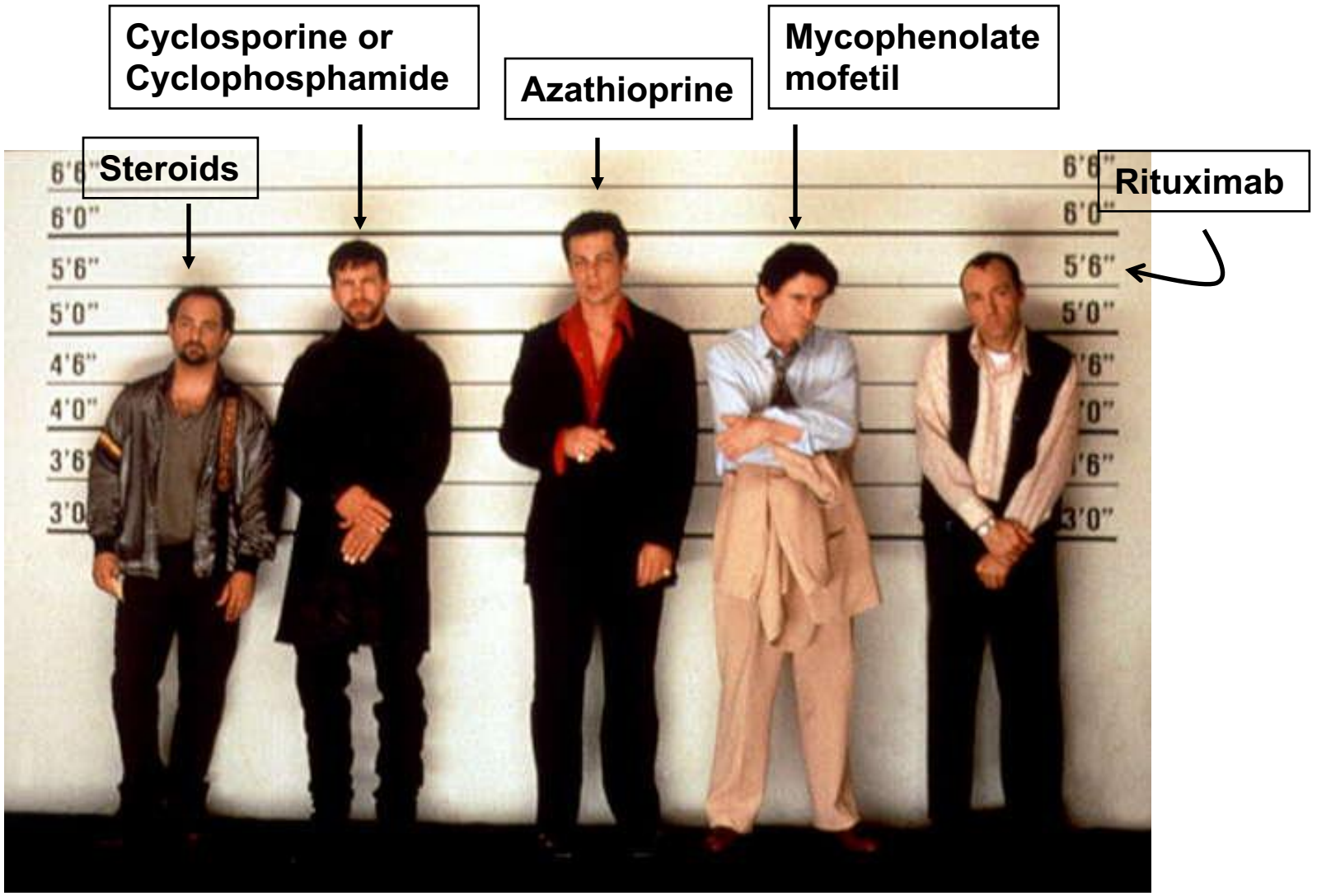
The Usual Suspects…



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Case Reports

- Lymphoproliferative
  - Glucocorticoids
  - Cyclophosphamide
  - Cyclosporine
  - Azathioprine
  - Mycophenolate mofetil
  - Rituximab
- Granulomatous Disease
  - ← Agents +
  - Methotrexate
  - TNF-αantagonists
    - (infliximab)
  - Hydroxychloroquine

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Treatment?

J Clin Immunol (2013) 33:30–39
DOI 10.1007/s10875-012-9755-3

ORIGINAL RESEARCH

Use of Combination Chemotherapy for Treatment of Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD) in Patients with Common Variable Immunodeficiency (CVID)

Nicole M. Chase · James W. Verbsky · Mary K. Hintermeyer · Jill K. Waukau · Aoy Tomita-Mitchell · James T. Casper · Sumit Singh · Kaushik S. Shahir · William B. Tisol · Melodee L. Nugent · R. Nagarjun Rao · A. Craig Mackinnon · Lawrence R. Goodman · Pippa M. Simpson · John M. Routes

Chase NM et al. J Clin Immunol 2013;33:30-39.

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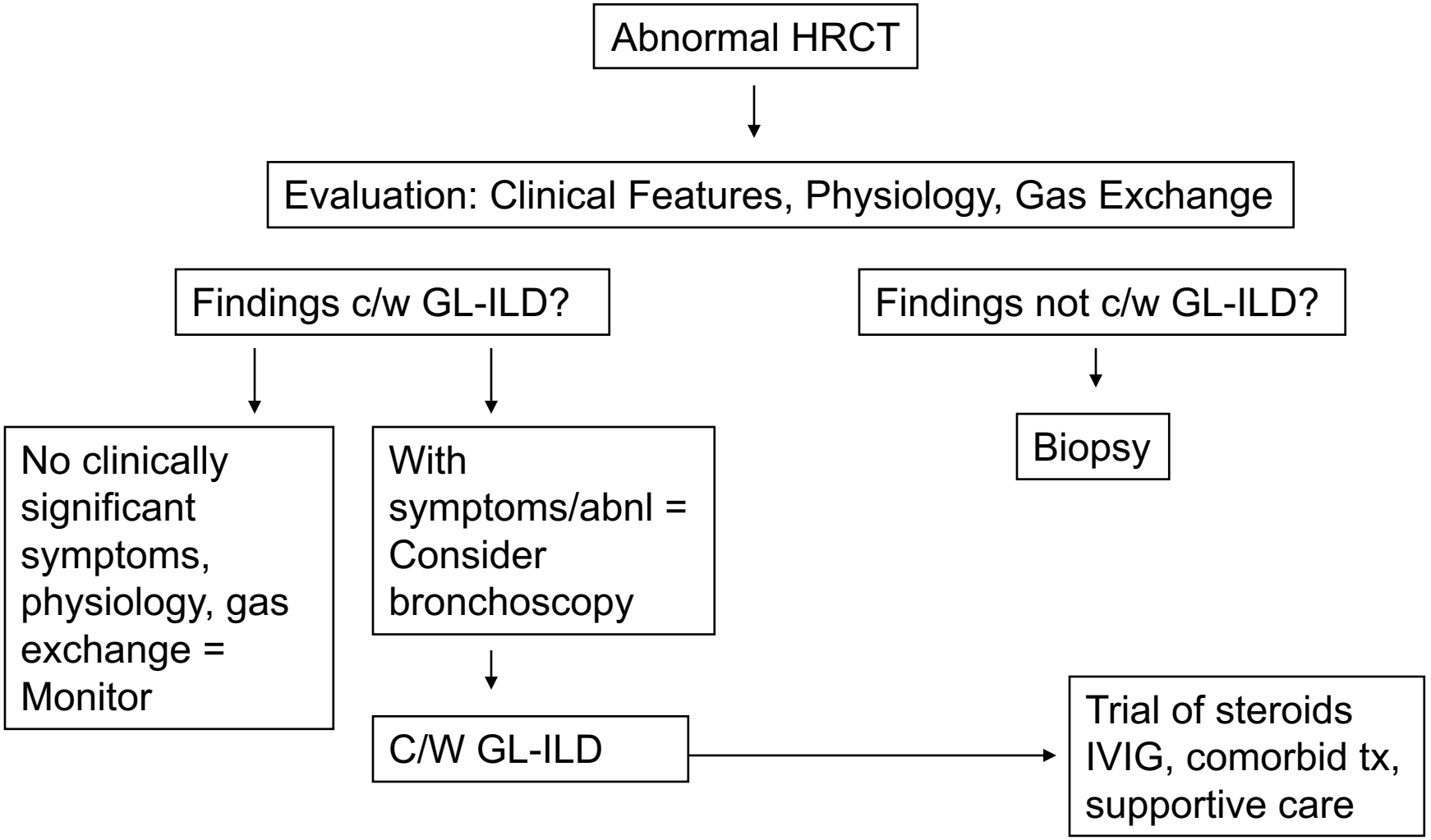
Our Algorithm…



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Case:

- 34 y/o male with ITP, and diagnosis of CVID
- Abnormal HRCT
- He has no pulmonary complaints

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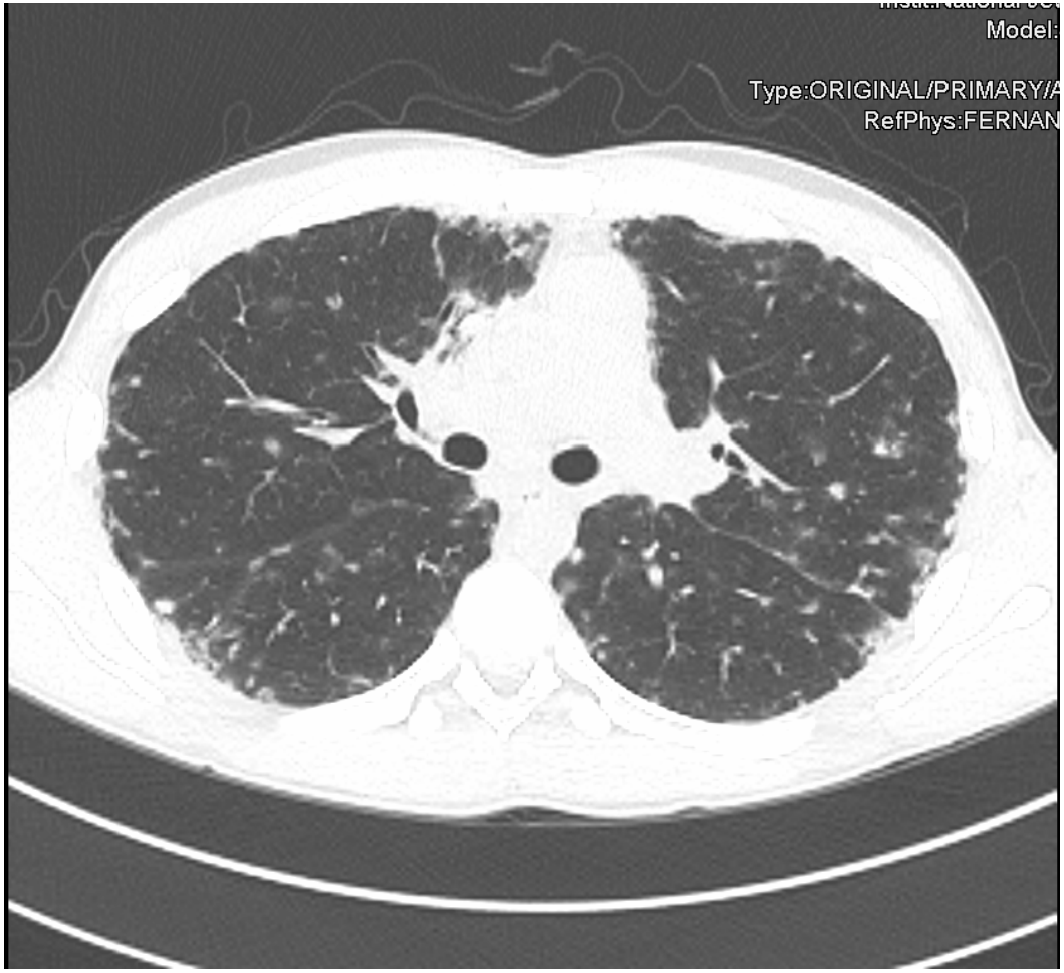
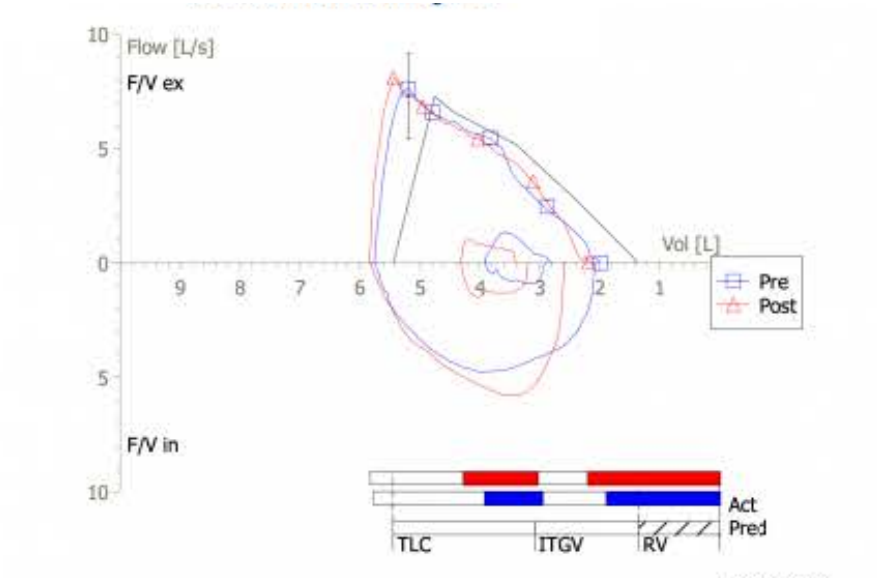
HRCT



Pulmonary Function Tests



Lung Volumes			06/06/11 03:35:56PM			06/06/11 03:49:55PM		
			Pred	Baseline	%Pred	Post	%Pred	%Change
TLC	[L]		5.68	5.78	102	5.84	103	1
FRC-PL	[L]		3.09	2.96	96	3.04	98	3
RV	[L]		1.36	1.89	139	2.21	163	17
Forced Expiration								
		LLN	Pred	Baseline	%Pred	Post	%Pred	%Change
FVC	[L]	3.35	4.10	3.74	91	3.63	88	-3
FEV 1	[L]	2.91	3.54	3.54	100	3.48	98	-2
FEV 1 / FVC	[%]	76	86	94		96		2
Additional Studies								
			Pred	Baseline	%Pred	Post	%Pred	%Change
Raw	[cmH2O*s/L]		1.42	1.93	136	1.58	112	-18
sGaw	[1/(cmH2O*s)]		0.228	0.175	77	0.207	91	18
DLCO SB	[ml/min/mmHg]		31.74			31.75	100	
VA	[L]		5.26			5.10	97	
DLCO/VA	[ml/min/mmHg/L]		6.03			6.22	103	

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Gas Exchange

- No desaturation on walk oximetry
- CPET study suggesting no ventilatory or gas exchange abnormalities; possible deconditioning

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Case:

- A/I is starting IVIG therapy.
- From a pulmonary perspective, for treatment:
  - A.) Monitor Closely
  - B.) Bronchoscopy
  - C.) Surgical Lung Biopsy
  - D.) Empiric Trial of Glucocorticoids

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Summary

- In CVID …
  - GL-ILD is common
  - GL-ILD portends a worse prognosis
  - If we see granulomatous disease or lymphoproliferative disease, we check immunoglobulin levels
- ILD requires a …
  - Multidisciplinary diagnosis
  - Clinician(s), Radiologist, Pathologist
- CVID & ILD
  - Multidisciplinary treatment
  - Frequent re-evaluation

Thank you