Diagnostic approach to Interstitial lung diseases. Is biopsy necessary?

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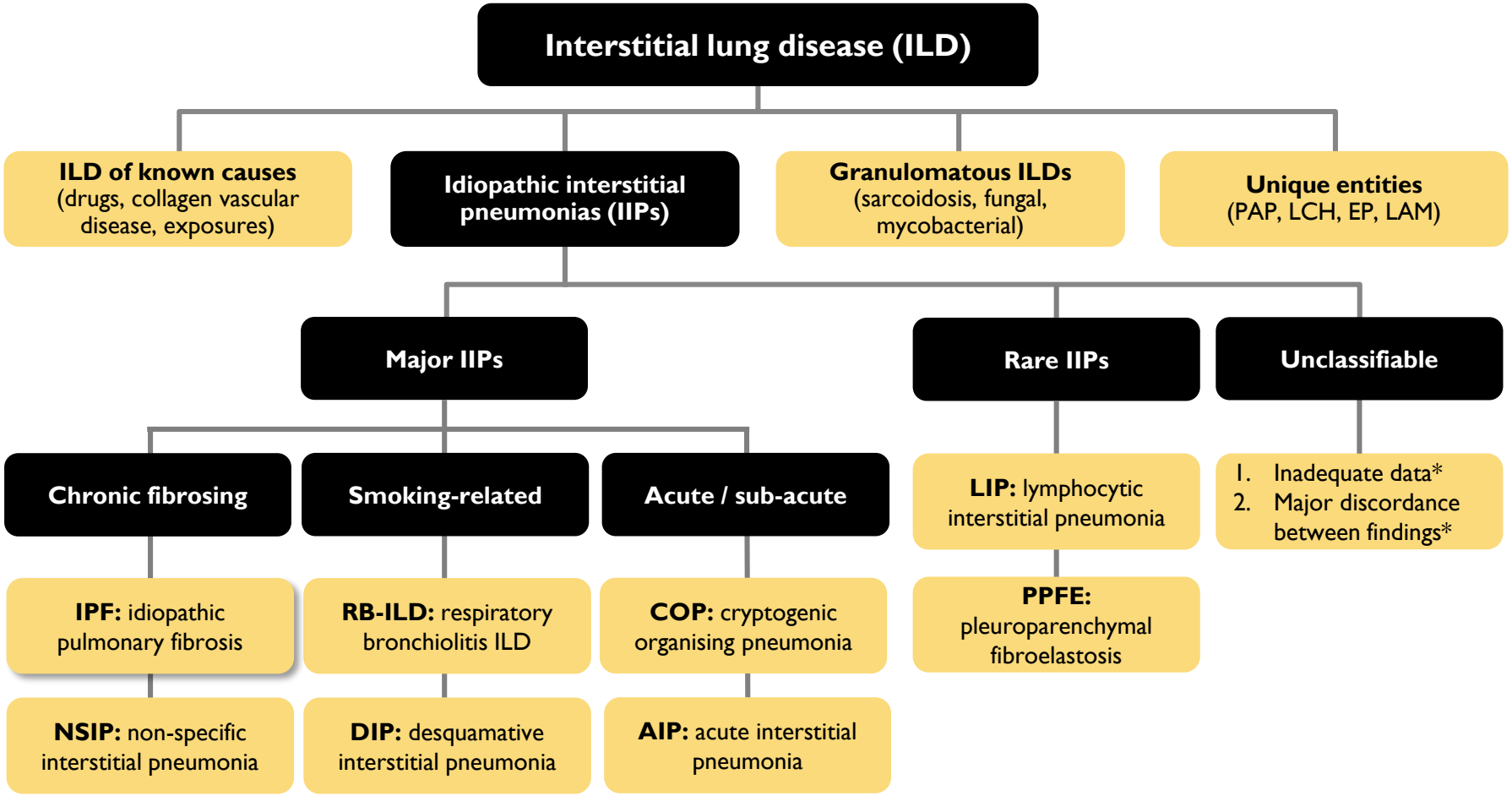
In a word

- **YES!!**
- But:
  - With safety for the patient
  - Competent pathologist
  - Multidisciplinary team

Idiopathic pulmonary fibrosis is the commonest IIP



*Clinical, radiological, pathological

EP, eosinophilic pneumonia;
LAM, lymphangioleiomyomatosis;
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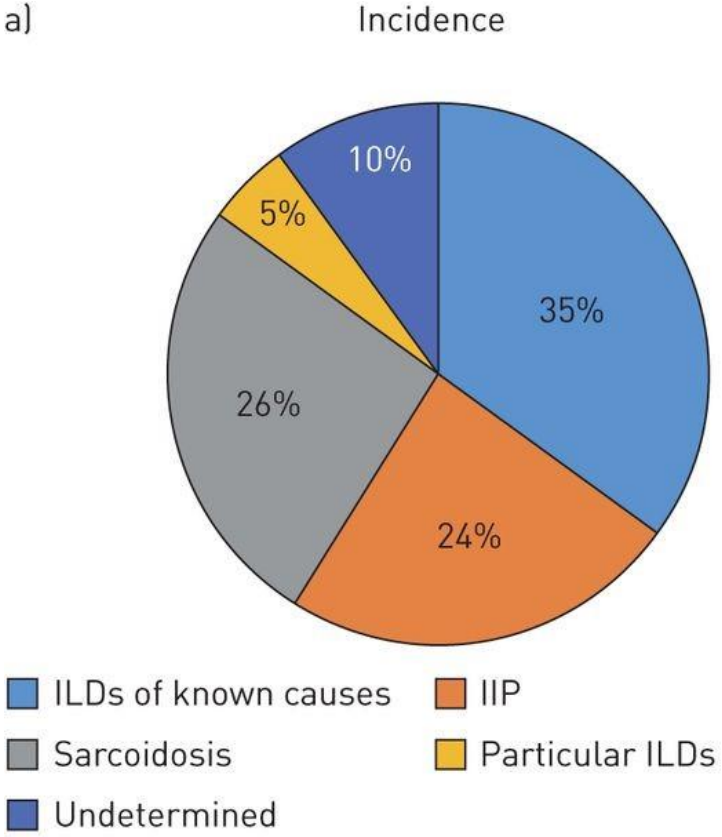
Incidence of Interstitial Lung Diseases



SMOKING/DRUG HISTORY

15. Have you ever smoked cigarettes? ☐ Yes ☐ No

If "Yes", answer A-D. If "No", move to question 16.

A. Do you smoke cigarettes now? (*at least one cigarette a day for the past year*) ☐ Yes ☐ No

B. What year did you start smoking? _____

C. What year did you stop smoking? _____ (if you are still smoking, mark N/A) ☐ N/A

D. On average, how many cigarettes do/did you smoke per day? _____

16. Have you ever lived in the same house with someone who smoked regularly for at least one year? ☐ Yes ☐ No

17. Have you ever smoked one or more cigars a week for a year? ☐ Yes ☐ No # of years: ____
If yes, list the number of years you have smoked cigars.

18. Have you ever smoked a pipe (more than 12 oz tobacco in your life)? ☐ Yes ☐ No # of years: ____
If yes, list the number of years you have smoked pipes.

19. Have you ever smoked marijuana? ☐ Yes ☐ No

20. Have you ever used cocaine? ☐ Yes ☐ No

21. Have you ever used intravenous drugs? ☐ Yes ☐ No

ENVIRONMENTAL HISTORY

22. The following questions ask about specific exposures you may have had in your home environment. If you were REGULARLY OR REPEATEDLY exposed to any of the following in the THREE YEARS BEFORE your breathing problem started, answer "Yes" and provide any additional information requested.

A. Humidifier ☐ Yes ☐ No

B. Air cleaner/purifier ☐ Yes ☐ No

C. Steam sauna/steam shower ☐ Yes ☐ No

D. Indoor hot tub ☐ Yes ☐ No

E. Swamp cooler ☐ Yes ☐ No

F. Water damage or mold/mildew in the home ☐ Yes ☐ No

G. Asbestos ☐ Yes ☐ No

H. Down pillows or comforters ☐ Yes ☐ No

I. Pigeons,parakeets or other birds ☐ Yes ☐ No Kind: _____

J. Dogs, cats, rabbits, gerbils, hamsters or guinea pigs in house ☐ Yes ☐ No Kind: _____

K. Does the house or office smell musty? ☐ Yes ☐ No

L. Has there been a history of flooding? ☐ Yes ☐ No

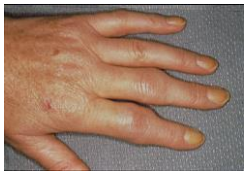
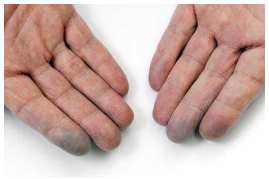
M. Is there water damage on the walls or ceilings? ☐ Yes ☐ No If yes, take digital pictures

Structured Questionnaire

Search for:

- Environmental exposure (work, home, hobbies)


- Connective tissue disease

- Familial disease (other affected family members)

- Drug exposure
  - Anti-cancer
  - Antirrheumatics
  - Antibiotics
  - Amiodarone

Diagnostic tests

- BAL
- Transbronchial biopsy
- Cryobiopsy
- E-BUS
- Surgical lung biopsy

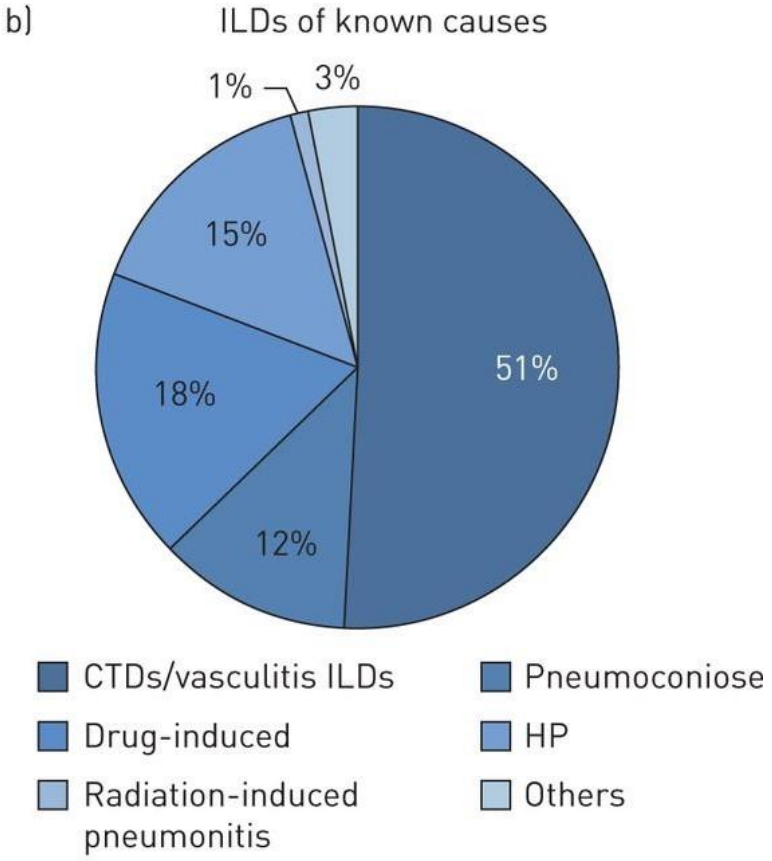
Bronchoscopy

Pathognomonic BAL

Finding	Diagnosis
Microorganisms	Infection
Increasing red blood cells with each successive aliquot	Alveolar hemorrhage/DAD
Malignant cells	Cancer
Milky fluid (+) PAS	Alveolar proteinosis
In vitro proliferative response to beryllium	Berylliosis

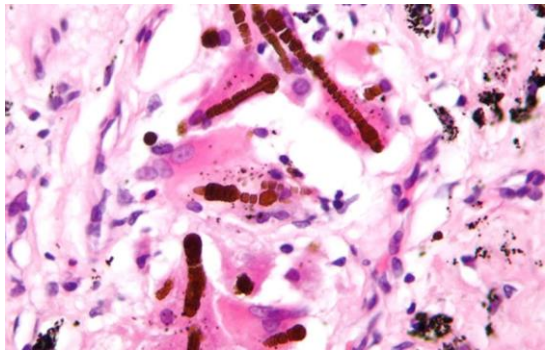
Am J Respir Crit Care Med Vol 185, Iss. 9, pp 1004–1014, May 1, 2012

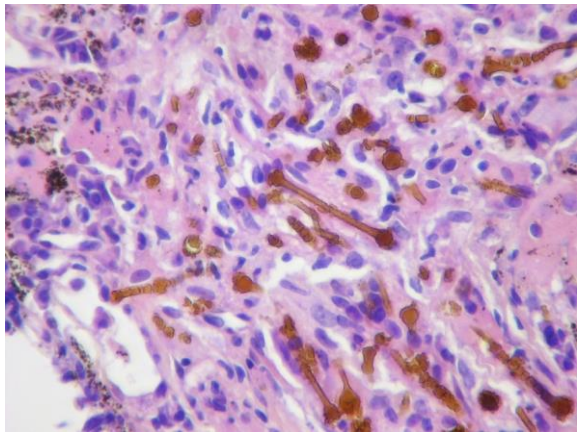
Incidence of ILD's of known causes

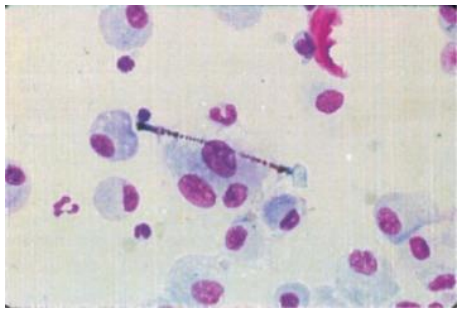


ERJ 2017;50:1602419

Pneumonoconioses







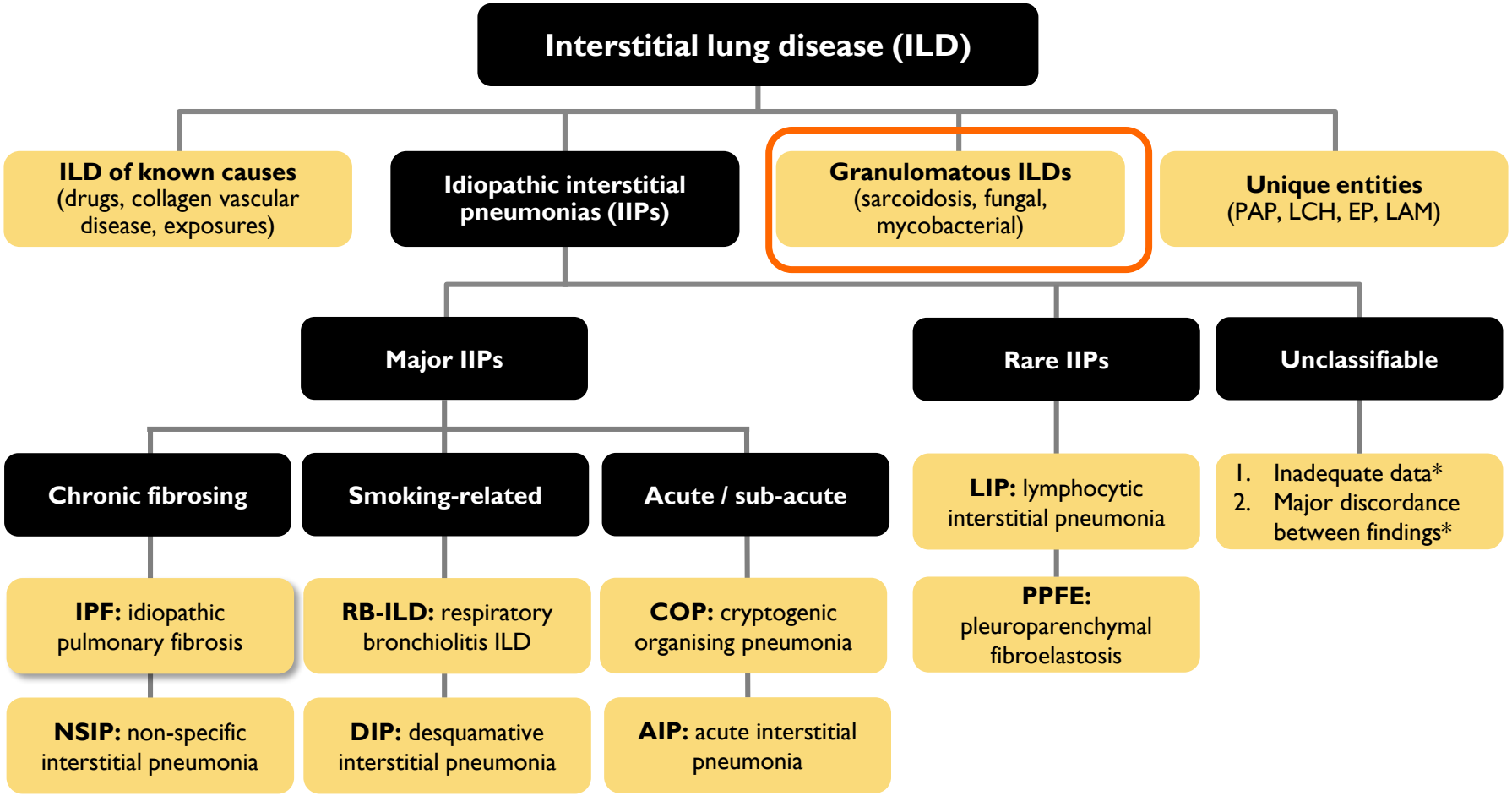
>1 asbestos fibre/ml BAL corresponds to 100 fibres/cm^3 of lung parenchyma

Positive lymphocyte transformation test to specific beryllium antigen → chronic beryllium disease

Ferruginous bodies → asbestosis

Dust particles by polarized microscope → silicosis

Idiopathic pulmonary fibrosis is the commonest IIP



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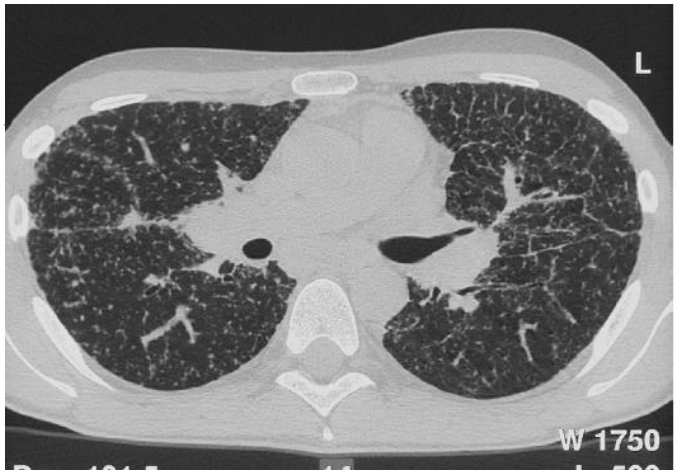
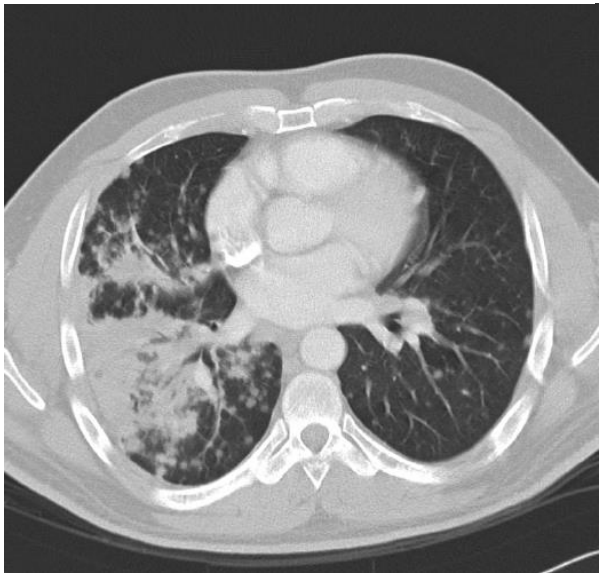
Sarcoidosis



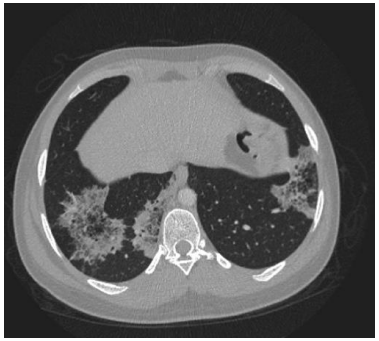
Variable lymphocytosis

Lymphocytic cellular pattern
>15% lymphocytes
Sarcoidosis
Nonspecific interstitial pneumonia (NSIP)
Hypersensitivity pneumonitis
Drug-induced pneumonitis
Collagen vascular diseases
Radiation pneumonitis
Cryptogenic organizing pneumonia (COP)
Lymphoproliferative disorders



$CD_{4/8}$>3,5:
Sensitivity: 52%, specificity: 94%

Lymphocytes>35%
Sarcoidosis
Hypersensitivity pneumonitis
Lymphoproliferative
Drug-induced ILD
Berylliosis



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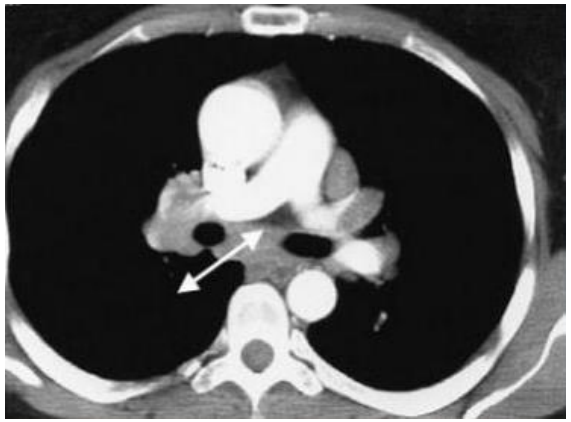
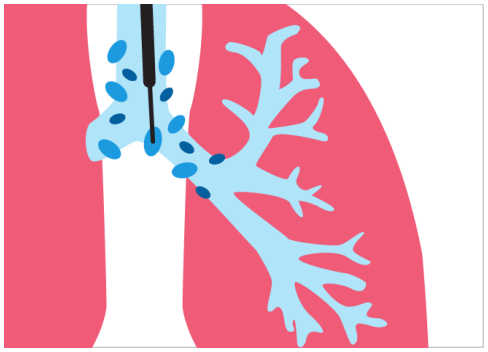
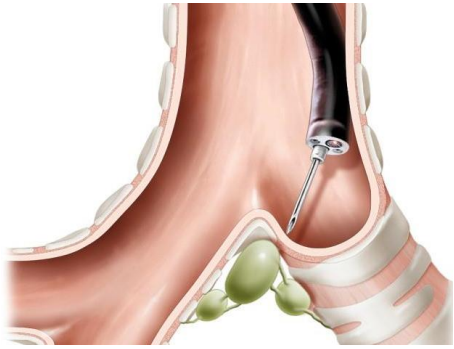
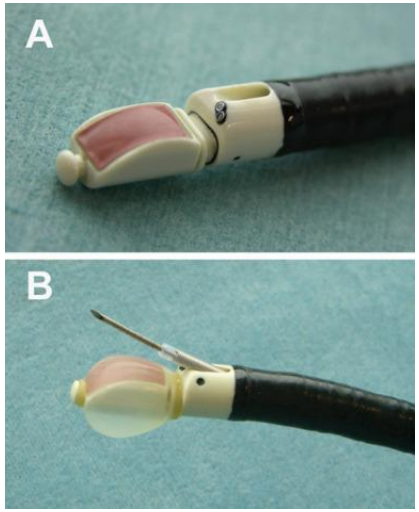
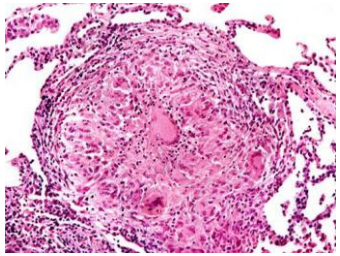


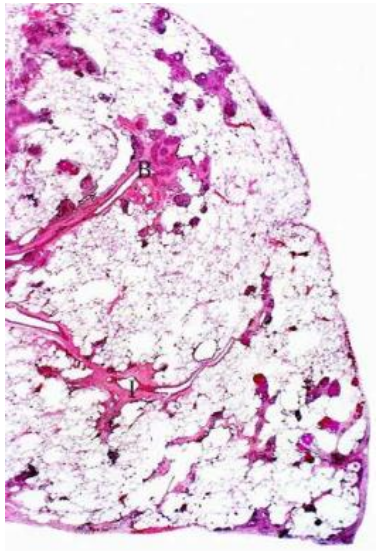






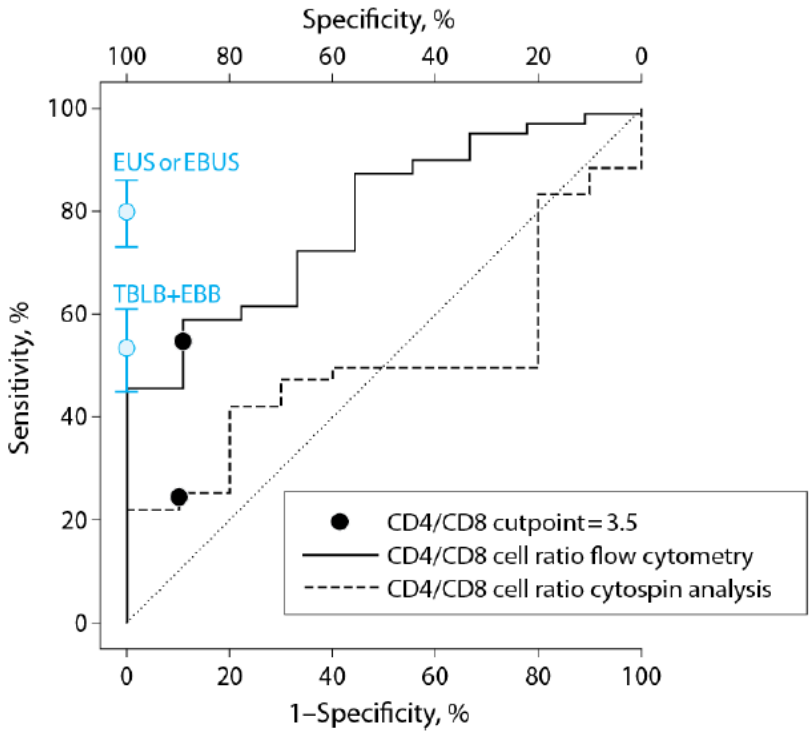
EndoBronchialUltraSound: E-Bus





JAMA 2013; 309 (23): 2457-64

Granuloma study

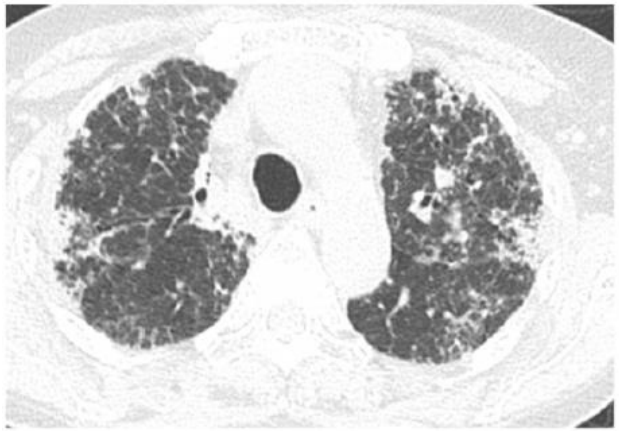


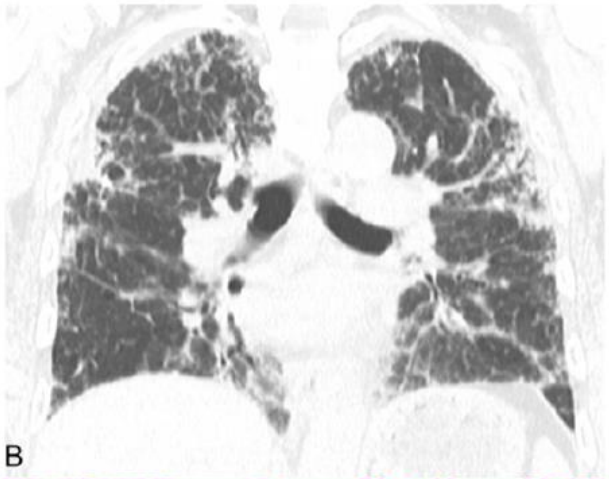
304 patients, stage I-II
149 typical bronchoscopy, 155 E-BUS

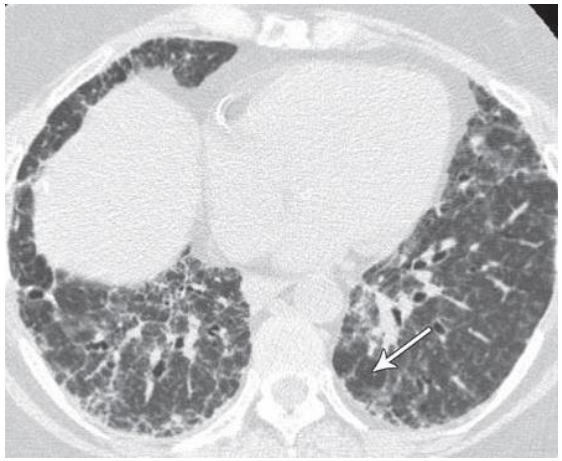
Diagnostic yield		
Bronchoscopy	53%	p<0.001
E-bus	80%	

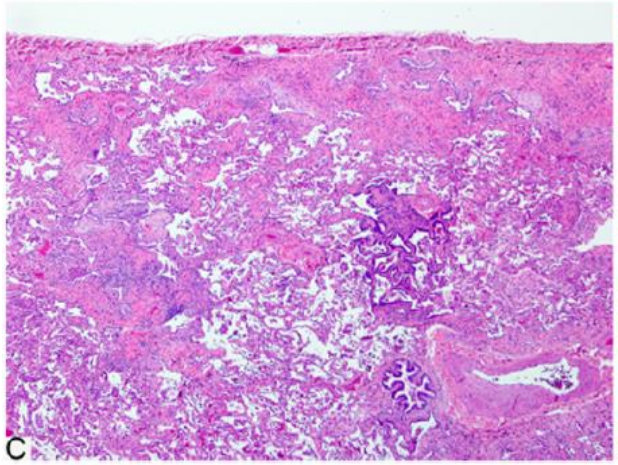
JAMA 2013; 309 (23): 2457-64

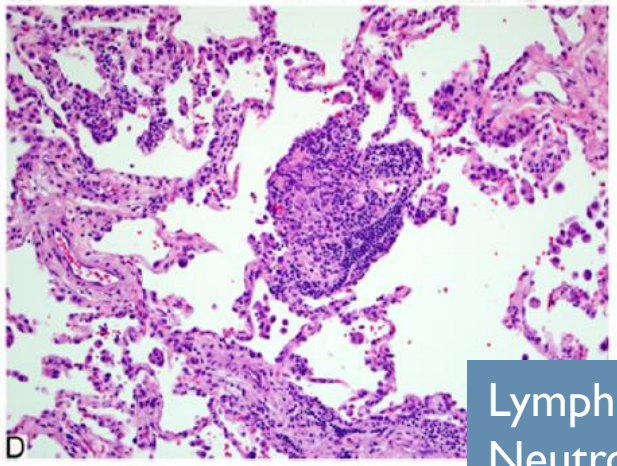
Fibrotic Hypersensitivity Pneumonitis





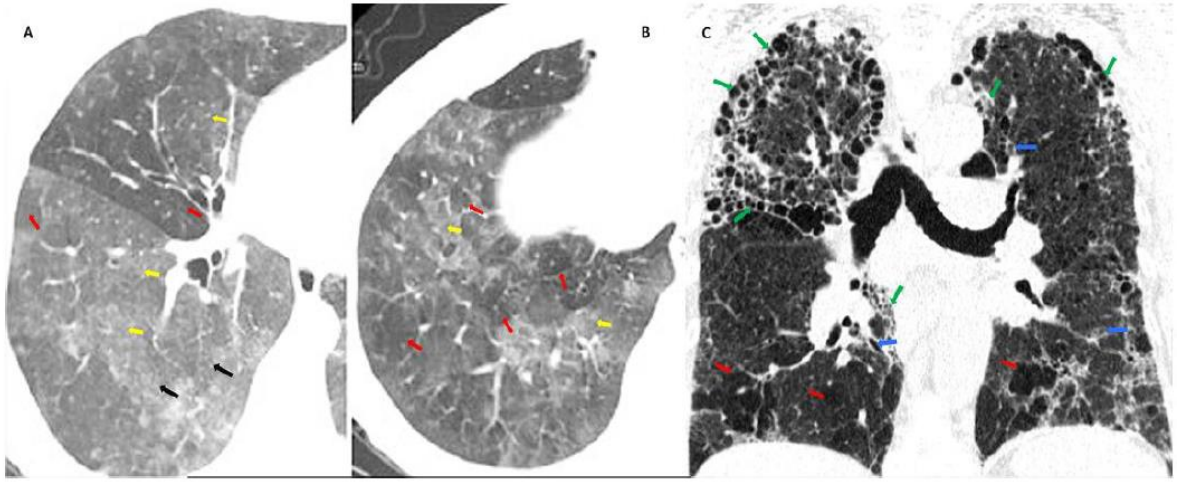






Lymphocytes: 28% CD4/8: 0.28
Neutrophils: 5%
Eosinophils: 3%

Hypersensitivity pneumonitis



- >80% of patients have >20% lymphocytes in BAL
- BAL lymphocyte count may be normal or lower than normal
- Low CD4/8 ratio nonspecific and insensitive-not recommended

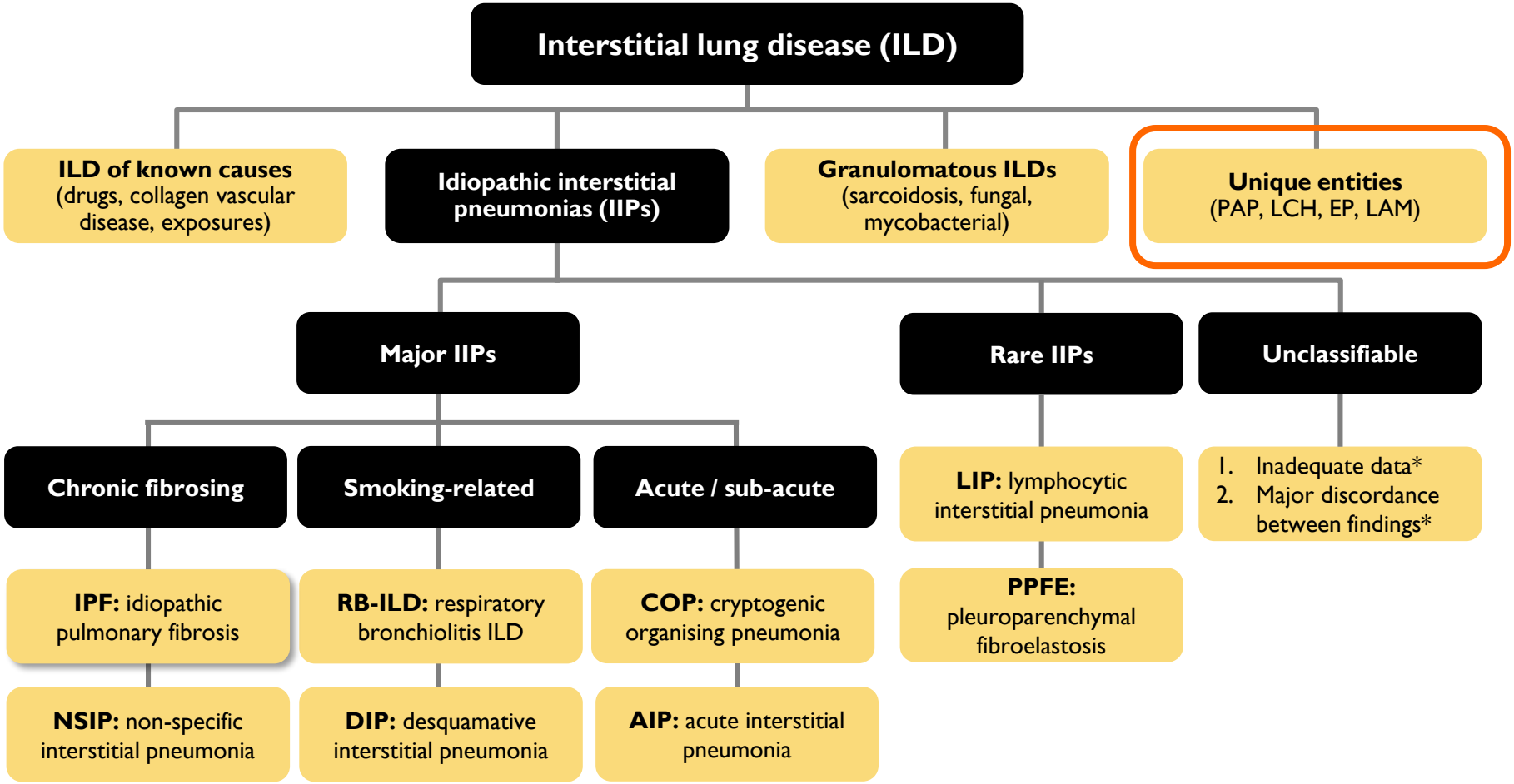
Lymphocyte counts :

BOOP and cellular NSIP

Fibrotic NSIP

UIP- like pattern in CHP compared to UIP pattern in IPF

Costabel, Clin Chest Med 2012, Ohtani Y, Thorax 2005, Vasacova 2017



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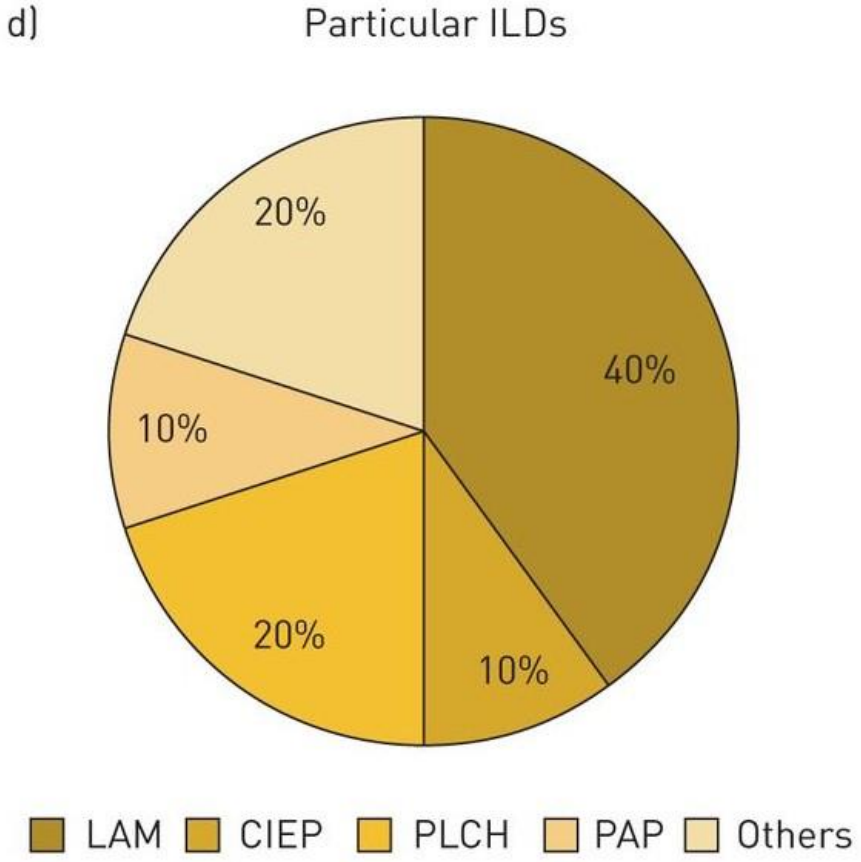
Incidence of particular ILD's

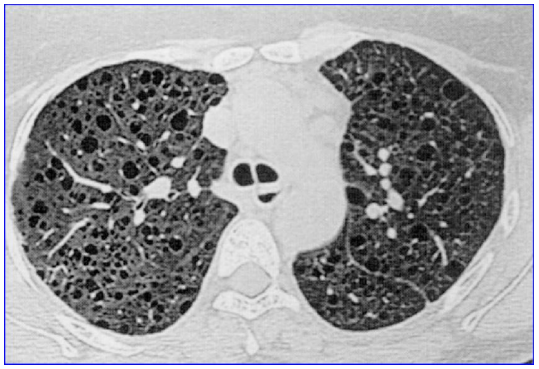


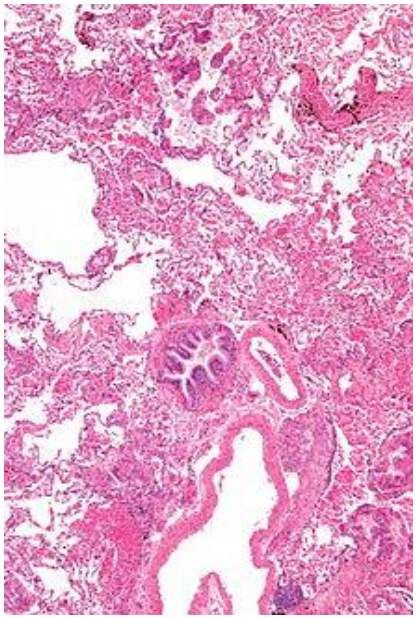
Lymphangioleiomyomatosis

2010 Experts LAM diagnostic criteria ERS Task Force

- Certain if characteristic or compatible HRCT AND either :
  - Lung biopsy
  - angiomyolipoma
  - chylothorax or chylous ascite
  - lymphangioleiomyoma *or* lymph node involvement
  - TSC diagnosis
- Probable if characteristic HRCT and compatible clinical history; or compatible HRCT and angiomyolipoma or chylous effusion
- Possible if characteristic or compatible HRCT only

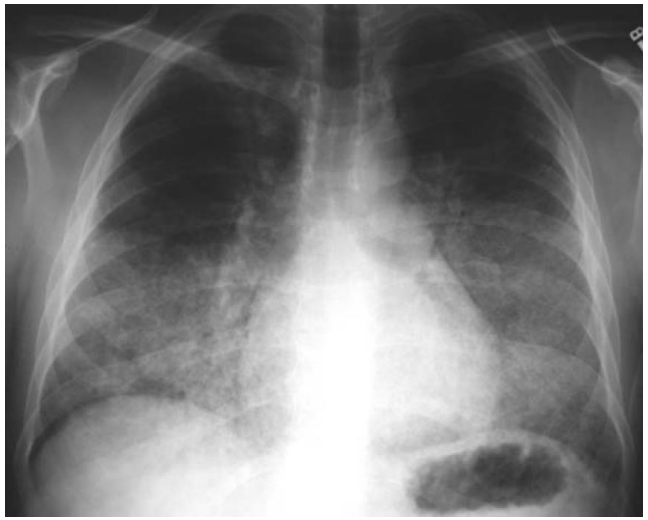
Johnson et al, ERJ 2010

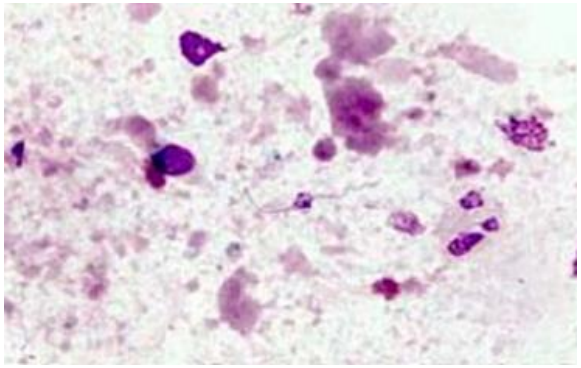


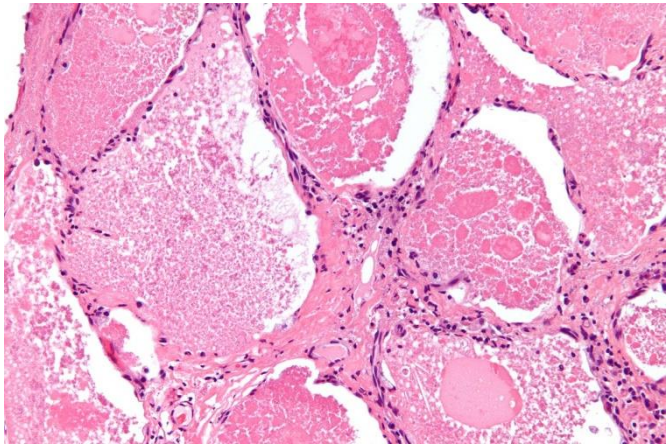


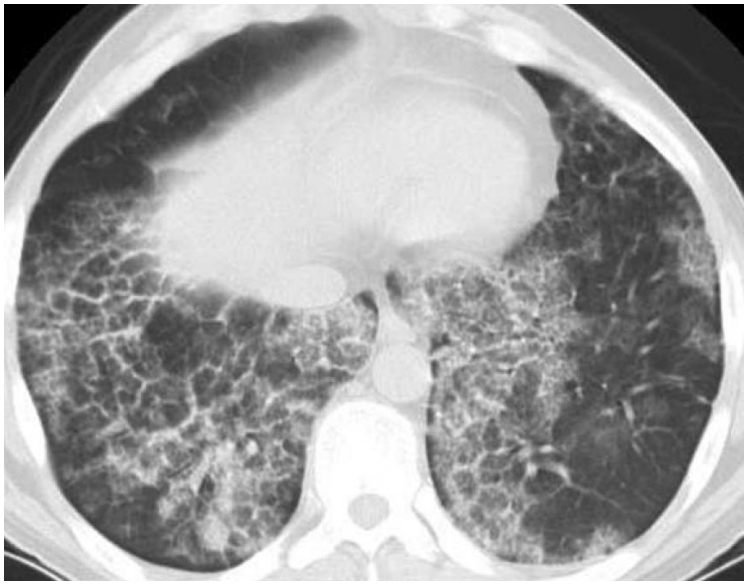
- 2010 Criteria : diagnosis without biopsy in 69% cases
- 2010 criteria + VEGF-D > 800pg/mL : diagnosis without biopsy in 79% cases
  - Chang, Respir Res 2012

* Pulmonary alveolar proteinosis



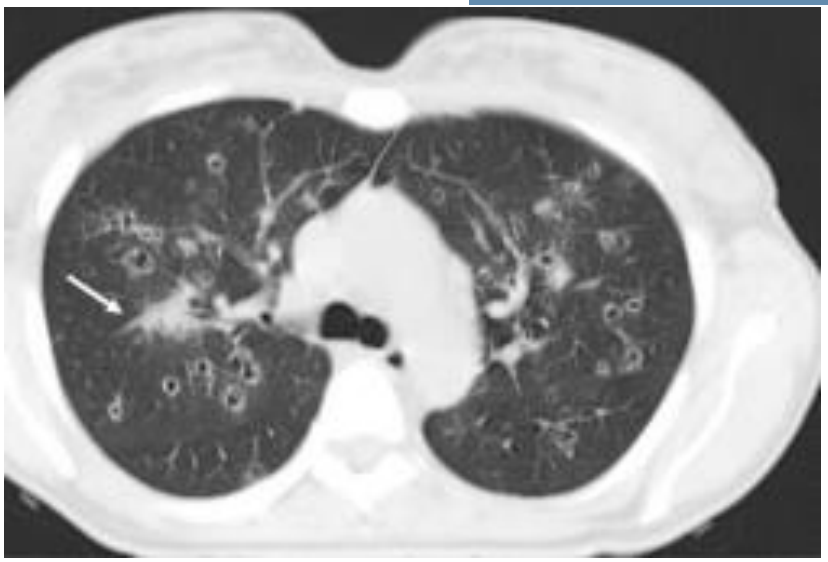


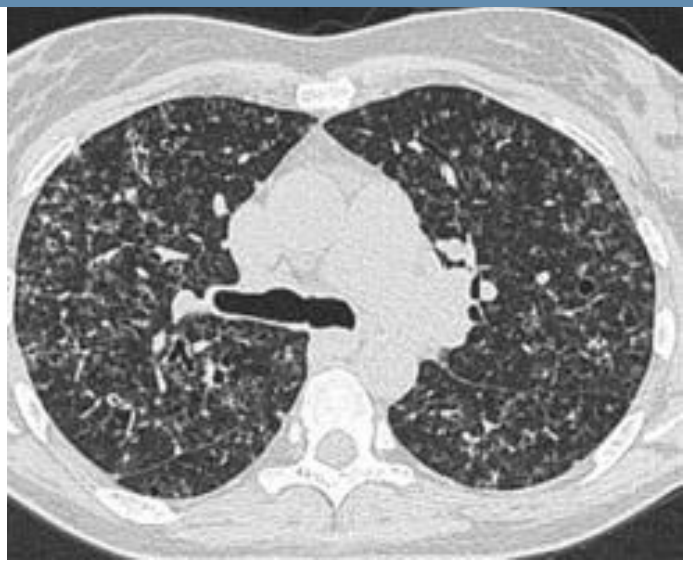


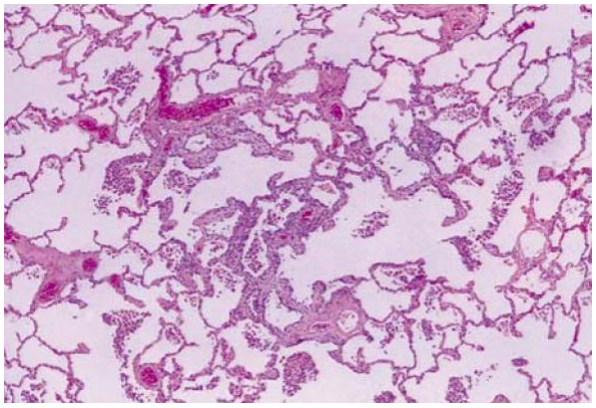


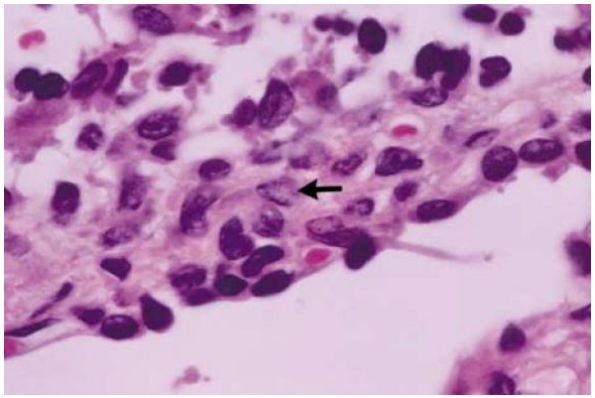
Langerhans Cell Histiocytosis

CD1a (+) >5%: sensitivity <25%

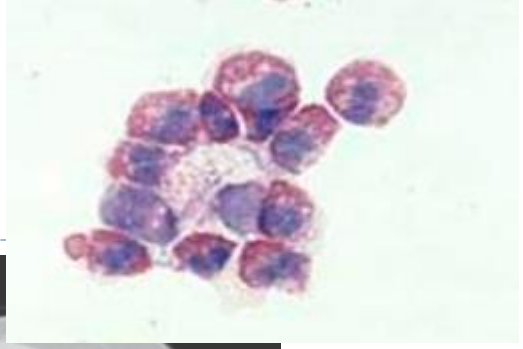


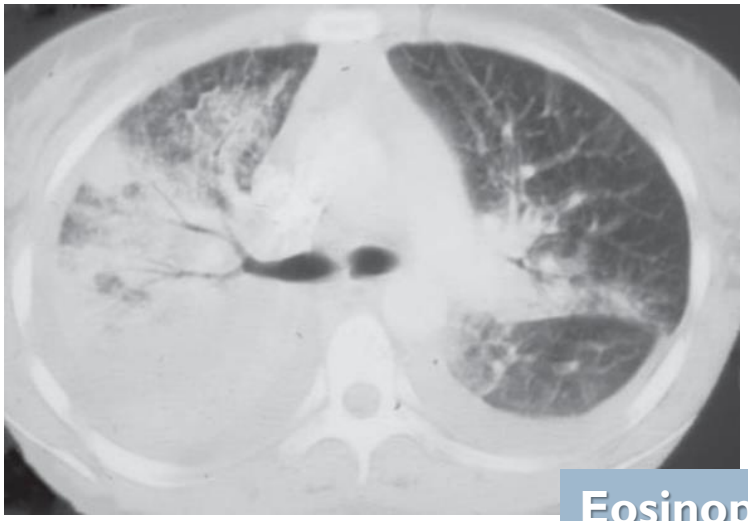


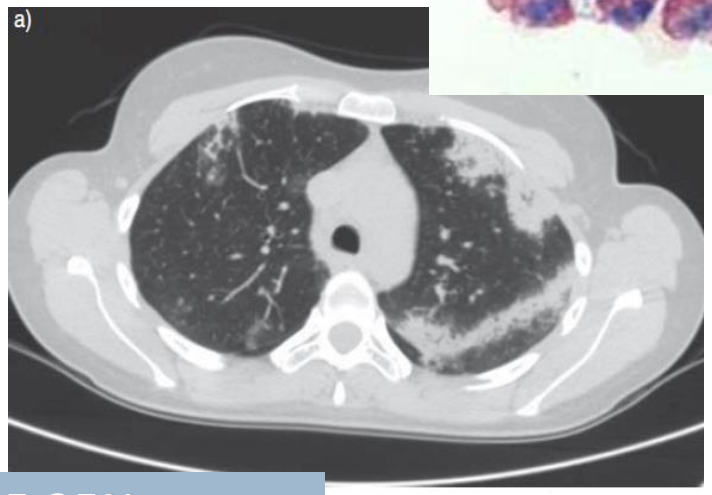




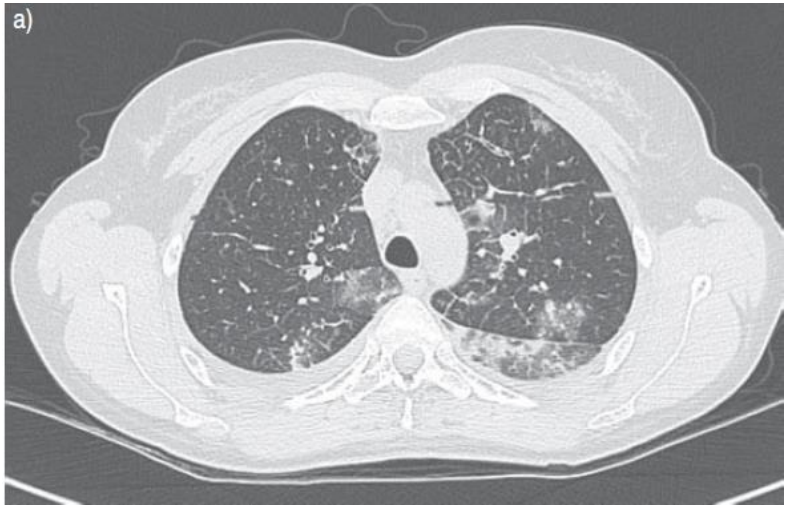
*Eosinophilic pneumonia

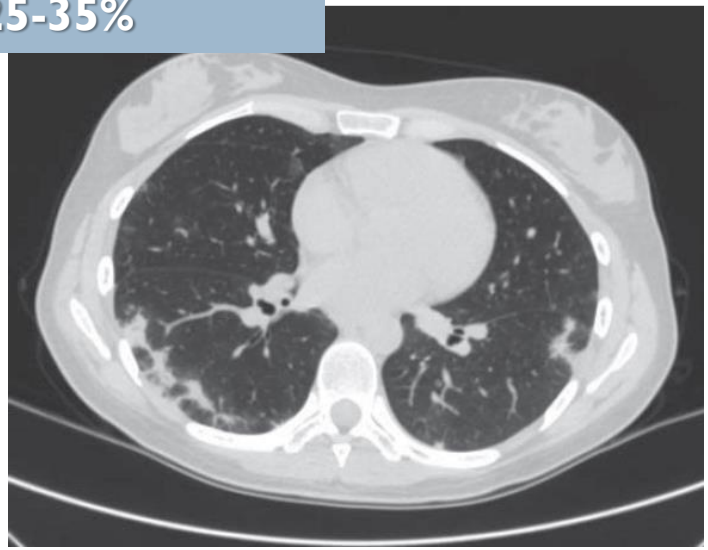




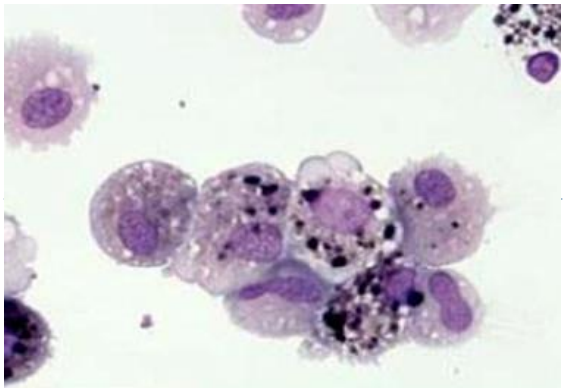


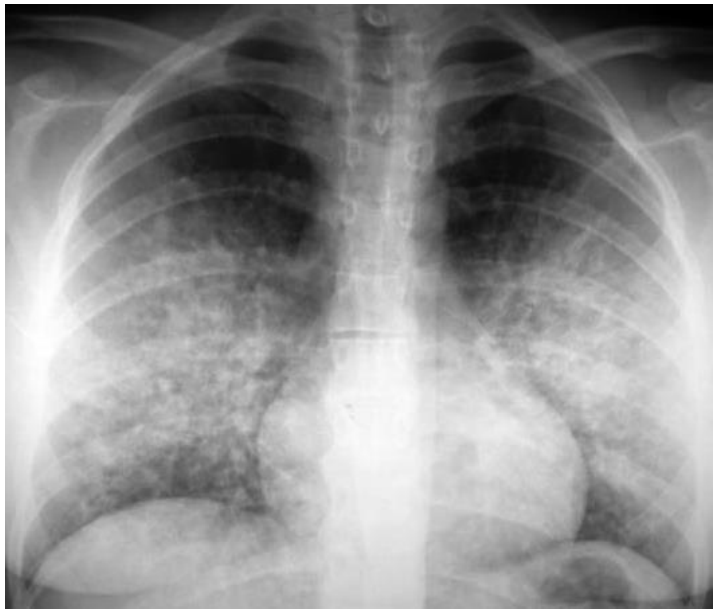
Eosinophils>25-35%

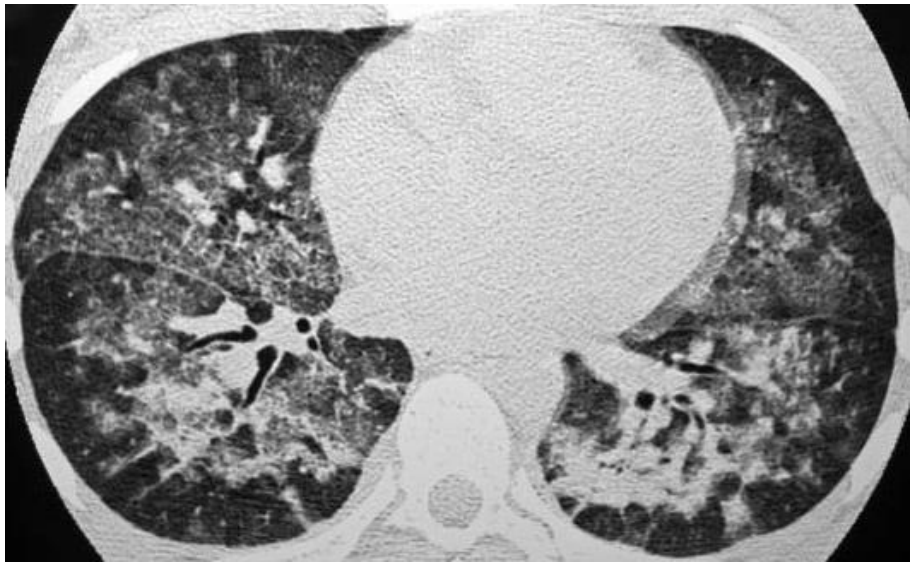


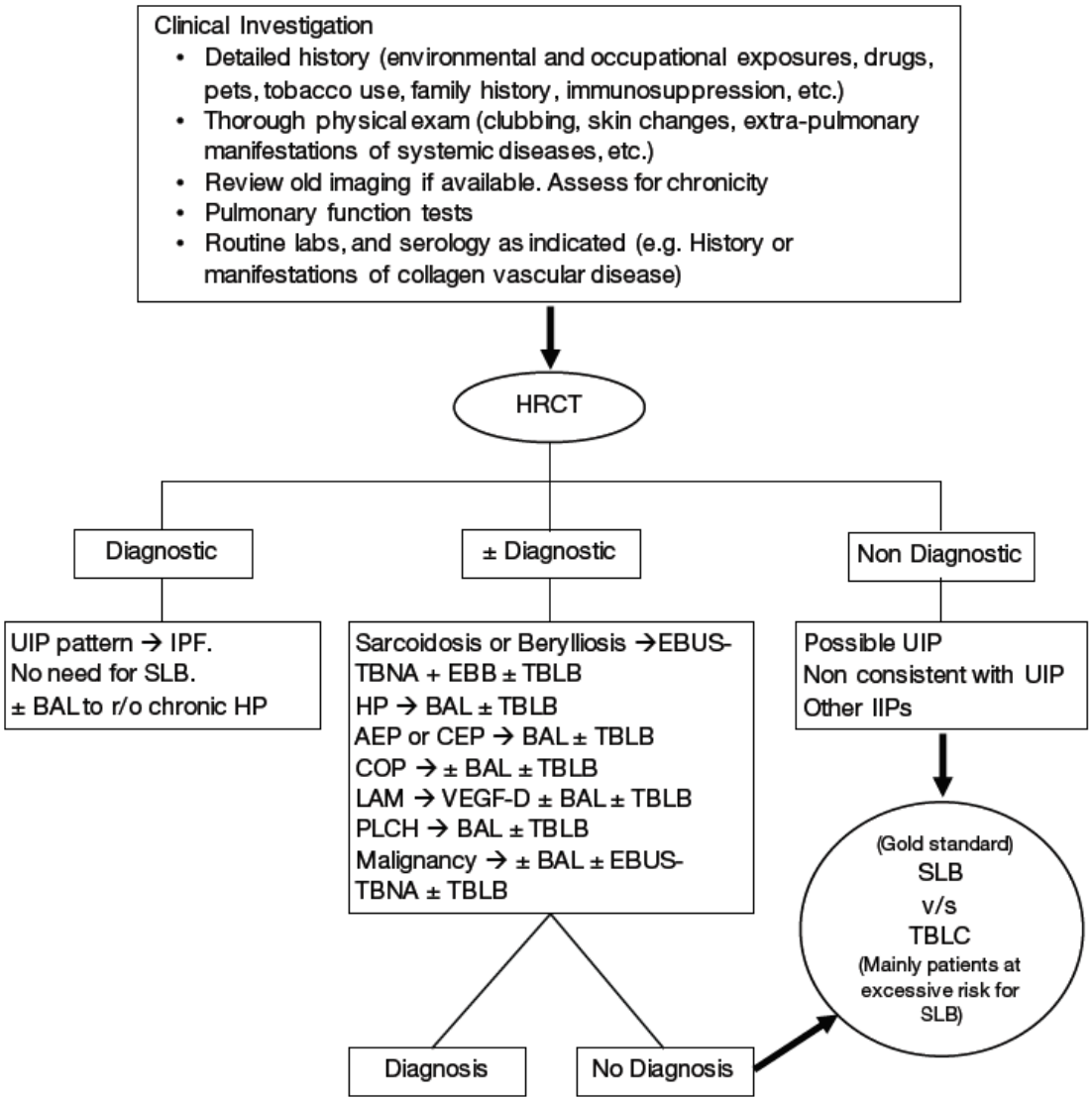


*Alveolar hemorrhage

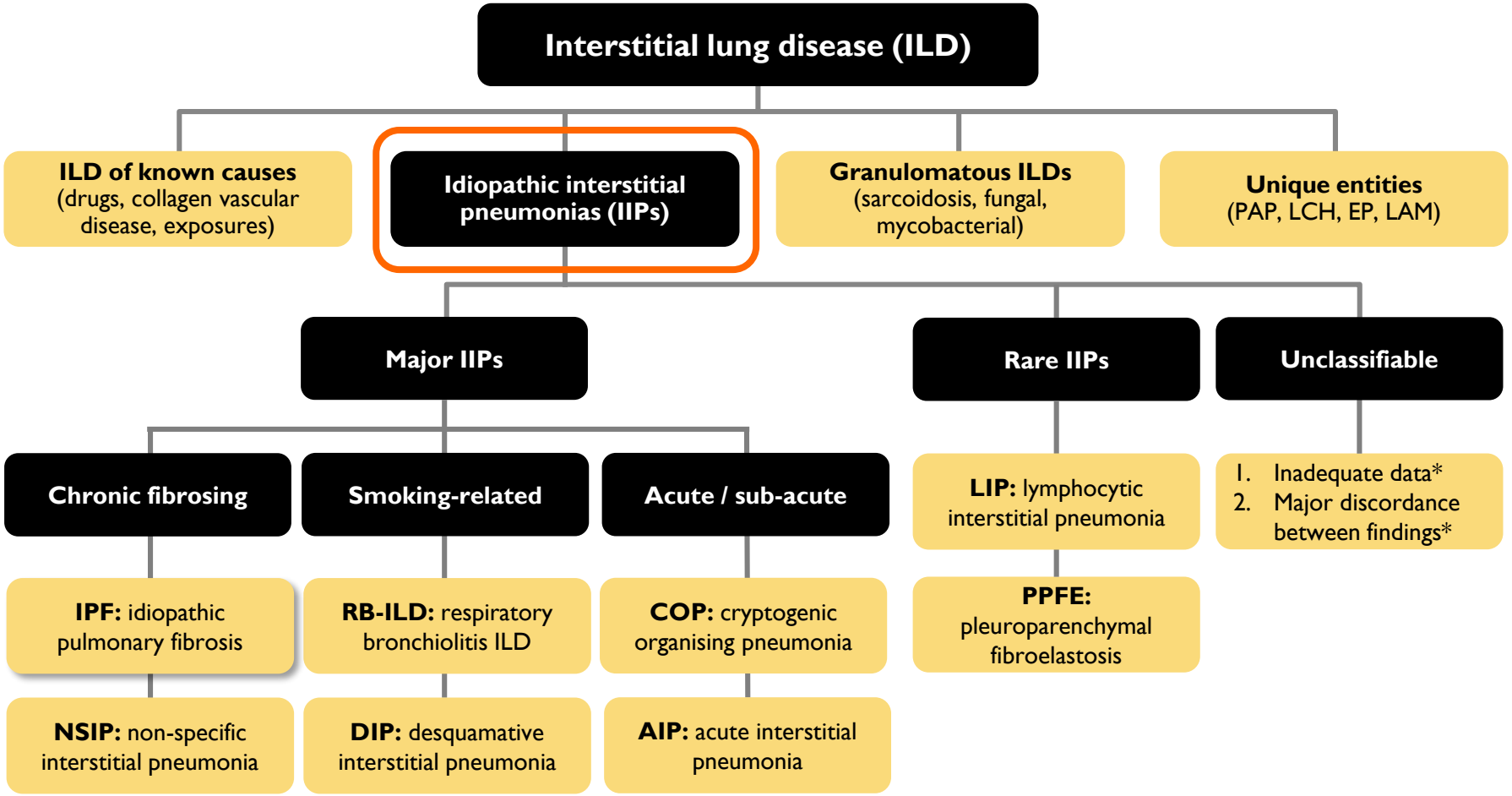







Clinical Investigation
• Detailed history (environmental and occupational exposures, drugs, pets, tobacco use, family history, immunosuppression, etc.)
• Thorough physical exam (clubbing, skin changes, extra-pulmonary manifestations of systemic diseases, etc.)
• Review old imaging if available. Assess for chronicity
• Pulmonary function tests
• Routine labs, and serology as indicated (e.g. History or manifestations of collagen vascular disease)
HRCT
Diagnostic
± Diagnostic
Non Diagnostic
UIP pattern → IPF.
No need for SLB.
± BAL to r/o chronic HP
Sarcoidosis or Berylliosis →EBUS-TBNA + EBB ± TBLB
HP → BAL ± TBLB
AEP or CEP → BAL ± TBLB
COP → ± BAL ± TBLB
LAM → VEGF-D ± BAL ± TBLB
PLCH → BAL ± TBLB
Malignancy → ± BAL ± EBUS-TBNA ± TBLB
Possible UIP
Non consistent with UIP
Other IIPs
(Gold standard)
SLB
v/s
TBLC
(Mainly patients at excessive risk for SLB)
Diagnosis
No Diagnosis

Idiopathic pulmonary fibrosis is the commonest IIP



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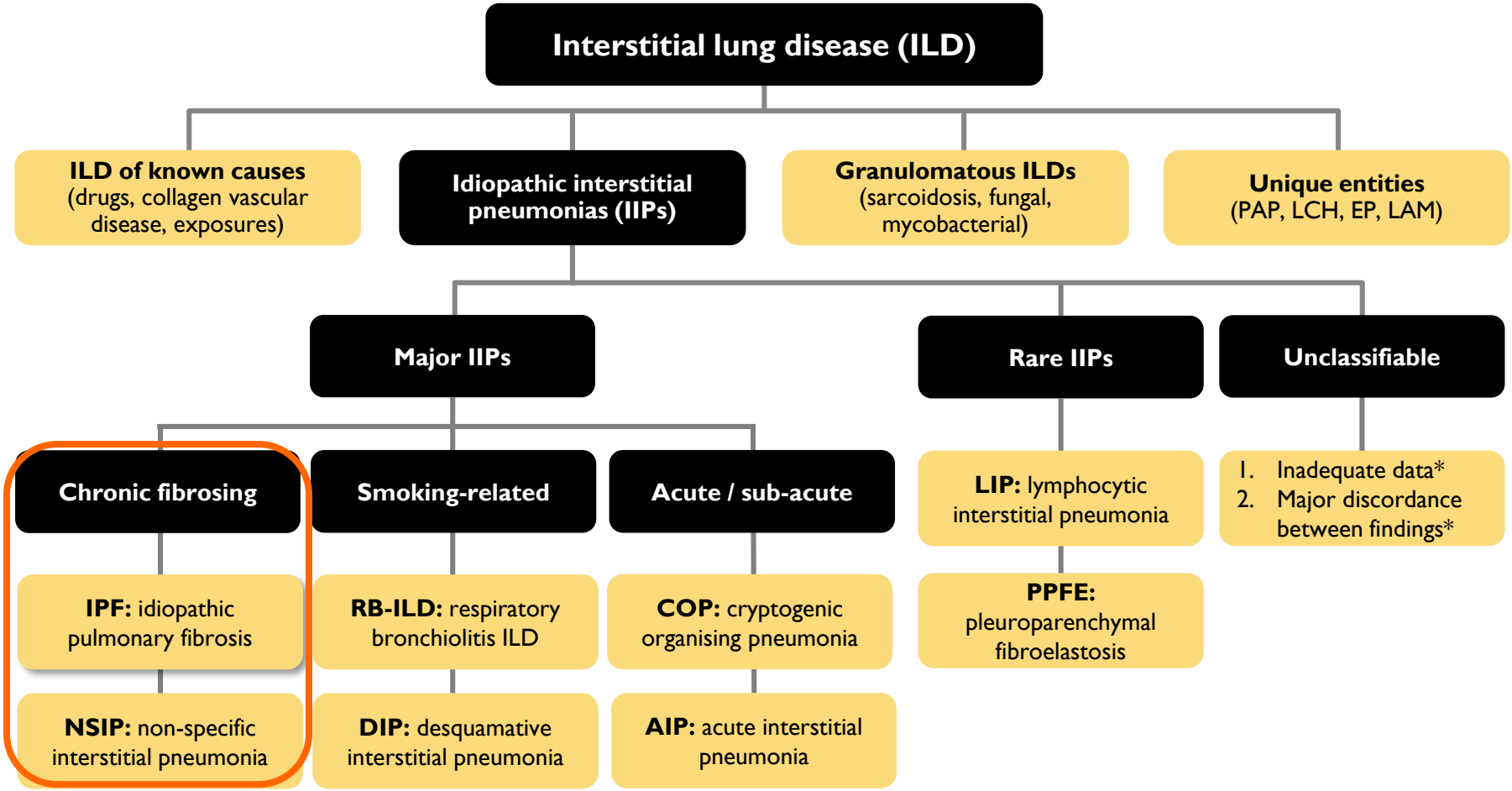

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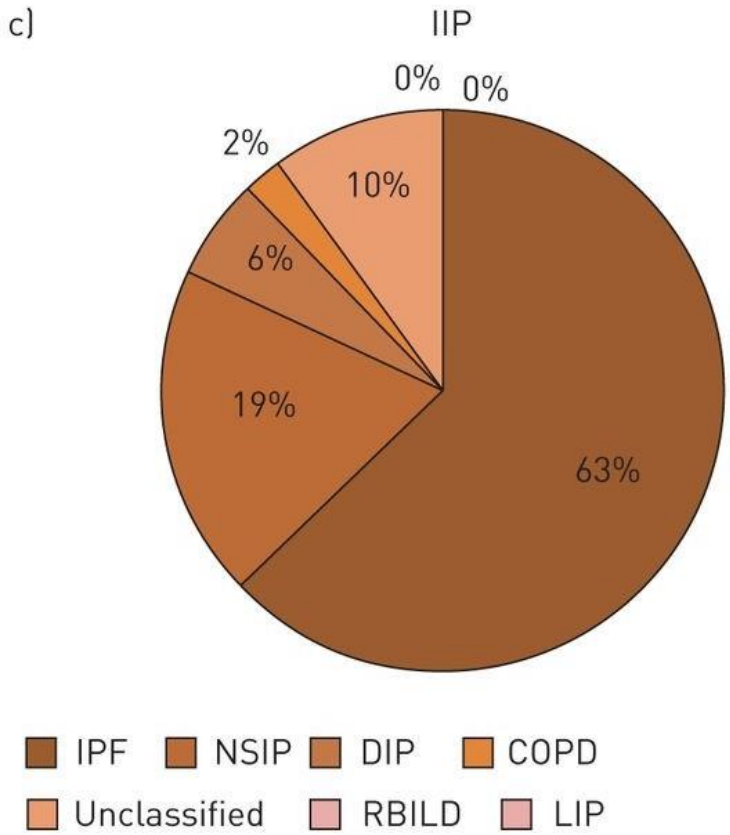
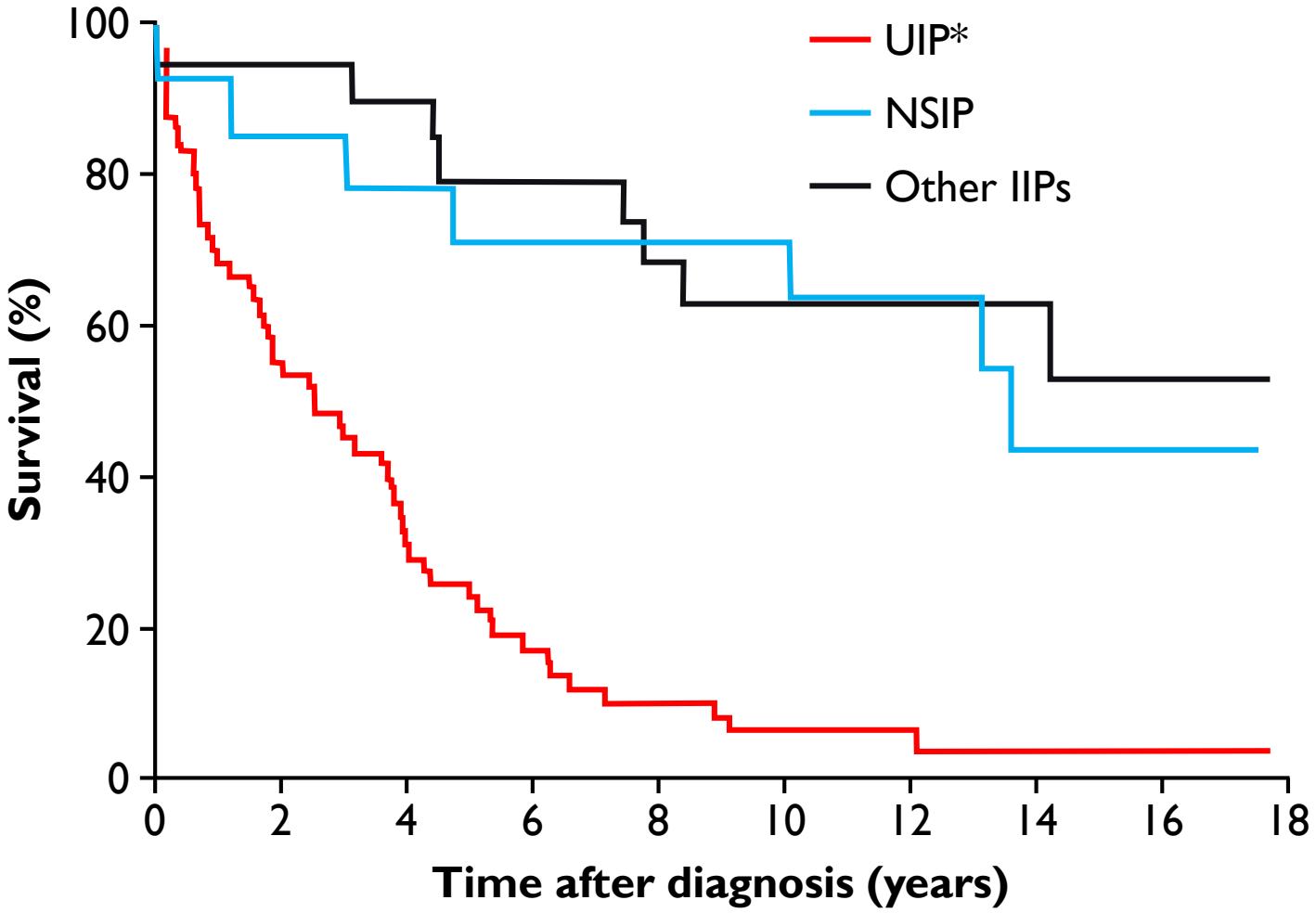
Incidence of Idiopathic Interstitial Pneumonias

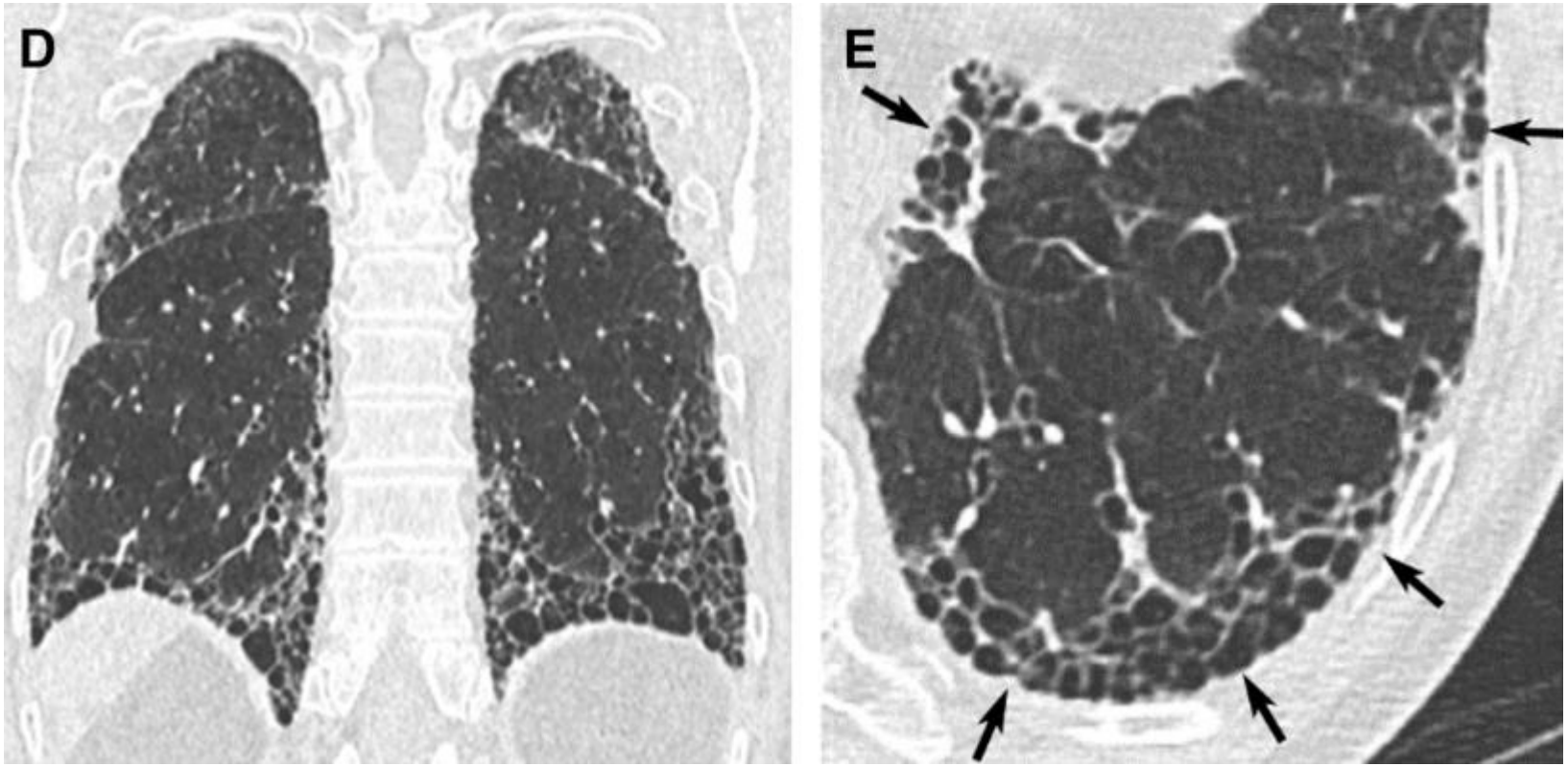


IPF: worst prognosis among IIP's

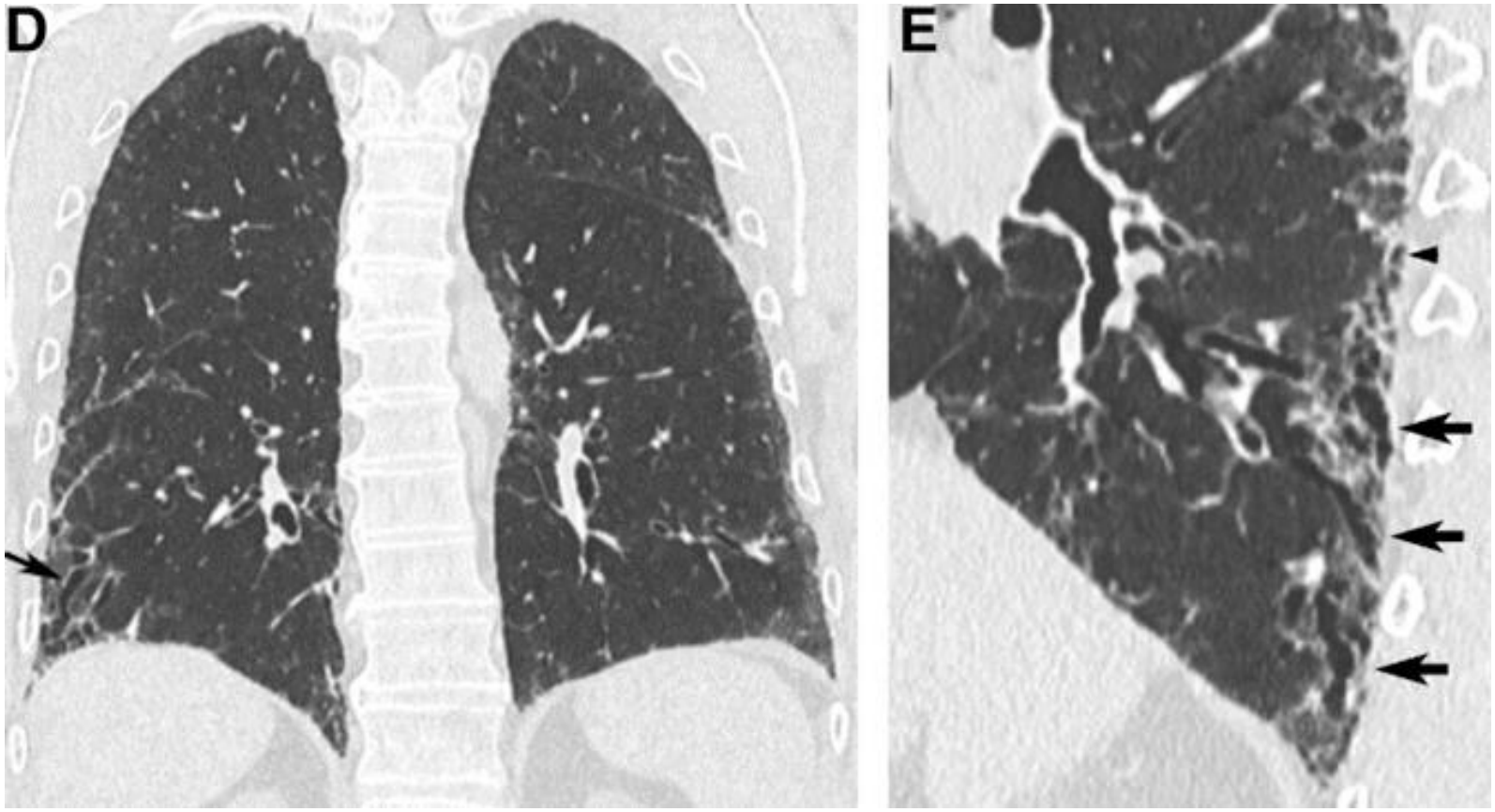


Bjoraker JA et al. Am J Respir Crit Care Med 1998;157:199-203

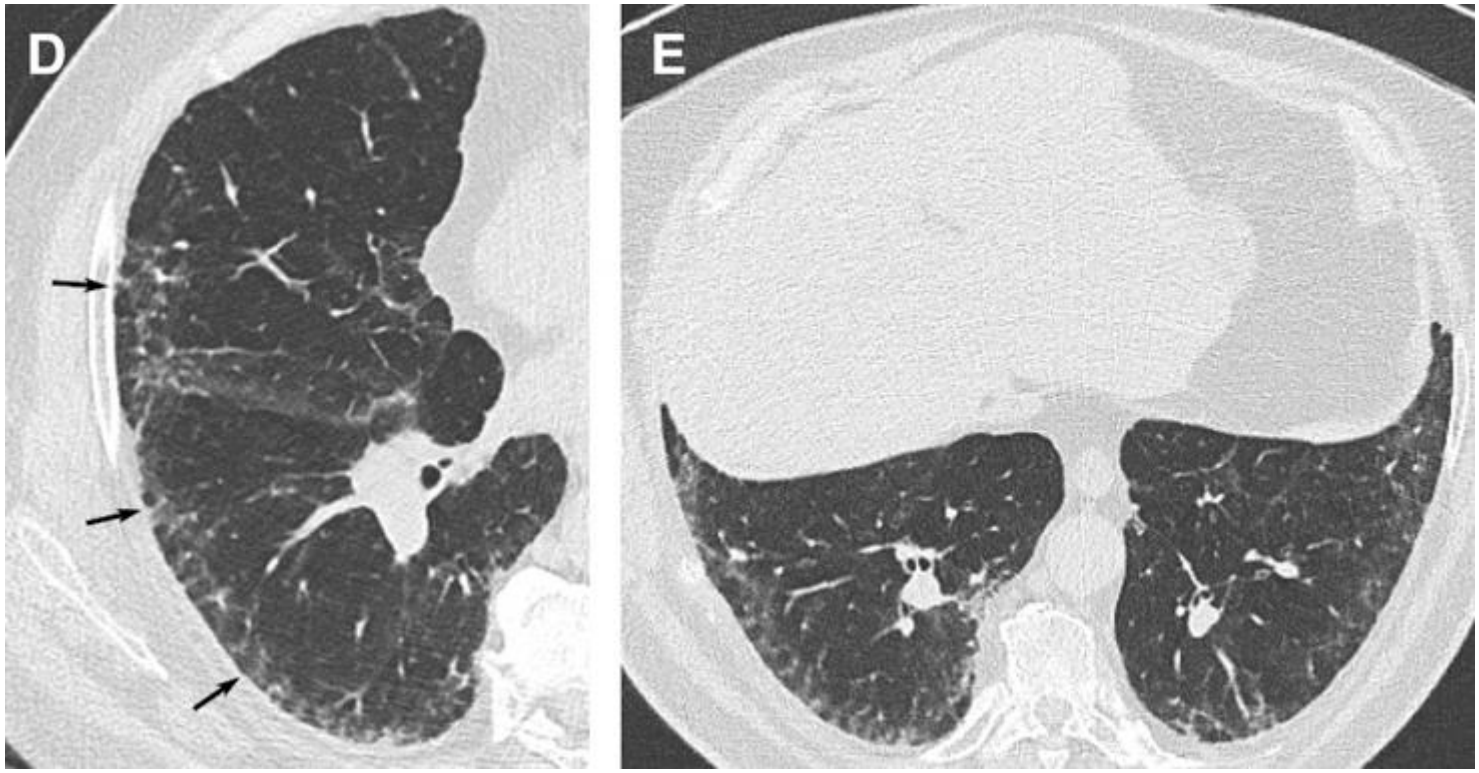
CT with typical UIP pattern



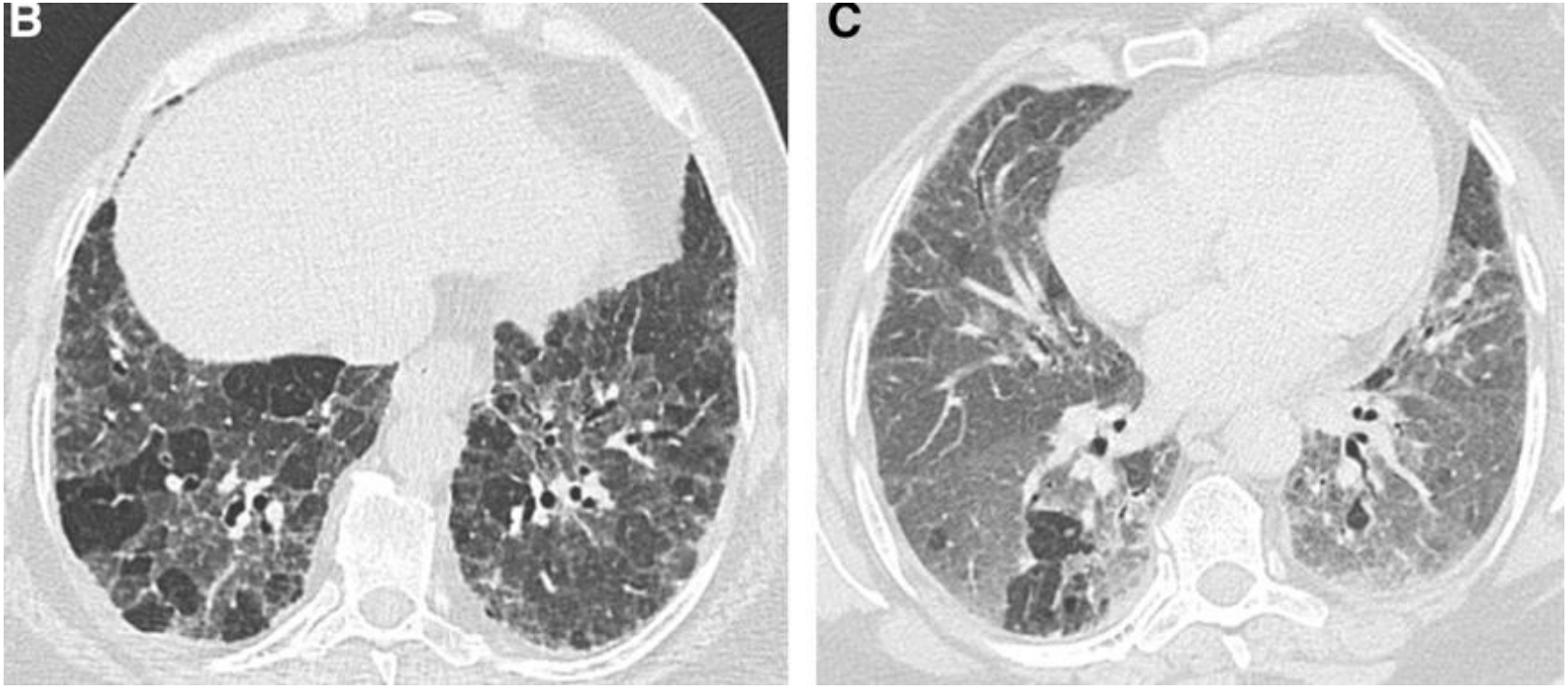
CT with probable UIP pattern



CT with indeterminate pattern

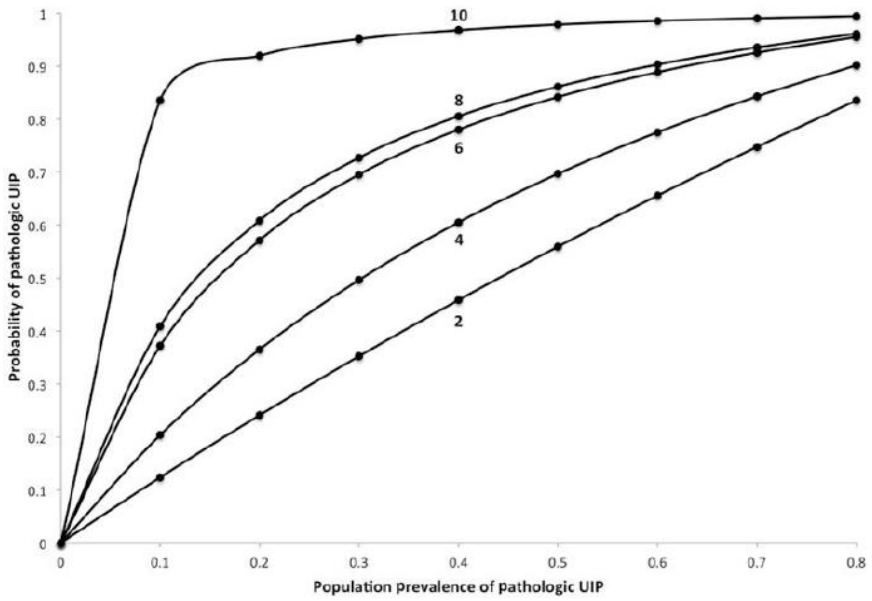


CT suggestive of alternative diagnosis



Pre-test probability of IPF based on HRCT

Characteristic	Points
Age, in years	
50–59	2
≥60	3
Male sex	1
Possible UIP+total traction bronchiectasis score ≥ 4	6
Total score possible	10

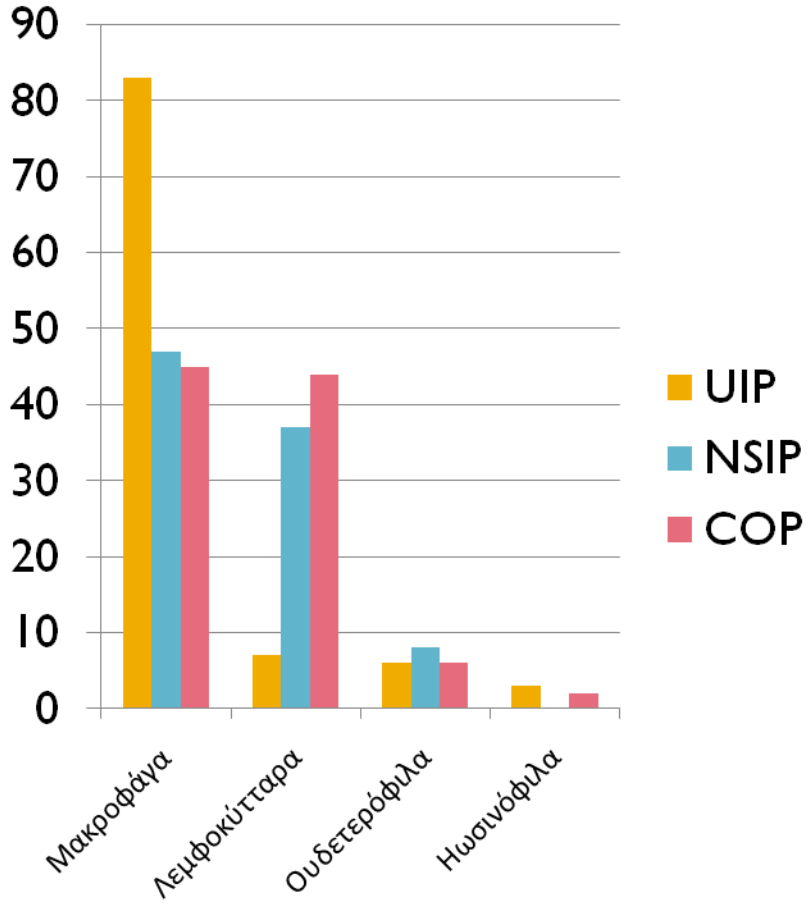


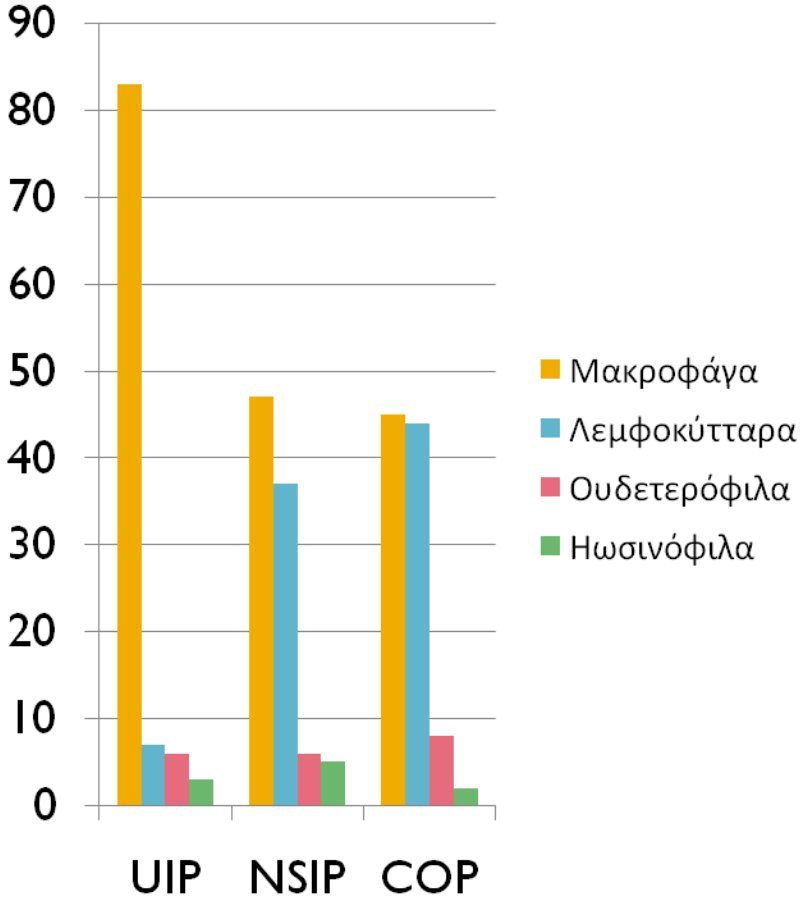
Thorax. 2017 May ; 72(5): 424–429. doi:10.1136/thoraxjnl-2016-209671.

How we proceed depending on the CT pattern

	Typical for UIP	Probable, indeterminate, alternative diagnosis
BAL	-	+
Transbronchial biopsy	-	+/-
Transbronchial Cryobiopsy	-	+/-
Surgical lung biopsy	-	+
Multidisciplinary discussion	*	*

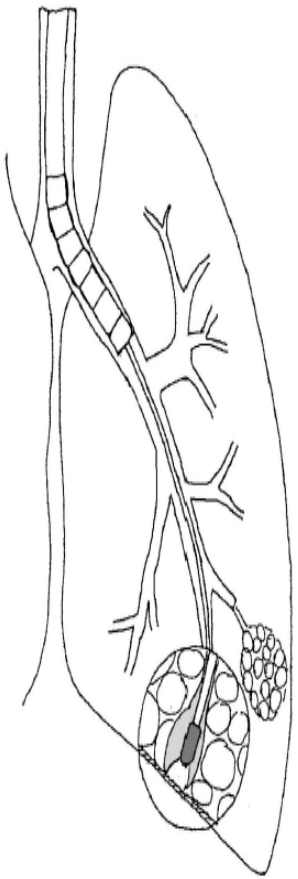
BAL cellular profiles in IPF, NSIP, COP





Nagai et al. Eur Respir J 1998; 12: 1010-19

Cryobiopsy



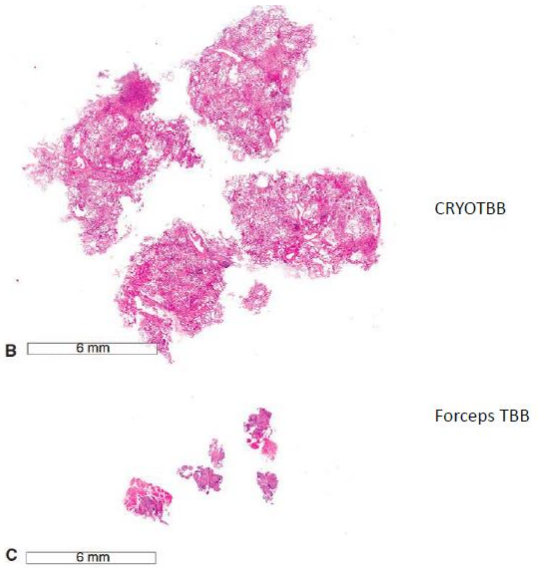
TRANSBRONCHIAL CRYOBIOPSY (MORGAGNI H's RECIPE)

(≈750 procedures so far)

- General anesthesia (Propofol/Remifentanil)
- Spontaneous breathing
- Rigid Tracheochoscope (*Storz* 14 or 12 mm-33 cm)+fiberoptic bronchoscope (6.2 mm)
- Fogarty balloon
- Fluoroscopic control (+/- radial EBUS) Cryoprobe 2.4 or 1.9 mm
- A distance of approximately <= 10 mm from the thoracic wall
- The 2.4 probe is cooled for > 5-6'
- The 1.9 probe is cooled for > 7-8'

4 samples: it takes 20 minutes!

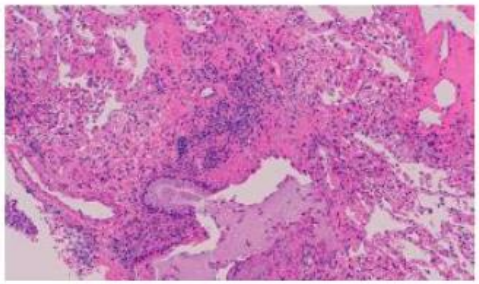
- 83% diagnosis
  - Mortality 0,2%



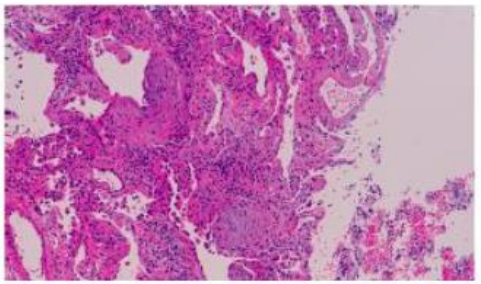
Histologic aspects of UIP pattern on cryobiopsy in patients with idiopathic pulmonary fibrosis

Claudia Ravaglia, Forlì (Italy) – September 13, 2017

Group A = with Honeycombing



Group B = without Honeycombing



	All patients (n 63)	Group A = with HC (n 18)	Group B = without HC (n 45)	p
Age at Biopsy, y	64 (45-78)	65 (53-76)	63 (45-78)	0.081 (*)
Gender M/F, n	45M/18F	11M/7F	34M/11F	0.354 [§]
HRCT pattern: Possible UIP / Inconsistent UIP	40/20	13/4	27/16	0.375 [§]
FVC, % pred	86.0 (59-136)	85.5 (59-110)	86.0 (59-136)	0.341 (*)
DLCO, % pred	56 (23-117)	48 (35-117)	58 (23-99)	0.089 (*)
Death, n (%)	10 (16%)	4 (22%)	6 (13%)	0.452 [§]
Median survival, days		1901	1948	0.1192 (#)

(*) Mann-Whitney test; [§] Fisher's exact test; (#) Kaplan-Meyer log rank

N=310

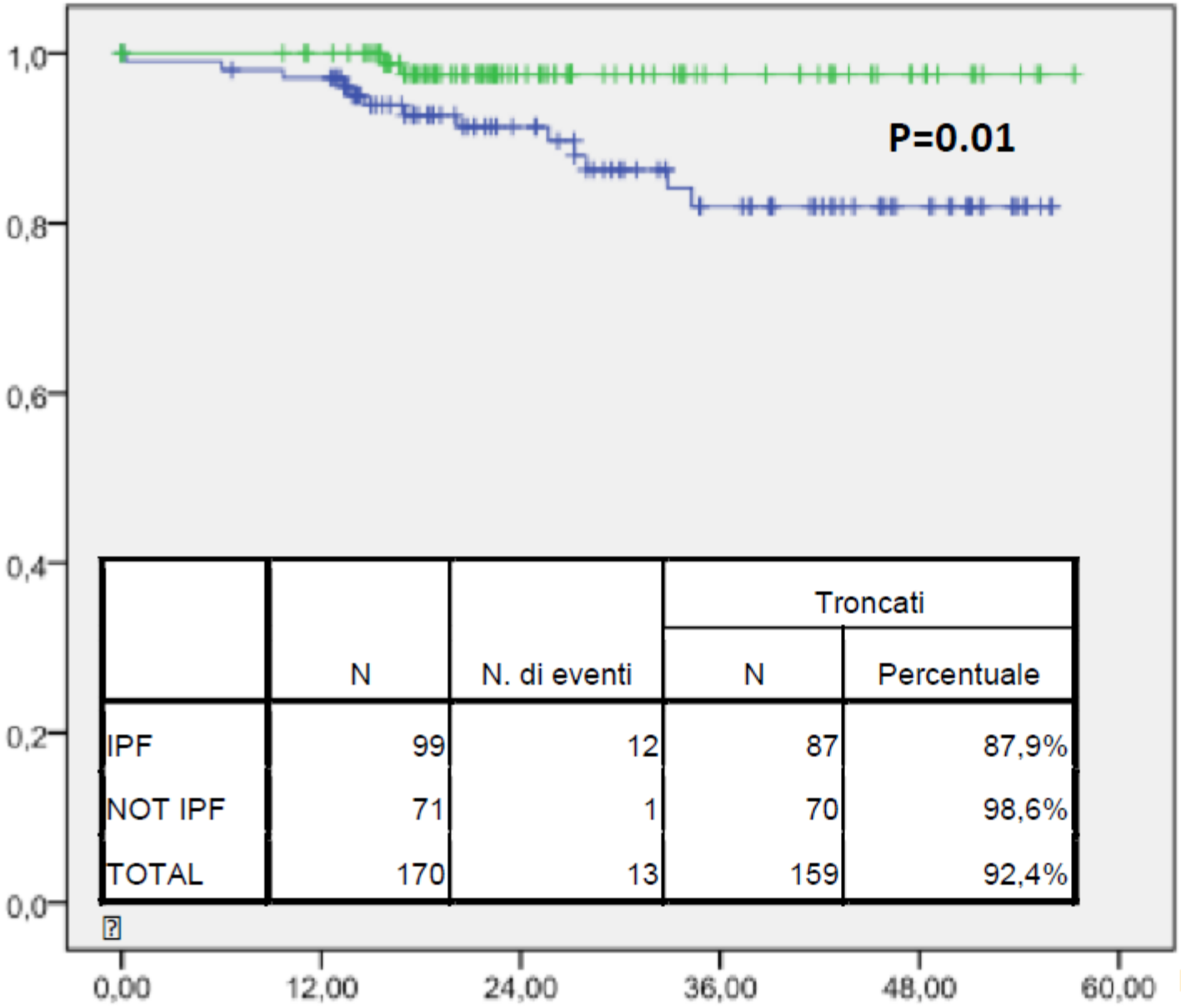
N=5, Excluded for lack of baseline HRCT
N=3, Excluded for not significant slides

N=302

HISTOLOGIC PATTERN	N= 302
UIP	116 (38%)
NSIP	34(11%)
HP	17 (6%)
SR-ILD	24 (8%)
GRANULOMATOSIS	20 (6%)
MALIGNANCIES	13 (4%)
OTHER	29 (10%)
NON DIAGNOSTIC	17 (6%)
DISAGREEMENT	32 (10%)

Poletti V et al, unpublished

Cryo has prognostic significance



	N	N. di eventi	Troncati	
			N	Percentuale
IPF	99	12	87	87,9%
NOT IPF	71	1	70	98,6%
TOTAL	170	13	159	92,4%

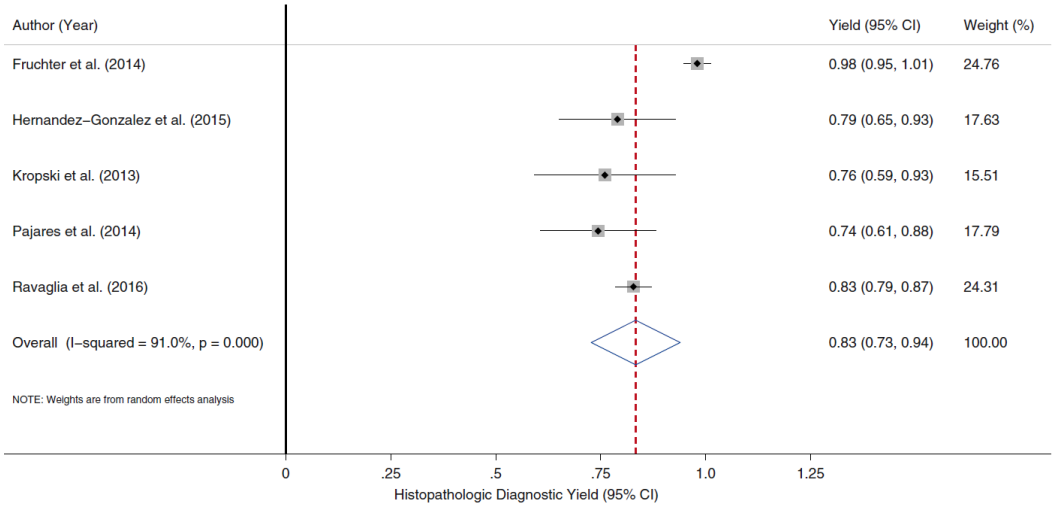
NOT-IP

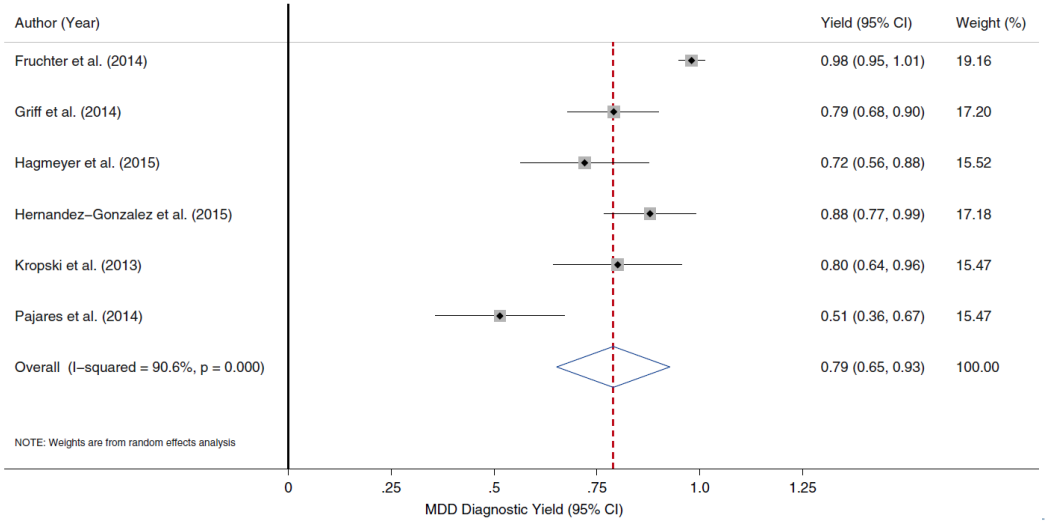
IPF

*iNSIP/HP/CVD-ILD/SR-ILD

Median survival
IPF 50.5mo (47-5
NOT IPF 56.6mo

Meta-analysis

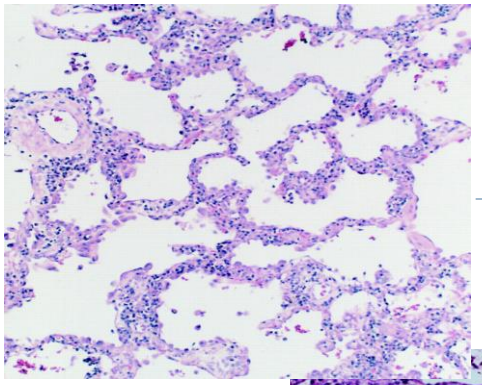


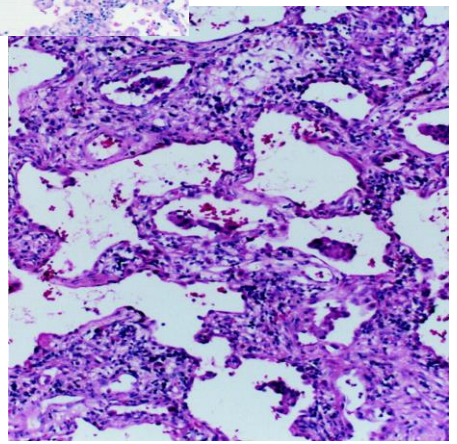


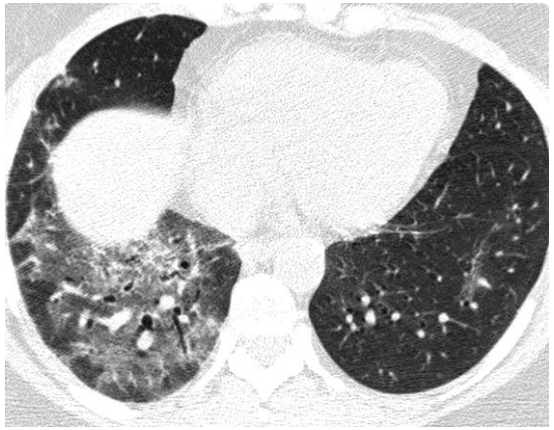
Ann Am Thorac Soc Vol 13, No 10, pp 1828–1838, Oct 2016

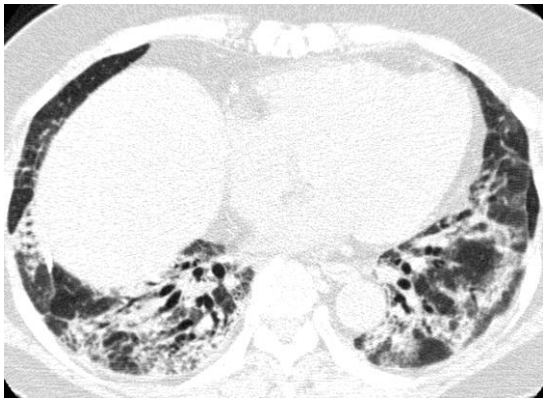
NSIP

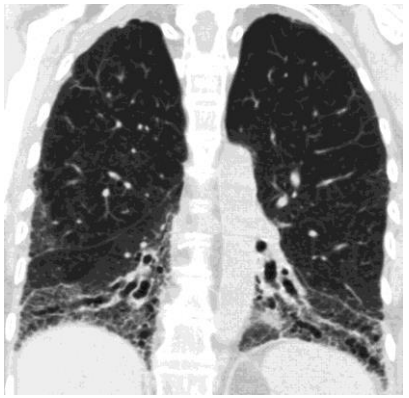
Lymphocytic cellular pattern
>15% lymphocytes
Sarcoidosis
Nonspecific interstitial pneumonia (NSIP)
Hypersensitivity pneumonitis
Drug-induced pneumonitis
Collagen vascular diseases
Radiation pneumonitis
Cryptogenic organizing pneumonia (COP)
Lymphoproliferative disorders



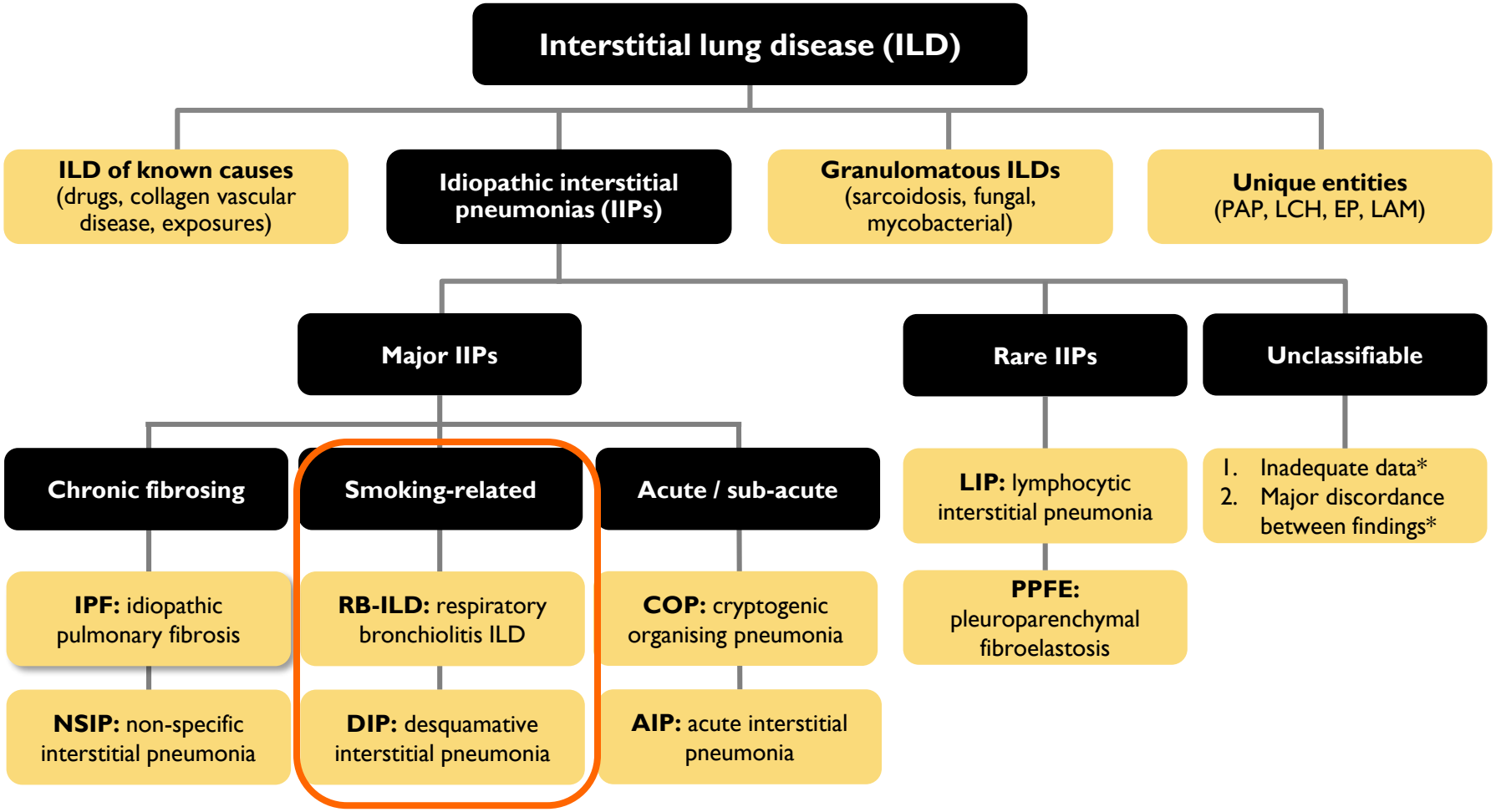








Idiopathic pulmonary fibrosis is the commonest IIP



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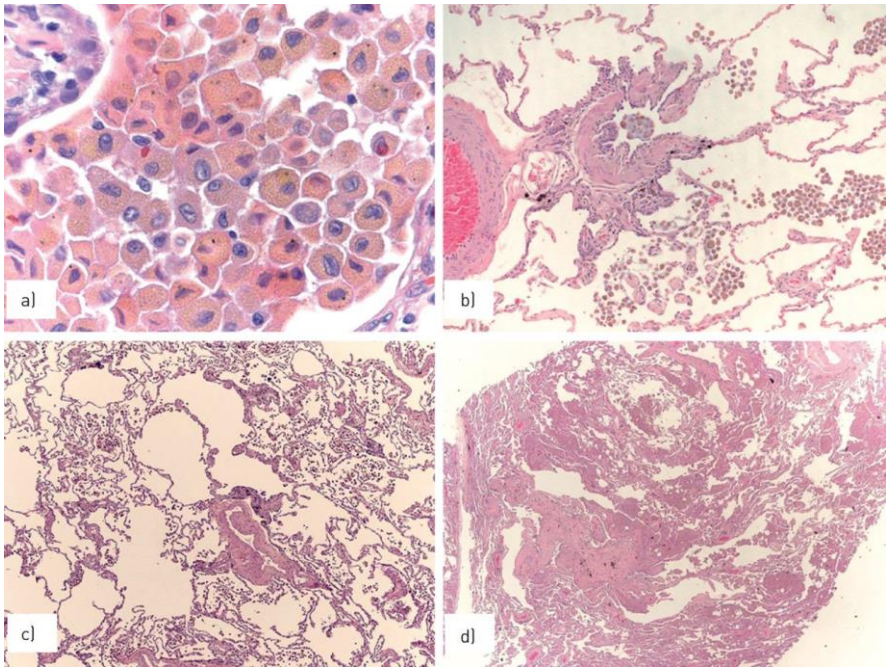
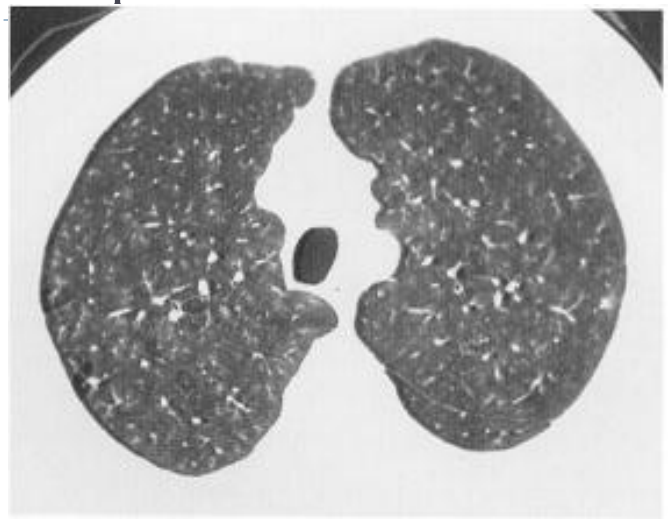
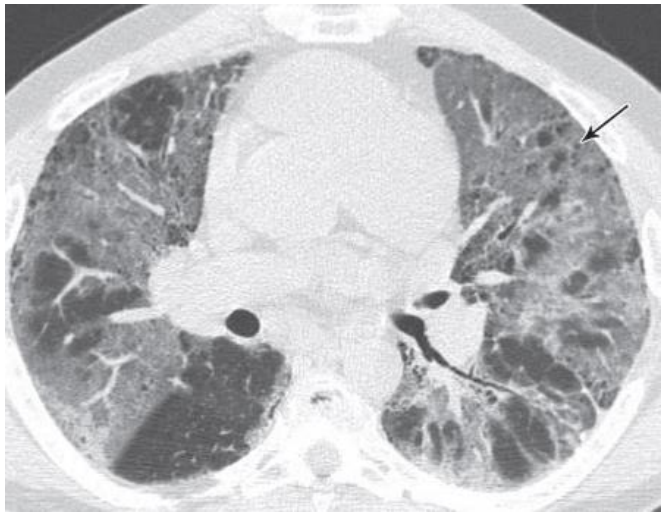
Travis WD et al. Am J Respir Crit Care Med 2013;188:733-748

Desquamative interstitial pneumonia
Respiratory Bronchiolitis interstitial pneumonia

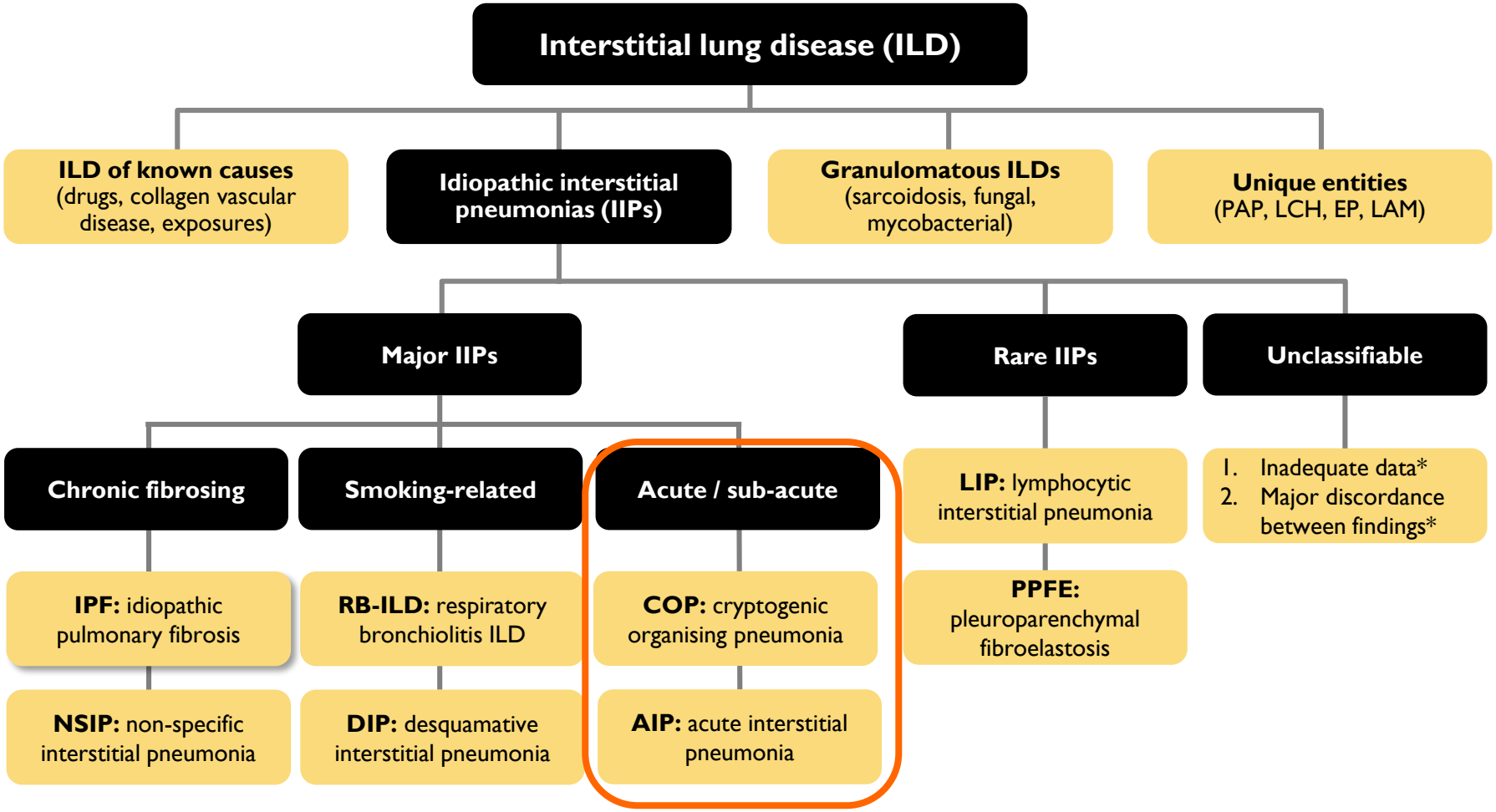






High number of alveolar pigmented macrophages

Idiopathic pulmonary fibrosis is the commonest IIP



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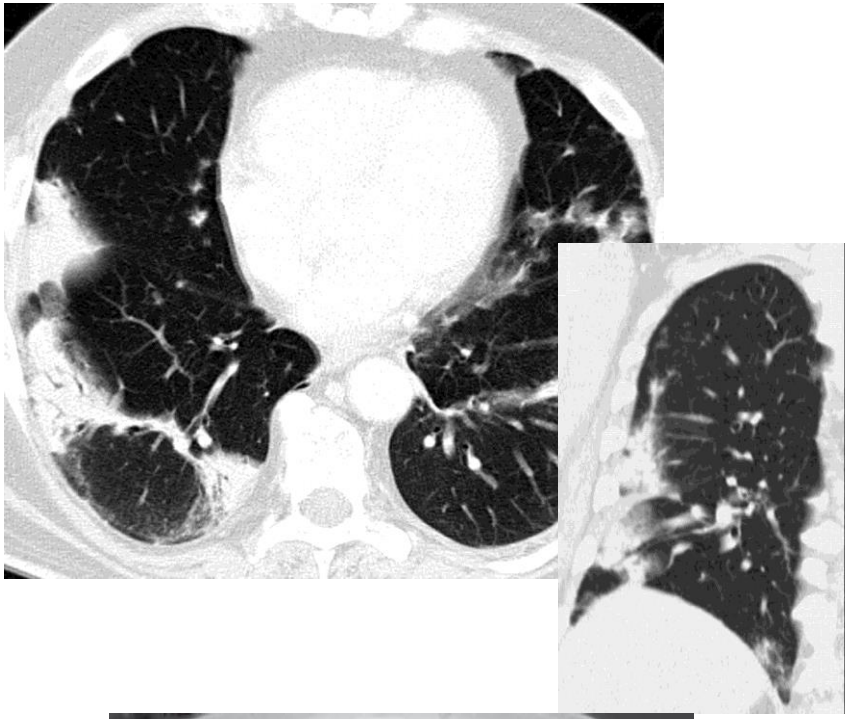
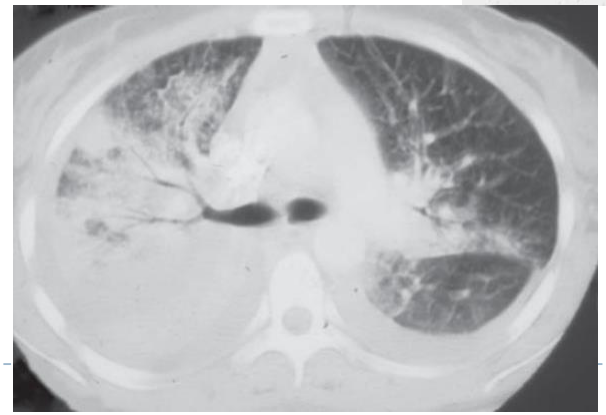
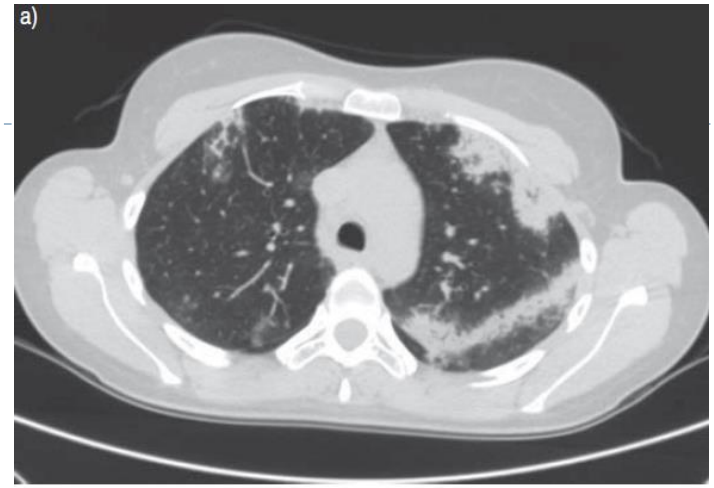
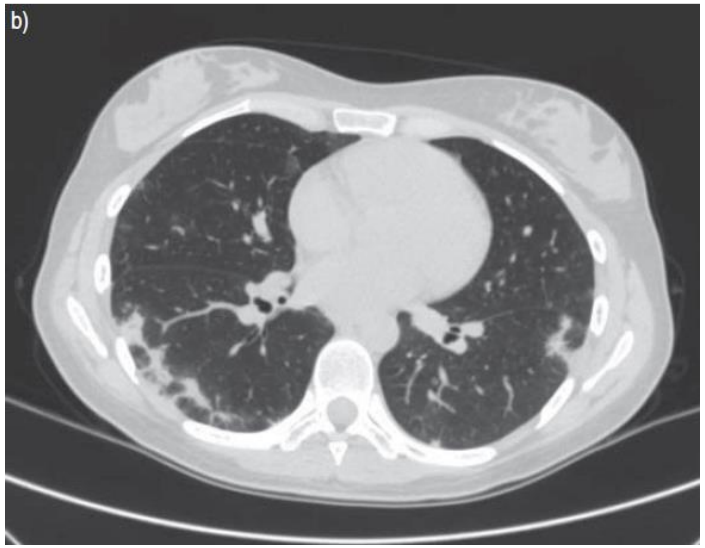
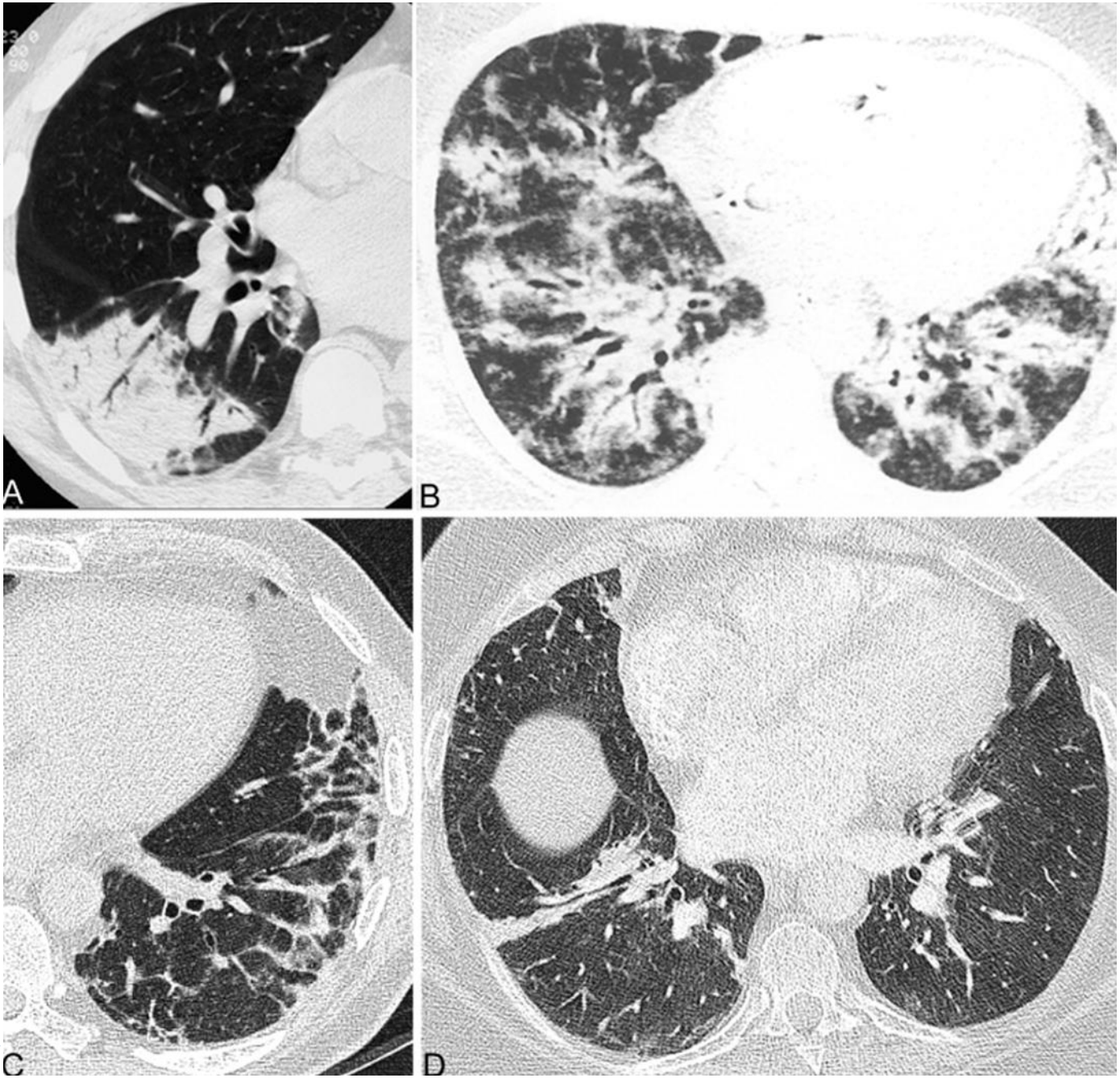
COP



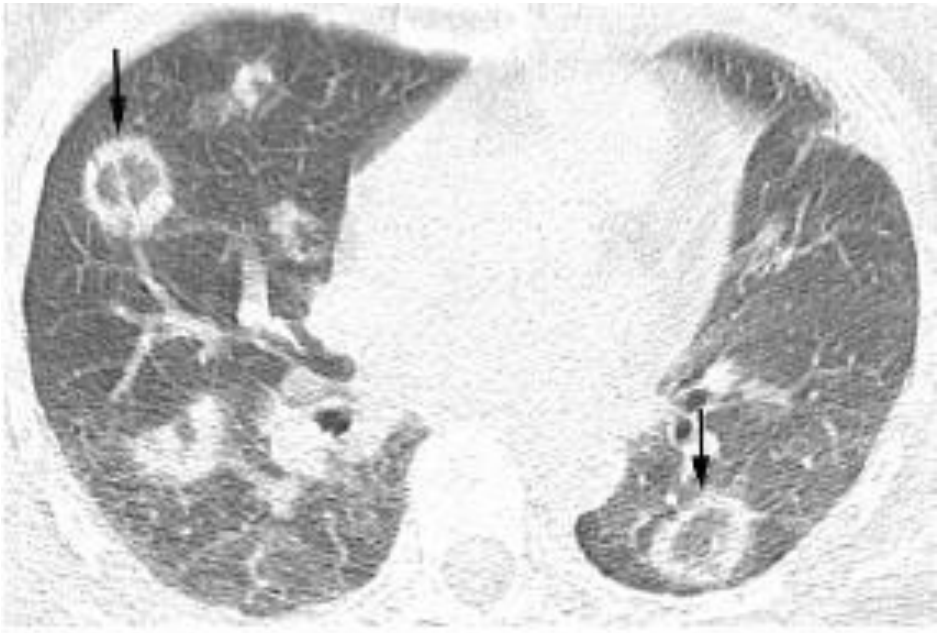







A
B
C
D

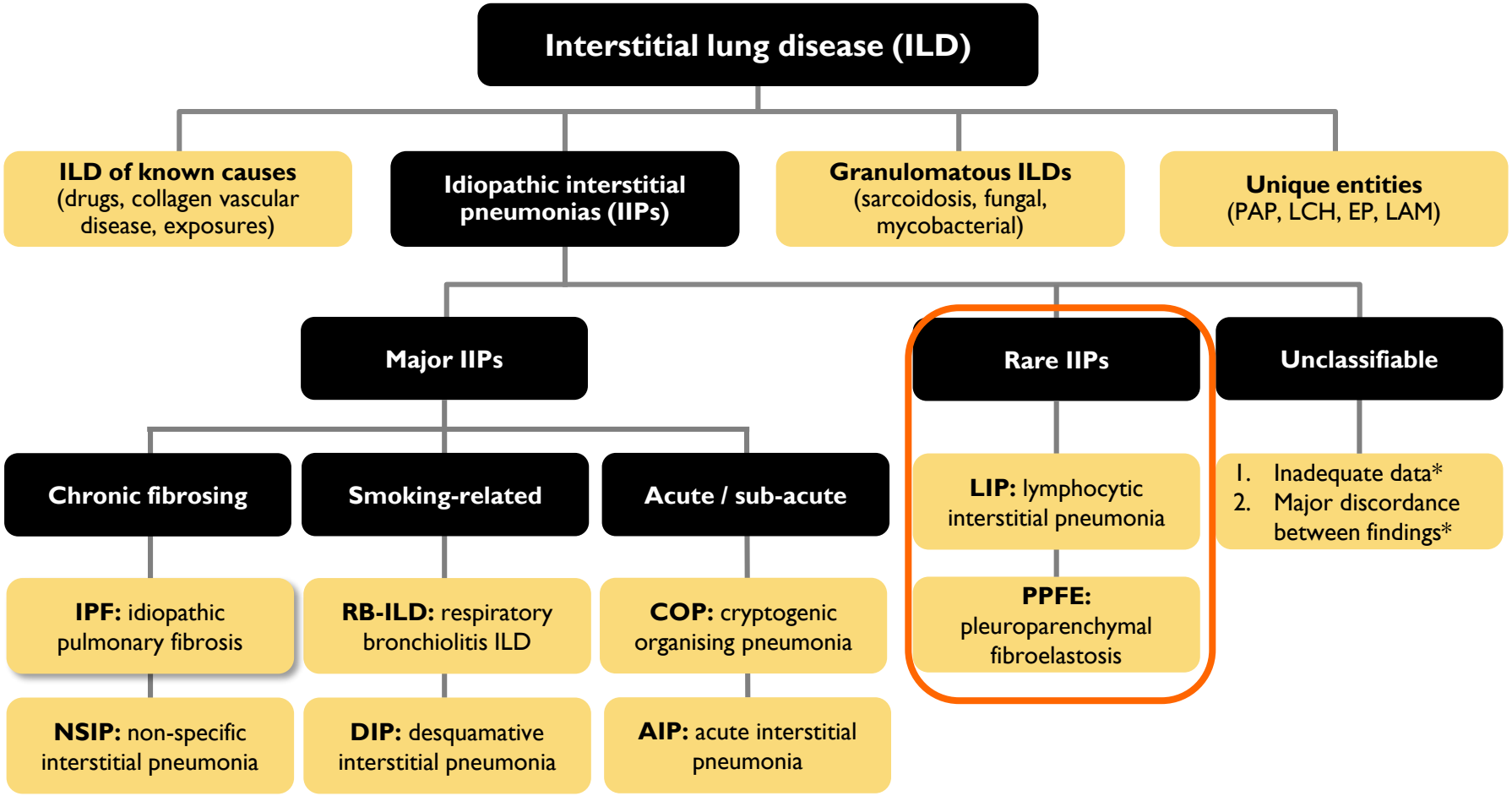
Reverse halo sign



Ακόμη σε:

- Tuberculosis
- Infectious pneumonia
- Aspergillosis
- Bronchoalveolar Ca
- Wegener's
- Sarcoidosis

Idiopathic pulmonary fibrosis is the commonest IIP



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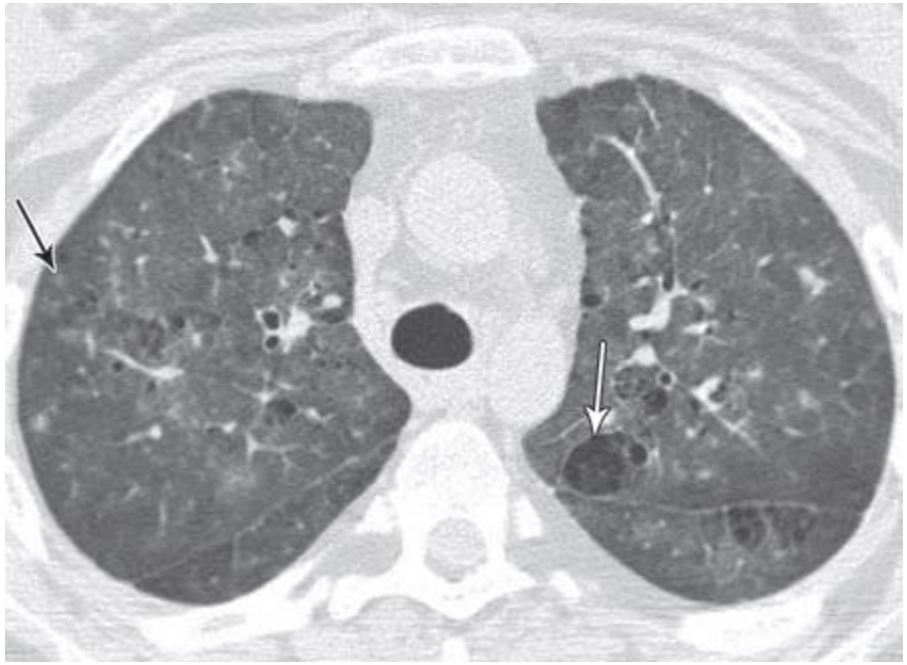
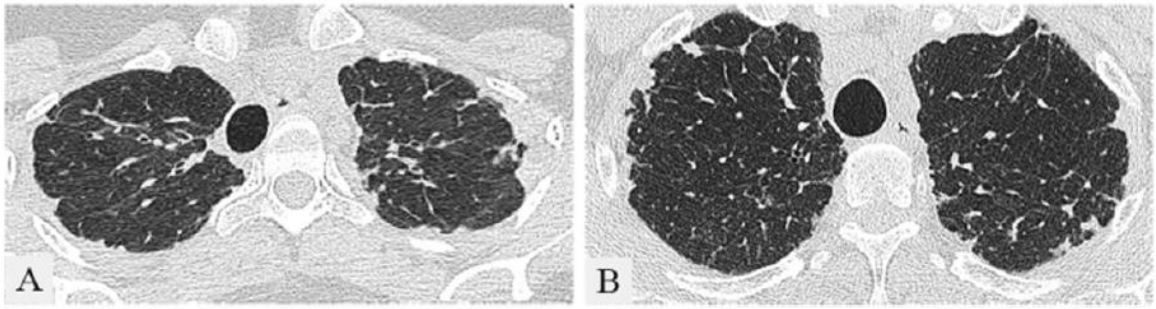
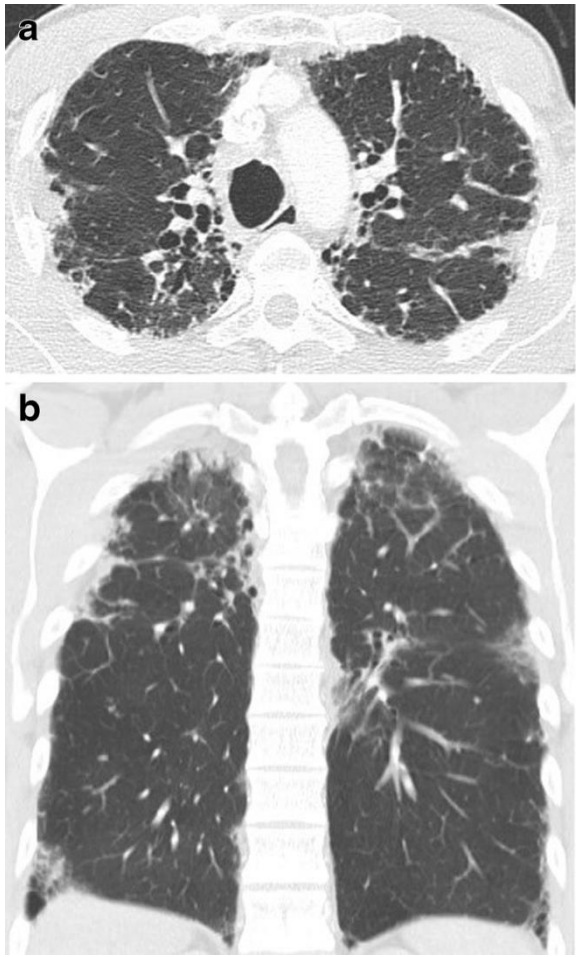
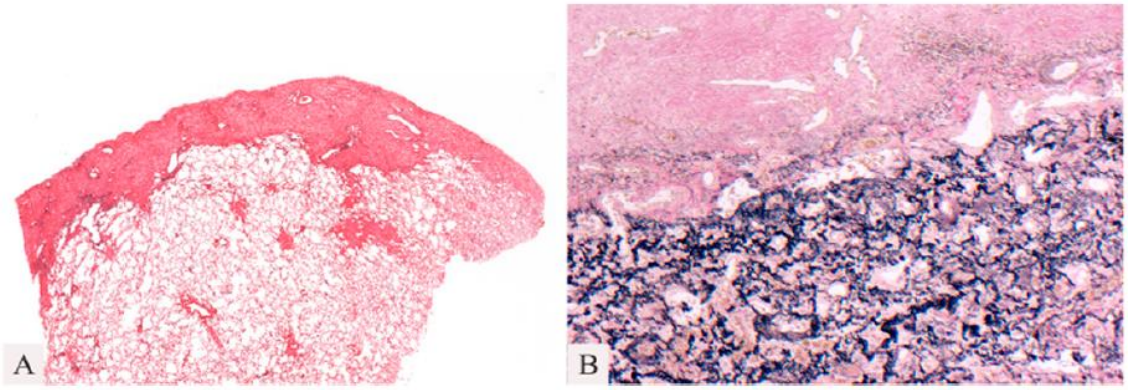
Lymphocytic Interstitial Pneumonia-LIP



PPFE-Pleuroparenchymal fibroelastosis



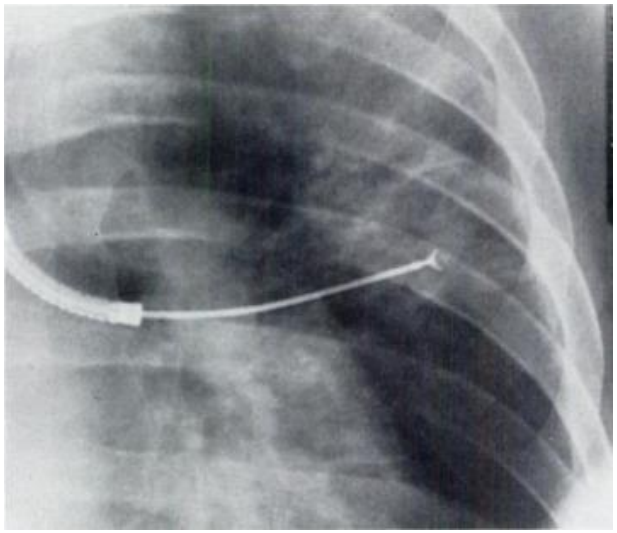




Am J Respir Crit Care Med Vol 188, Iss. 6, pp 733–748, Sep 15, 2013

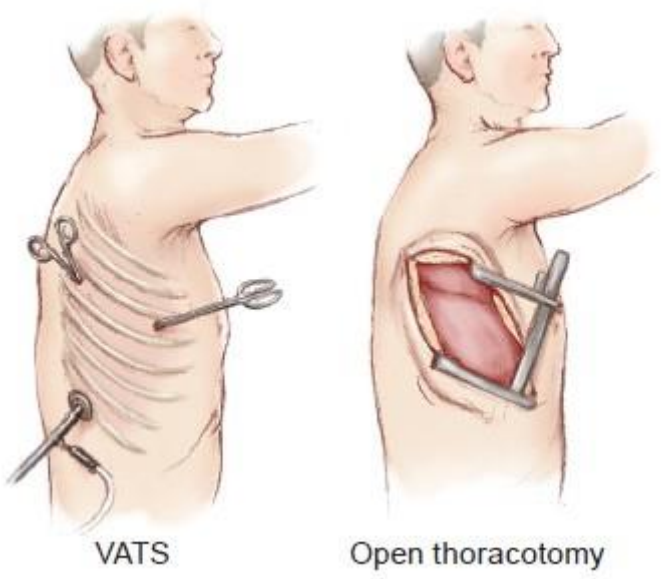
Tranbronchial lung biopsy

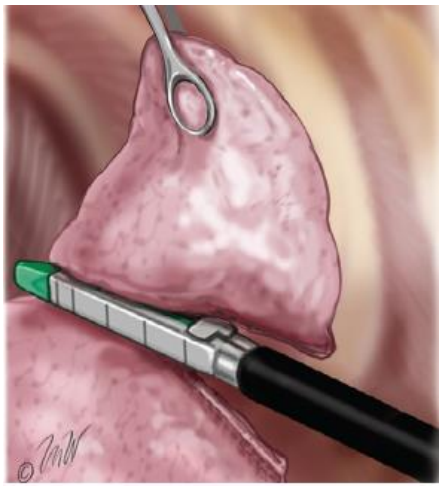
- Diagnosis in 36%
  - Pneumothorax 10%
  - Prolonged air leak 6%



Surgical lung biopsy

- Open lung biopsy
- VATS- video assisted thoracoscopy





Surgical lung biopsy

- Open lung biopsy
- Video-Assisted Thoracoscopic Surgery-VATS

- Diagnostic in 88%
  - 32%: IPF
  - 68%: Infection, sarcoidosis, HP, eosinophilic pneumonia, LAM, COP, vasculitis

  - Mortality: 3,5%
  - Minor side effects: 25%

- Significant rise in mortality and morbidity if DIco <50% pred.

Eur J Cardiothorac Surg. 2007 Jun;31(6):1115-9. Epub 2007 Apr 5,

Am J Respir Crit Care Med Vol 193, Iss 10, pp 1161–1167, May 15, 2016

- 2820 patients in Britain in 1997-2008
- Mortality:

	In-hospital	30-day	90-day
Elective	1%	1,5%	2,8%
Non-elective	4,6%	6,3%	8,8%

- Pneumothorax 4,2%
- Pneumonia 2,8%
- Pleural effusion 1,4%

- Median hospital stay 4 days (0-82)

ERJ 2016; 48:1274-77

Multidisciplinary discussion (MDT)

•Pulmonologist •Radiologist •Pathologist •Rheumatologist	
	➢Live ➢Teleconference ➢By phone ➢E-mail

Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study

Dr Simon L F Walsh, MD, Prof Athol U Wells, MD, Sujal R Desai, MD, Prof Venerino Poletti, MD, Sara Piciucchi, MD, Alessandra Dubini, MD, Prof Hilario Nunes, MD, Prof Dominique Valeyre, MD, Prof Pierre Y Brillet, MD, Marianne Kambouchner, MD, Prof António Morais, MD, José M Pereira, MD, Conceição Souto Moura, MD, Prof Jan C Grutters, MD, Daniel A van den Heuvel, MD, Hendrik W van Es, MD, Matthijs F van Oosterhout, MD, Cornelis A Seldenrijk, MD, Elisabeth Bendstrup, PhD, Finn Rasmussen, MD, Line B Madsen, PhD, Bibek Gooptu, PhD, Sabine Pomplun, FRCPath, Hiroyuki Taniguchi, MD, Prof Junya Fukuoka, MD, Takeshi Johkoh, MD, Prof Andrew G Nicholson, DM, Charlie Sayer, FRCR, Lilian Edmunds, FRCPath, Joseph Jacob, FRCR, Maria A Kokosi, MD, Prof Jeffrey L Myers, MD, Prof Kevin R Flaherty, MD, Prof David M Hansell, FRSM

	Clinicians (κ)		Radiologists (κ)		Pathologists (κ)		MDTM (κ)	
	Total (n=70)	No biopsy (n=48)	Total (n=70)	No biopsy (n=48)	Total (n=70)	No biopsy (n=48)	Total (n=70)	No biopsy (n=48)
Overall total	0·45	0·50	0·33	0·31	0·31	..	0·50	0·57
Idiopathic pulmonary fibrosis total	0·59	0·71	0·46	0·42	0·46	..	0·60	0·70
Non-specific interstitial pneumonia total	0·19	0·19	0·25	0·25	0·23	..	0·25	0·25
Connective tissue disease-related interstitial lung disease total	0·57	0·62	0·10	0·11	0·22	..	0·64	0·73
Hypersensitivity pneumonitis total	0·25	0·38	0·27	0·22	0·20	..	0·24	0·31

Lancet Respir Med 2016;4(7):557-565

Σας ευχαριστώ!