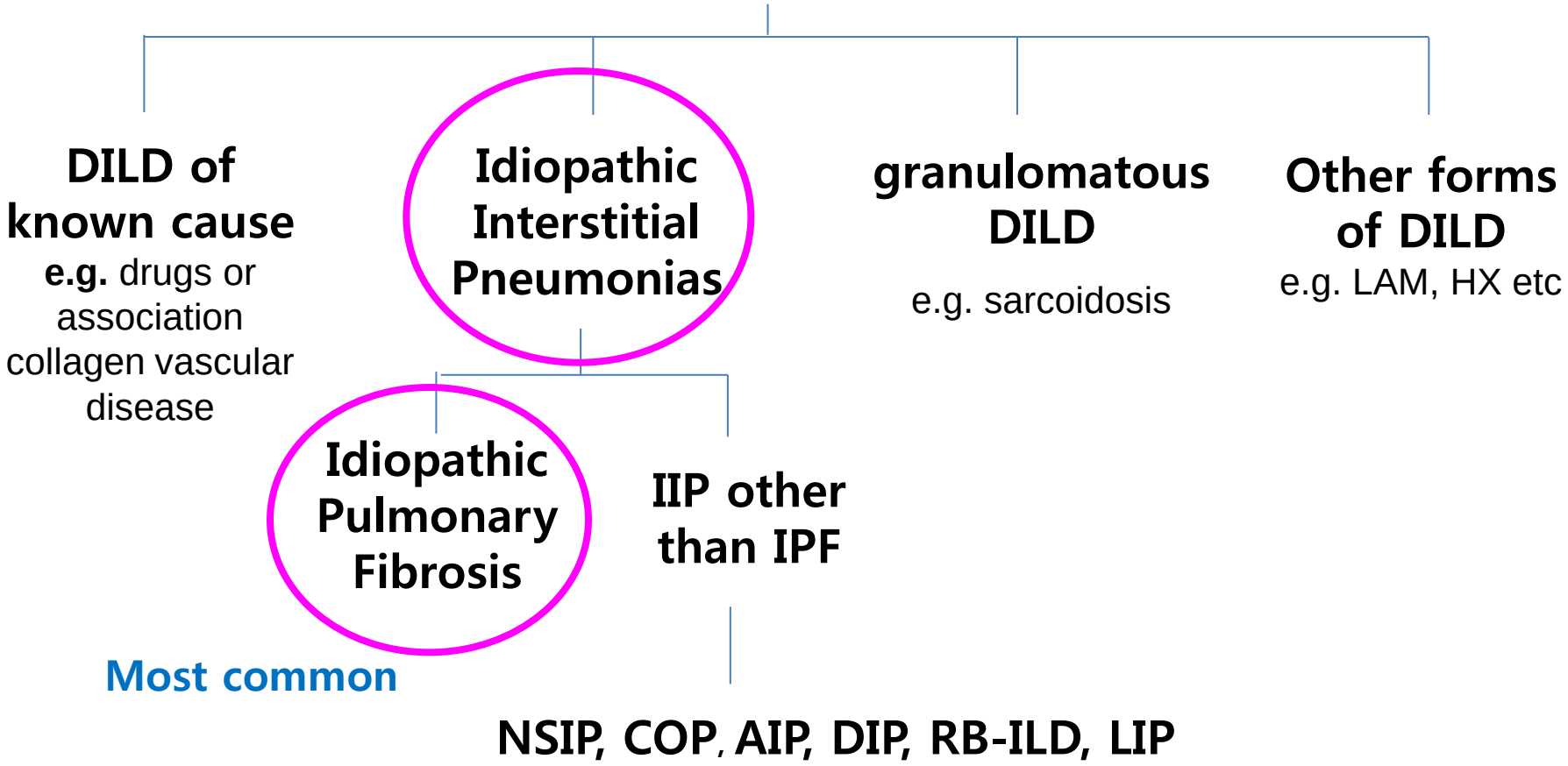
ILD진단의 guideline과 실제
- 2011, 2013 guideline을 중심으로

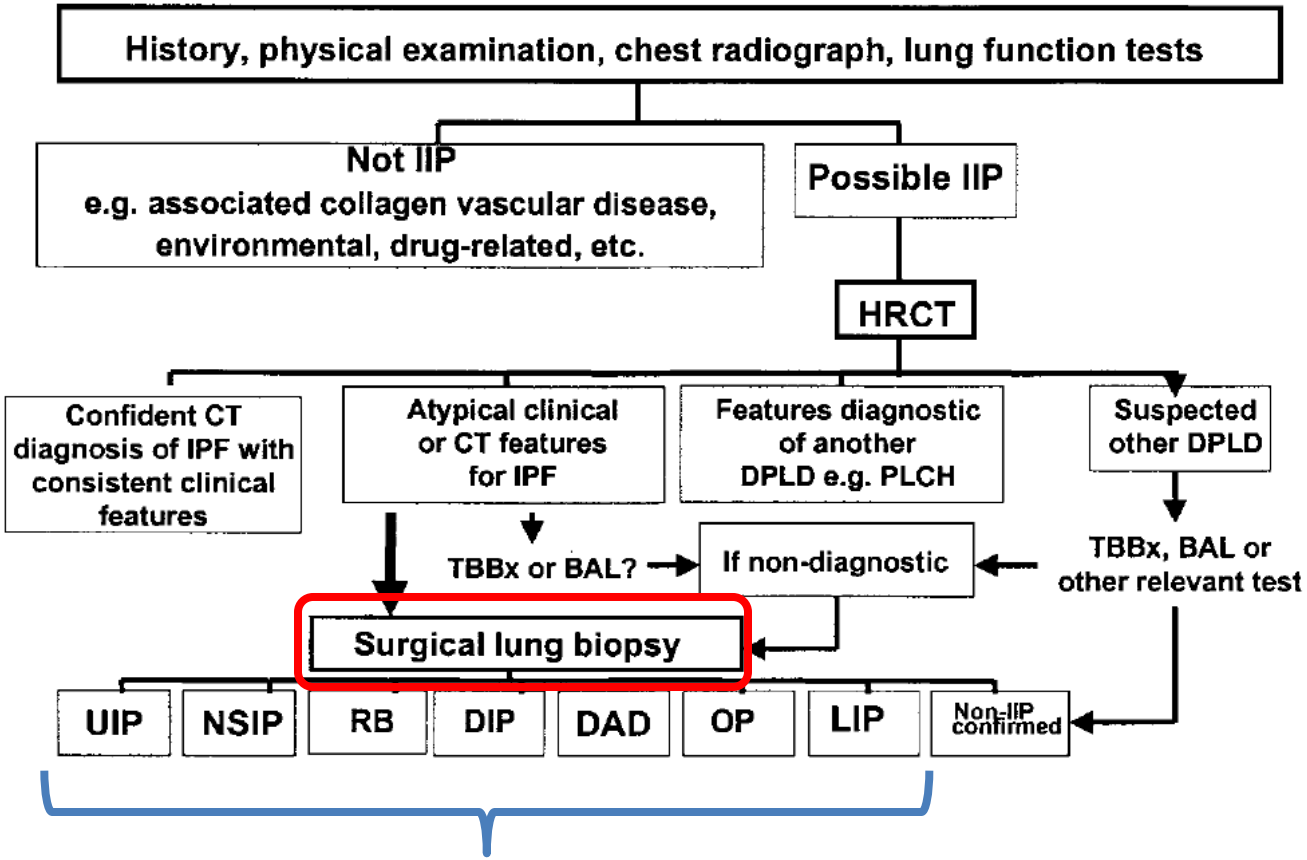
분당서울대학교병원 호흡기내과
박종선
2016.3.19
ILD school

Diffuse Parenchymal Lung Disease



AJRCCM 2002;165:277-304

Diagnostic process in DPLD



Clinical evaluation

Radiologic evaluation

Pathologic evaluation

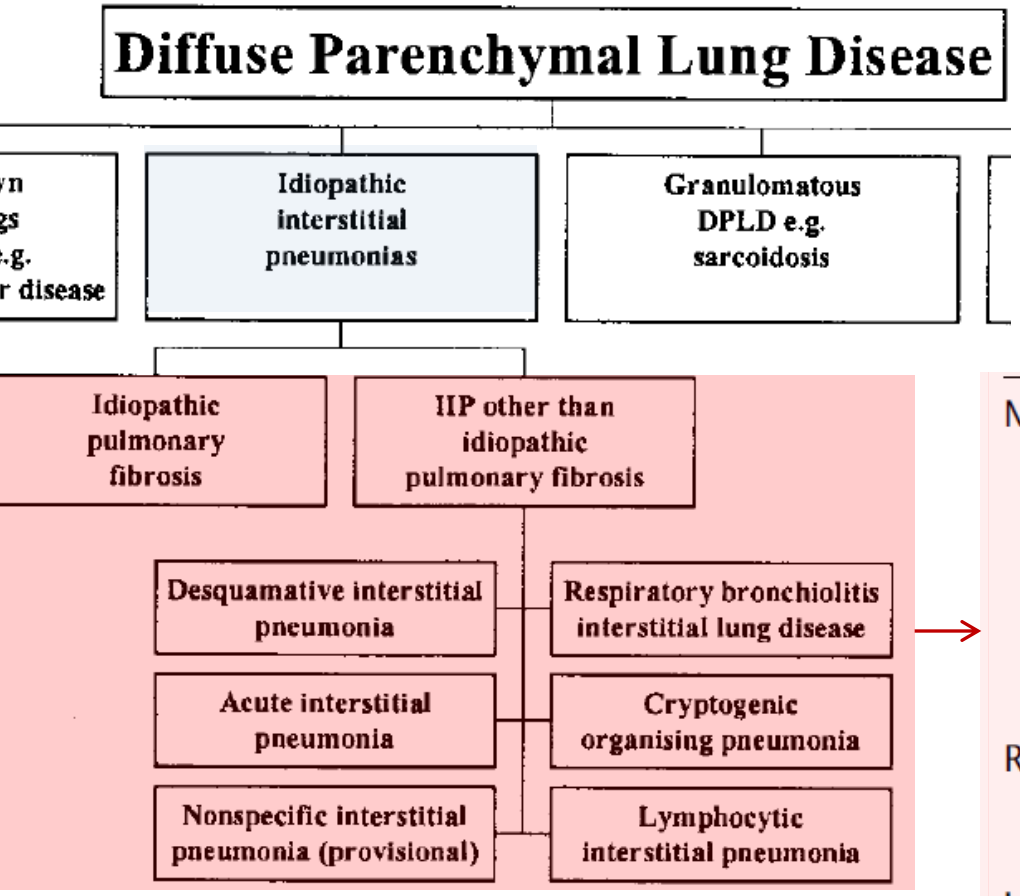
AJRCCM 2002;165:277
AJRCCM 2013;188:733

Classification of idiopathic interstitial pneumonia (IIP)

	CPR Diagnosis	Morphologic "Pattern"
chronic fibrosing IPs	idiopathic pulmonary fibrosis (IPF)	usual IP (UIP)
	idiopathic nonspecific IP (NSIP)	nonspecific IP (NSIP)
smoking-related IPs	respiratory bronchiolitis interstitial lung disease (RBILD)	respiratory bronchiolitis
	desquamative IP (DIP)	desquamative IP (DIP)
acute/subacute IPs	cryptogenic organizing pneumonia	organizing pneumonia
	acute IP (AIP)	diffuse alveolar damage (DAD)

AJRCCM 2013;188:733

2013 Revised ATS/ERS Classification of IIP



→

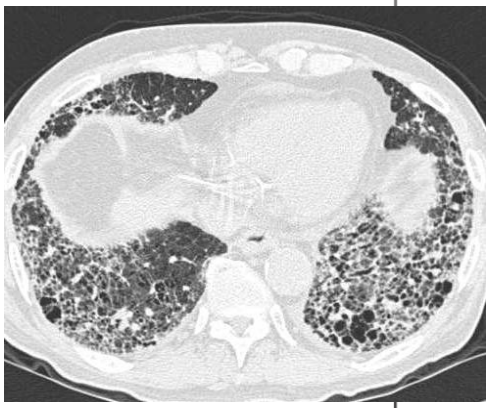
Major idiopathic interstitial pneumonias
- Idiopathic pulmonary fibrosis
- Idiopathic nonspecific interstitial pneumonia
- Respiratory bronchiolitis–interstitial lung disease
- Desquamative interstitial pneumonia
- Cryptogenic organizing pneumonia
- Acute interstitial pneumonia

Rare idiopathic interstitial pneumonias
- Idiopathic lymphoid interstitial pneumonia
- Idiopathic pleuroparenchymal fibroelastosis

Unclassifiable idiopathic interstitial pneumonias*

AJRCCM 2013;188:733

Diagnostic algorithm for IPF



Suspected IPF

Identifiable causes for ILD?

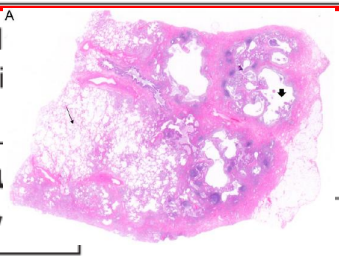
Yes

No

HRCT

Possibl

Inconsi



Surgical Lu Biopsy

Not UIP †

UIP †

Probable UIP † / Possible UIP †

Non-classifiable fibrosis †

MDD

Multidisciplinary discussion

IPF

IPF/Not IPF per Table 6

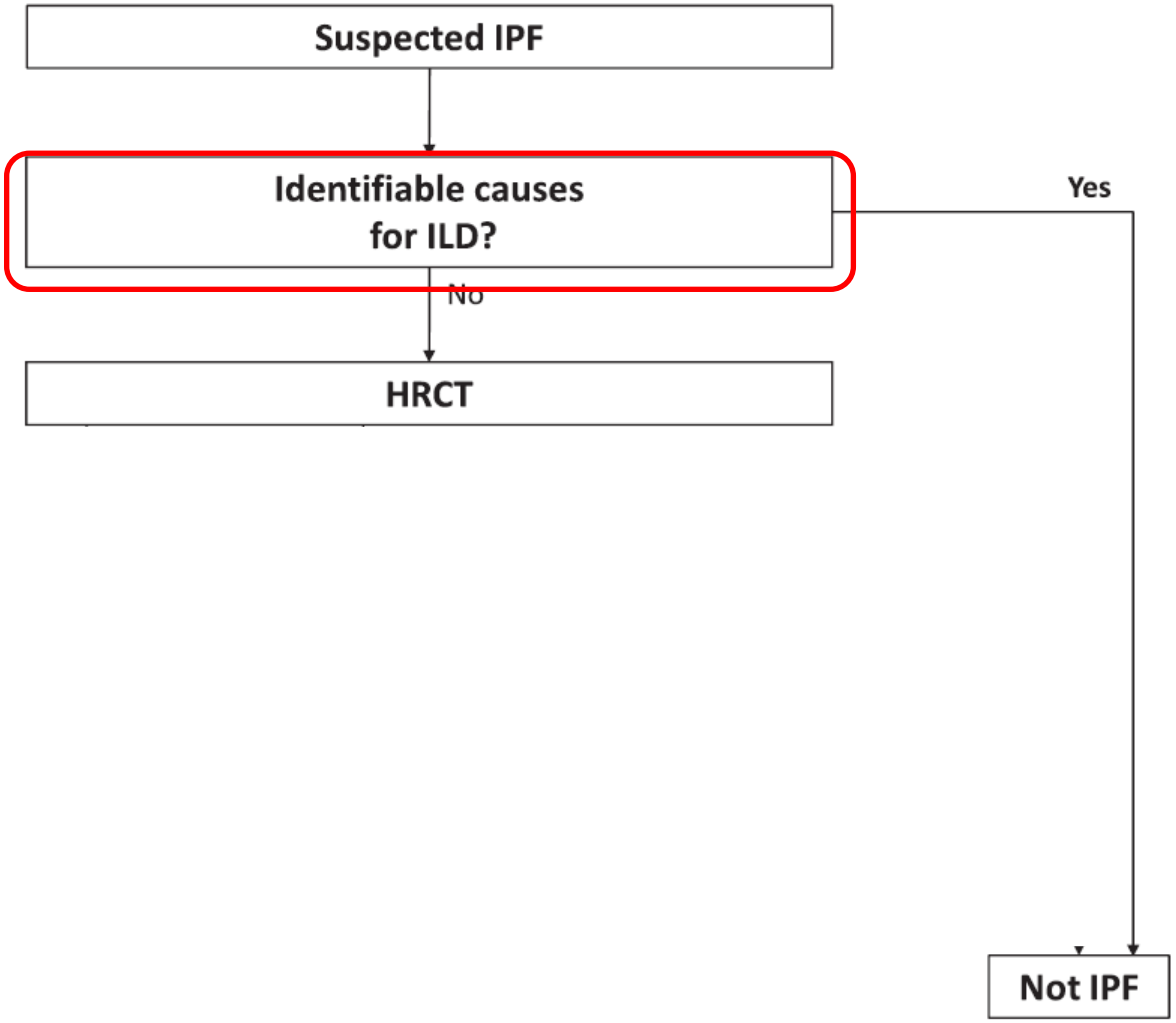
Not IPF

Diagnosis of IPF

Historical "gold standard" of histologic diagnosis

" Dynamic integrated approach" using multidisciplinary discussion

Diagnostic algorithm for IPF



Identifiable causes for ILD

- Connective tissue disease
- Environmental exposure
- Occupational exposure
- Drug exposure

Careful Hx taking, P/Ex & Clinical suspicion !

- Differential diagnosis with IPF
  - Chronic hypersensitivity pneumonitis
  - Asbestosis

Identifiable causes for ILD; CTD

- Symptoms & signs suggesting connective tissue diseases
  - Morning stiffness
  - Arthralgia
  - Dysphagia
  - Skin lesion (facial rash, finger ulceration, purpura..)
  - Dry mouth, dry eye
  - Raynaud phenomenon..

Role of serologic test for CTD in Dx of ILD

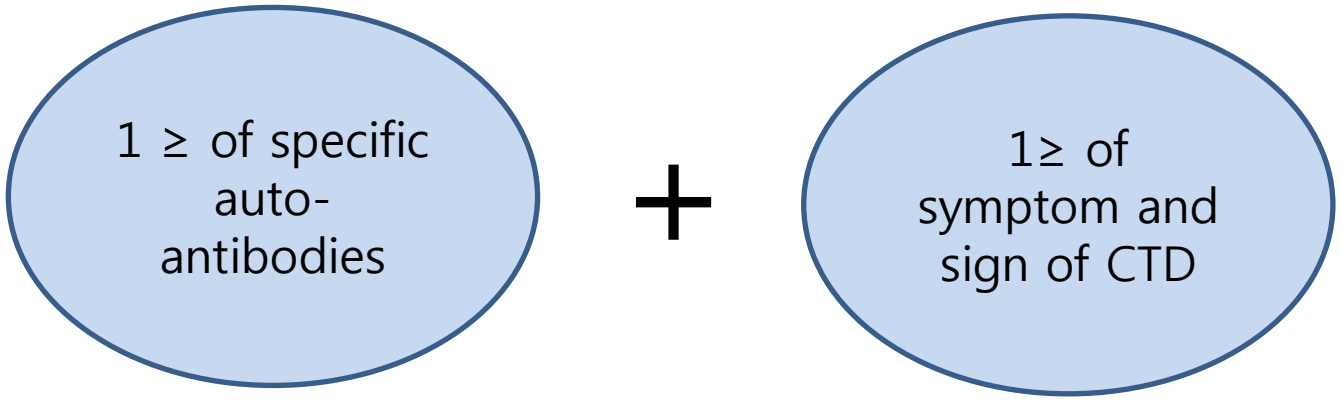
- ILD may precede the overt manifestation of a specific CTD.

- RF, anti-CCP, ANA
  - Recommend even in the absence of signs and symptoms of CTD.

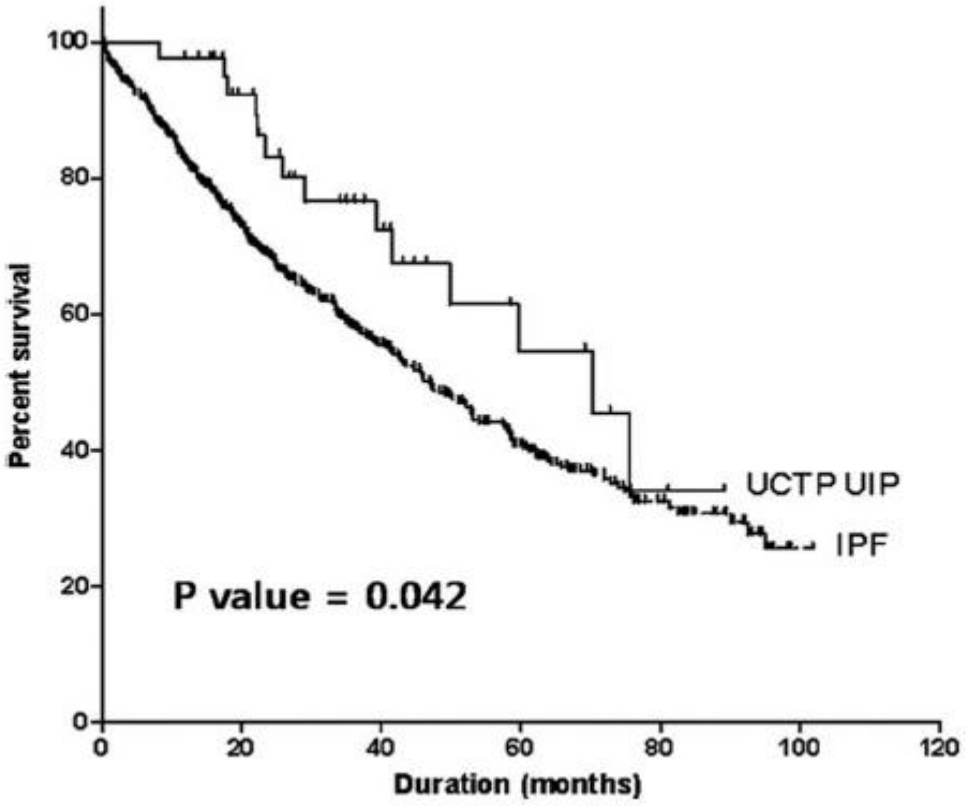
- Role of other serologic tests for CTD in Dx of ILD is unclear.

Autoimmune associated ILD

- Various names
  - Undifferentiated CTD (UCTD) with ILD
  - Autoimmune featured ILD
  - Lung dominant CTD



Prognosis of UCTD-UIP



CHEST 2015; 147(1) : 165

Identifiable causes for ILD ; Chronic HP

Bird Breeder's Disease
Bird Fancier's Lung

→ Acute form

→ Chronic form

Morell F, et al. Bird fancier's lung. A series of 86 patients. *Medicine*. 2008;87(2):110-30

→ Pulmonary Fibrosis

Morell F, et al. Hypersensitivity pneumonitis by feather duvet. ERS Congress. Viena 2012

Major antigens causing HP

Type of Antigen	Examples of Sources
Mushrooms, fungi, yeasts	Contaminated wood, humidifiers, central hot air heating ducts, peat moss plants
Bacteria	Dairy barns (farmer's lung)
Mycobacteria	Metalworking fluids, sauna, hot tub
Bird proteins	Pigeons, dove feathers, ducks, parakeets
Chemicals	Isocyanates (auto painters), zinc, dyes

HP = hypersensitivity pneumonitis.

CHEST 2012; 142(1):208

ILD Questionnaire

CHEST™

Interstitial and Diffuse Lung Disease Patient Questionnaire

1. **How often do you cough?** *(Do not include clearing your throat.)*
   - ____ Not at all or rarely
   - ____ Occasionally, but not bothersome
   - ____ Most days
   - ____ Often or in severe attacks that interfere with activity

2. **How long have you been coughing?** _____ *(indicate in months, years)*

3. **Do you cough at night?** Yes ____ No ____
   If you cough at night, does it awaken you? Yes ____ No ____

4. **The cough produces (check all that apply):**

   _____ No phlegm _____Phlegm _____Blood _____I don't cough

17. Have you performed any of the following occupations?

____ Farm work	____ Automotive mechanic	____ Carpenter
____ Painter	____ Welder	____ Laboratory worker
____ Sand blaster	____ Insulator	____ Longshoreman
____ Pipe fitter	____ Vineyard worker	

18. Have you worked in any of the following locations:

____ Mine	____ Foundry
____ Quarry	____ Railroad
____ Pulp mill	____ Paper mill
____ Bakery	____ Smelting
____ Plastic factory	____ Tunnel construction

19. Have you ever been exposed to the following at work/ home/ elsewhere?

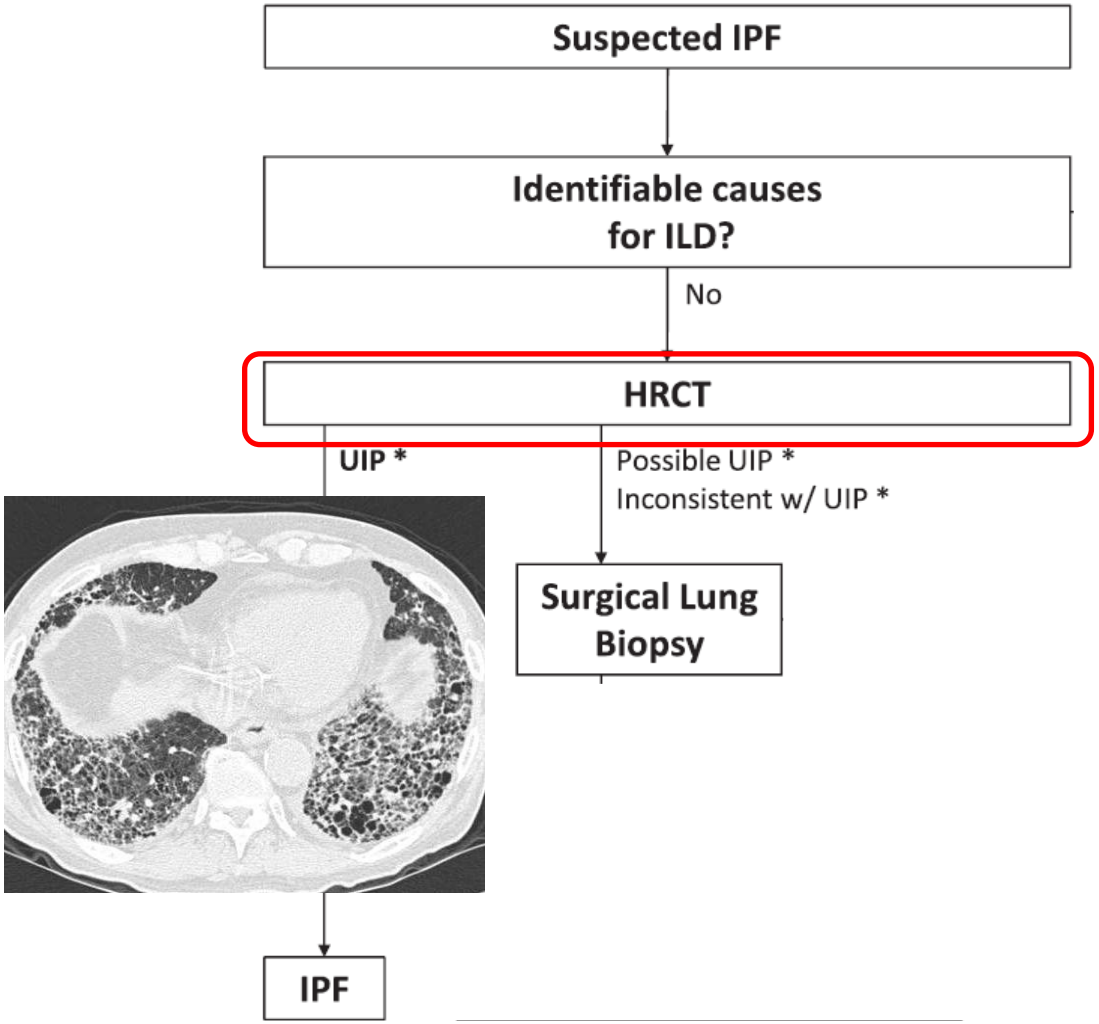
Animals and farming		Metals/rocks		Food/plant Production		Miscellaneous		Skilled	
Birds		Beryllium		Cheese		Cotton		Cork	
Feathers		Cobalt		Maple Bark		Wood		Detergent *(isocyanates)*	
Fishmeal		Tin		Wheat		Industrial strength cleaning solution		Pottery	
Insecticide		Iron oxide		Coffee/ tea		Oily Nosedrops		Talc	
Fertilizer		Aluminum		Mushroom				Paint	
		Mica		Oil				Cement	
		Silica		Sugar cane				Pipes	
		Asbestos		Malt				Brakes	
		Coal		Meat				Tile (ceramic)	

IPF vs. chronic HP

- **In IPF,** comprehensive study with re-evaluation
  - specific IgG, BAL > 20% of lymphocytes, provocation test, cryobiopsy, surgical lung biopsy
  - **IPF**: 50% can be chronic HP

Morell et al. LANCET RESPIR MED. 2013

Diagnostic algorithm for IPF

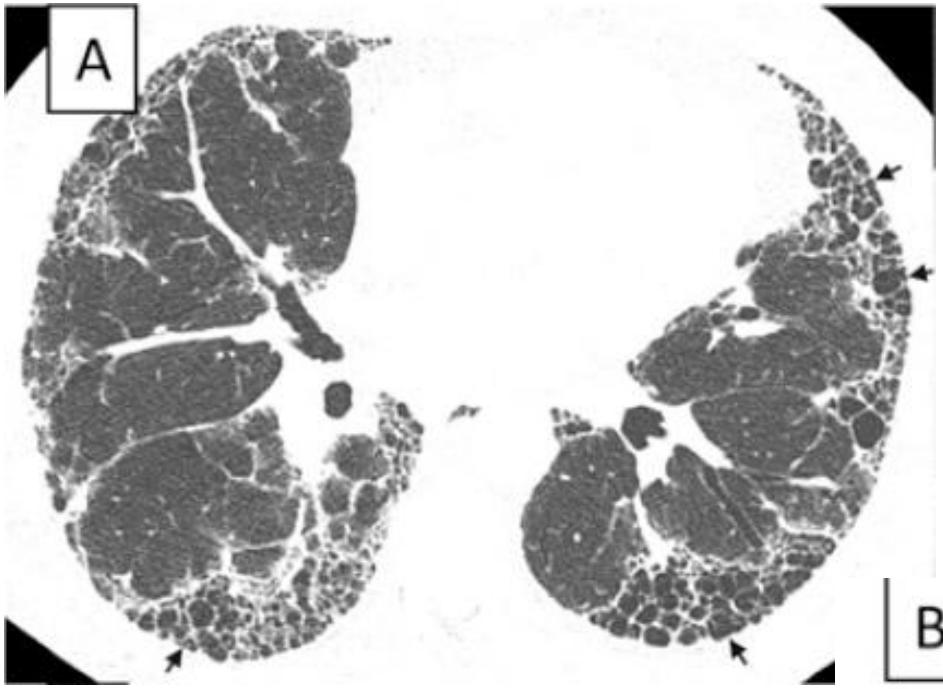


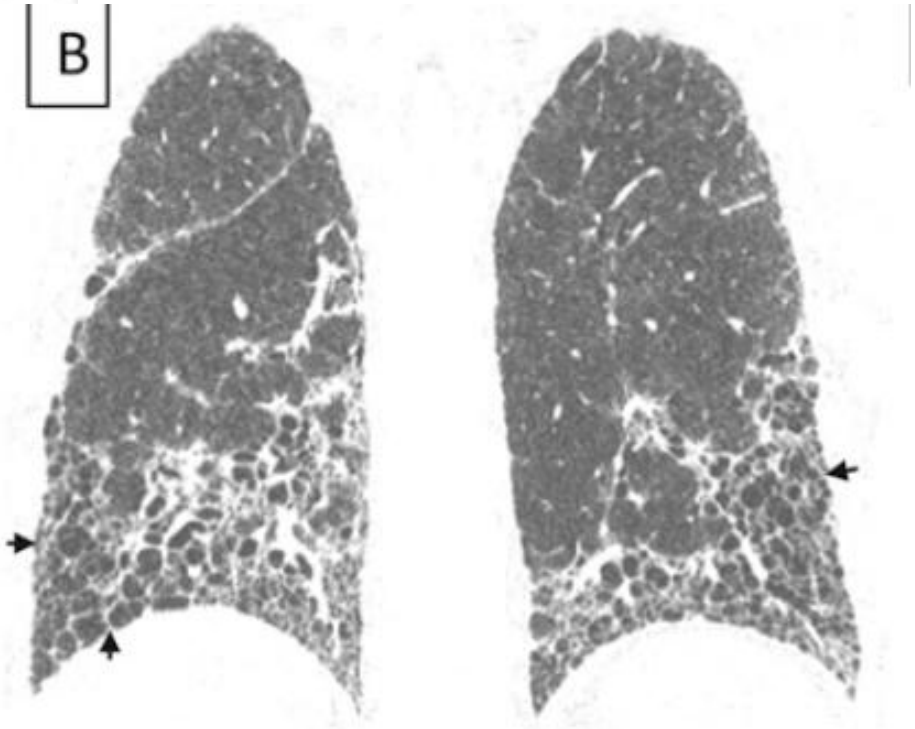
UIP Pattern : HRCT features

TABLE 4. HIGH-RESOLUTION COMPUTED TOMOGRAPHY CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Features)
• Subpleural, basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Subpleural, basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality (extent > reticular abnormality) • Profuse micronodules (bilateral, predominantly upper lobes) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes) • Consolidation in bronchopulmonary segment(s)/lobe(s)

UIP pattern

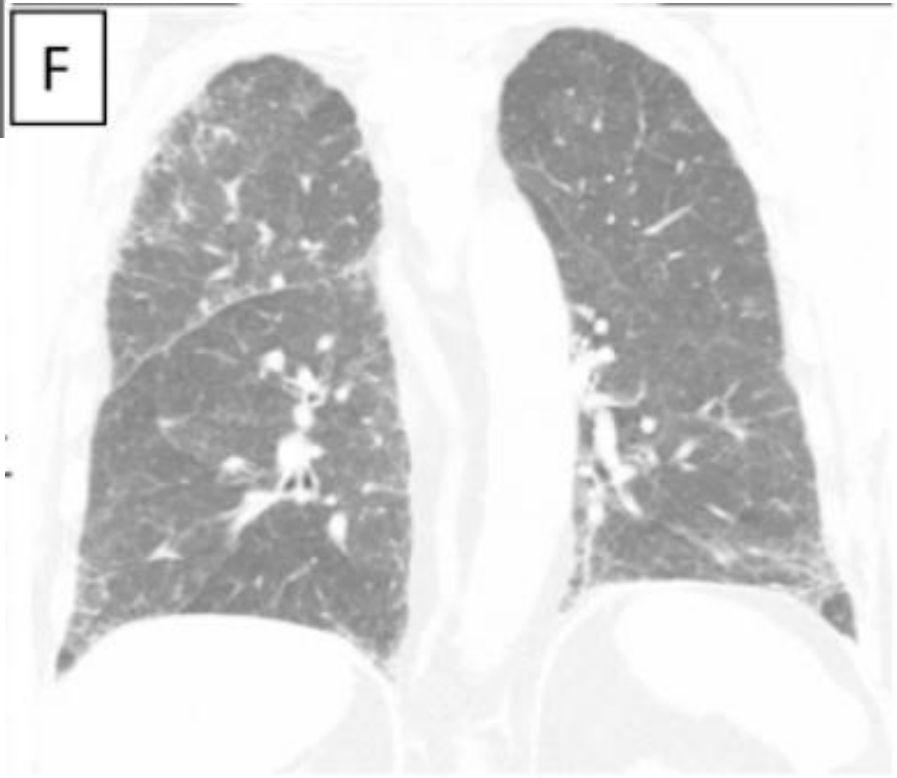




UIP pattern (All four features)

- Subpleural, basal predominance
- Reticular abnormality
- Honeycombing with or without traction bronchiectasis
- Absence of features listed as inconsistent with UIP pattern

Possible UIP pattern



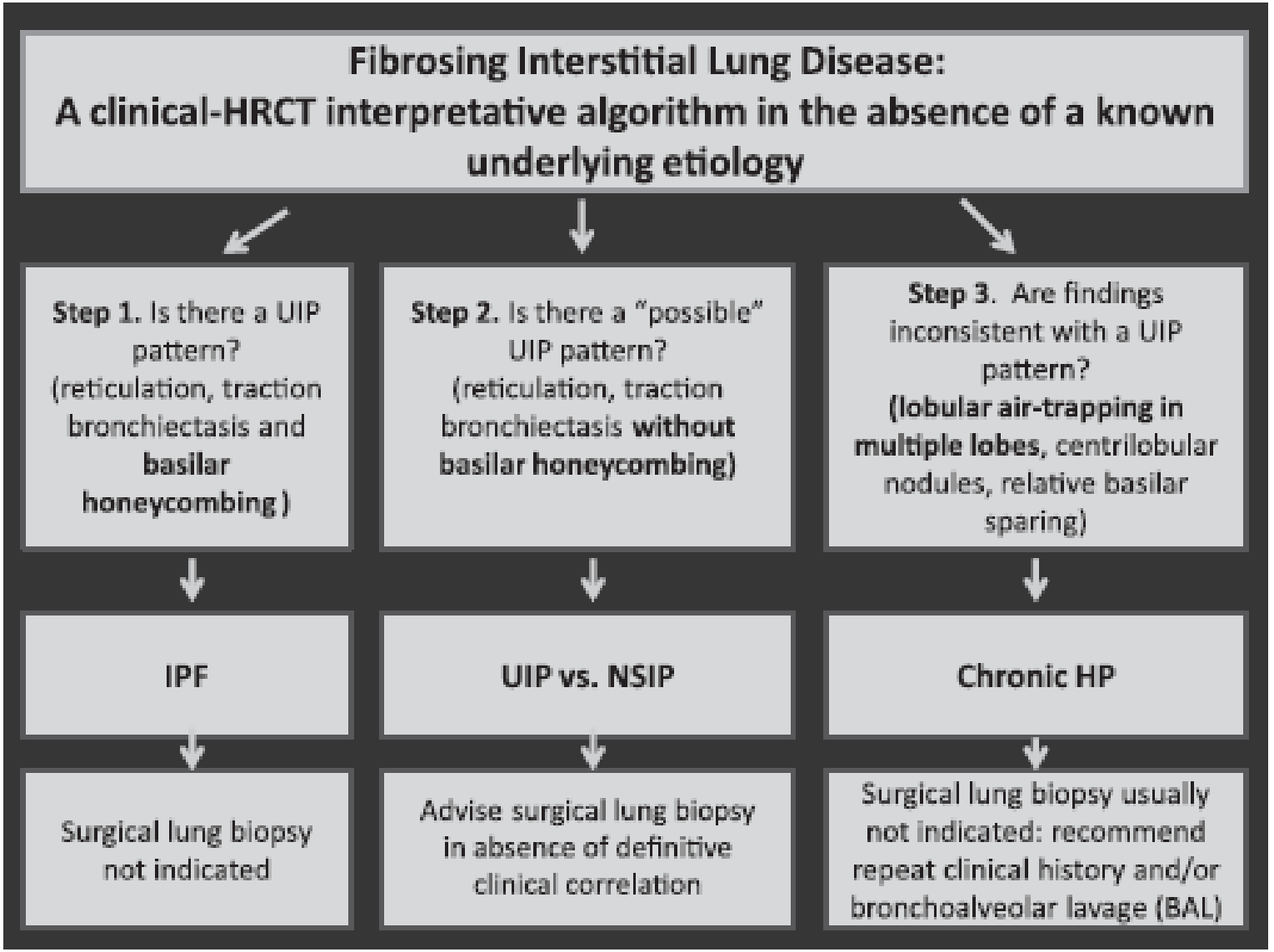
Possible UIP pattern (All three features)

- Subpleural, basal predominance
- Reticular abnormality
- Absence of features listed as inconsistent with UIP pattern

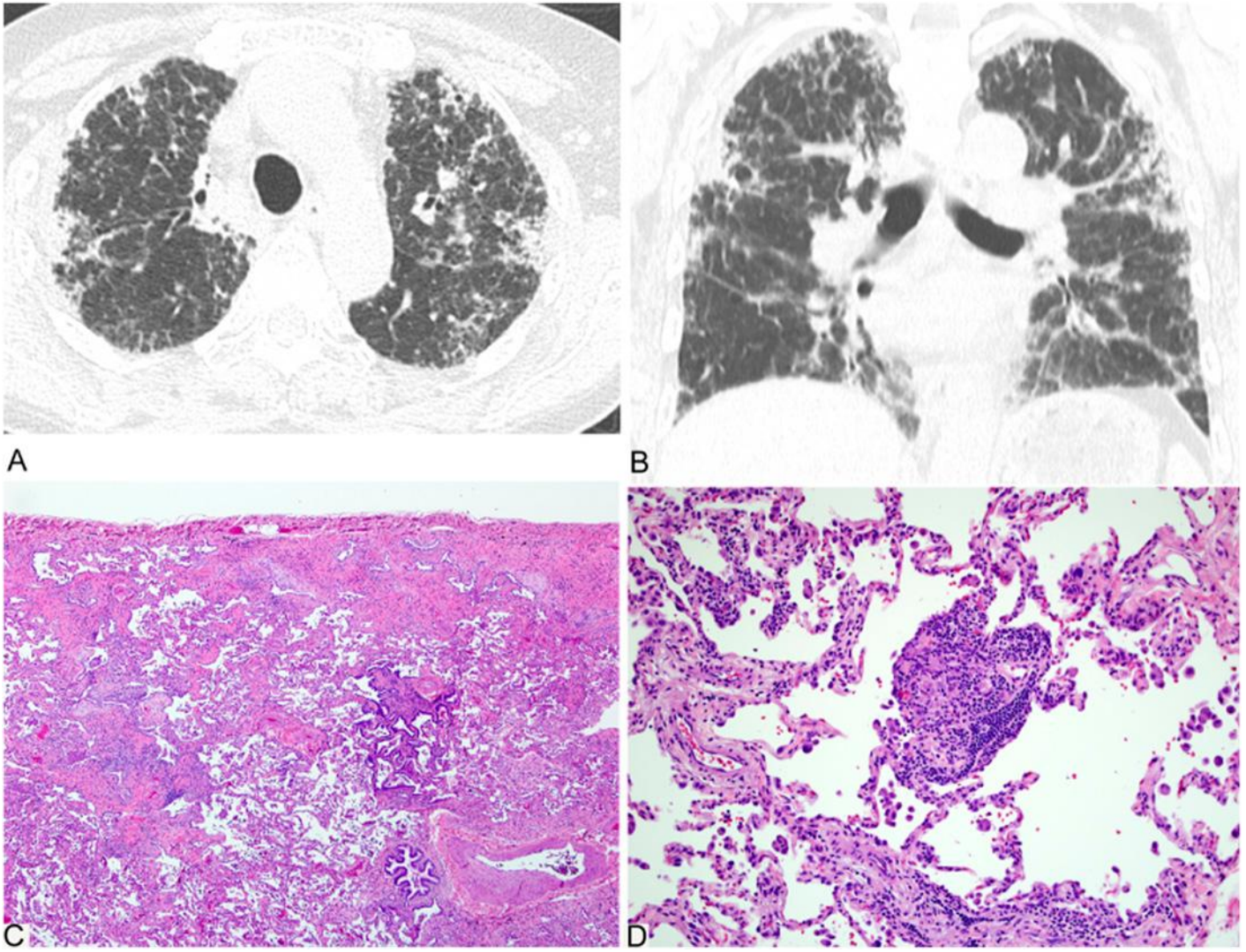
Inconsistent with UIP pattern

- Upper or mid-lung predominance
- Peribronchovascular predominance
- Extensive ground glass abnormality
  - extent >reticular abnormality
- Profuse micronodules
  - bilateral, predominantly upper lobes
- Discrete cysts
  - multiple, bilateral, away from areas of honeycombing
- Diffuse mosaic attenuation/air-trapping
  - bilateral, in three or more lobes
- Consolidation in bronchopulmonary segment(s)/lobe(s)

*Any of 7 features



AJRCCM 2013;188:141



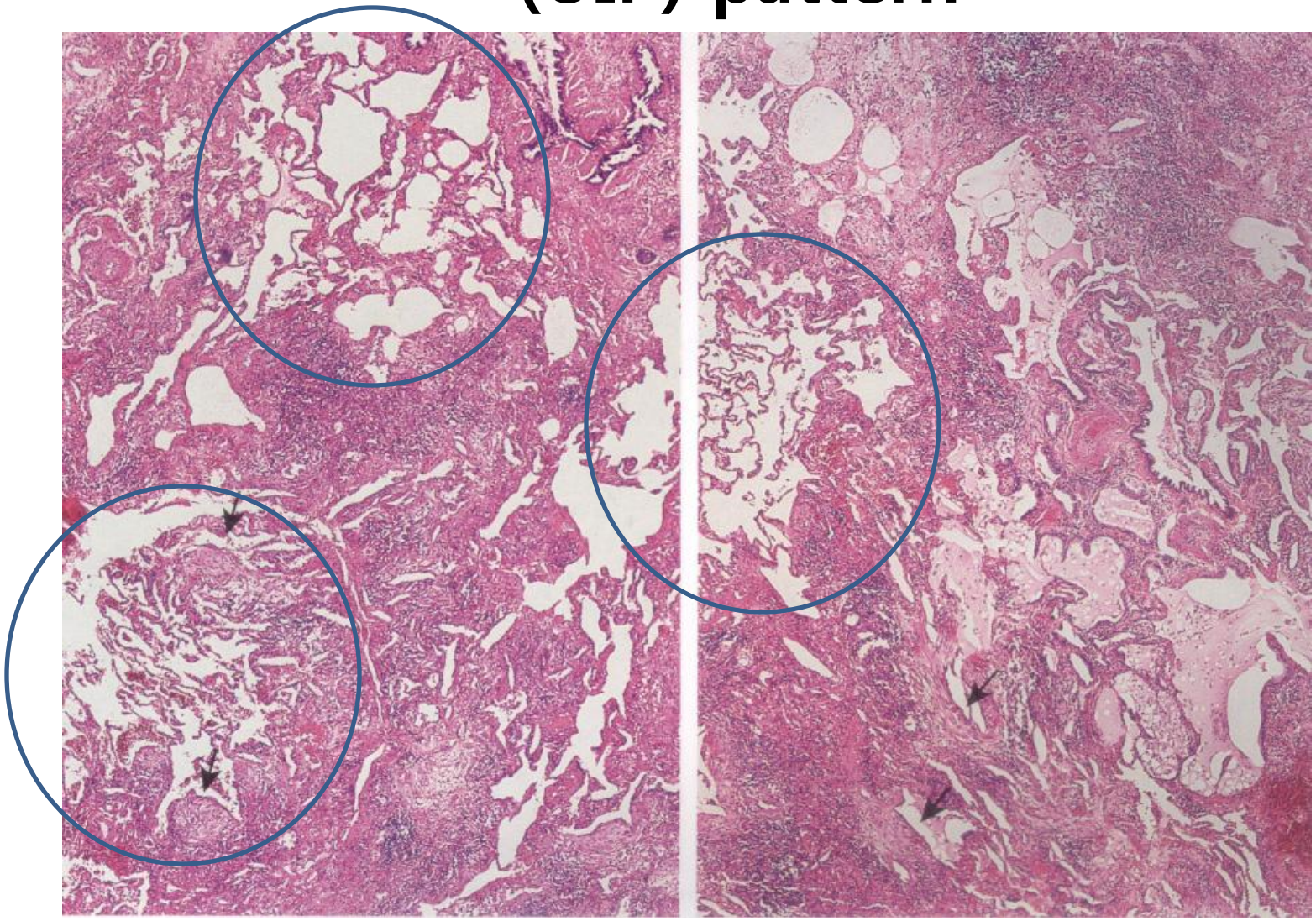
- 76-year-old bird-keeper with progressive shortness of breath over 6 years → Chonic HP !

UIP pattern : Histopathology features

UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
• Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	• Evidence of marked fibrosis / architectural distortion, ± honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column) OR • Honeycomb changes only‡	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (*see* UIP PATTERN column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)	• Hyaline membranes* • Organizing pneumonia*† • Granulomas† • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis

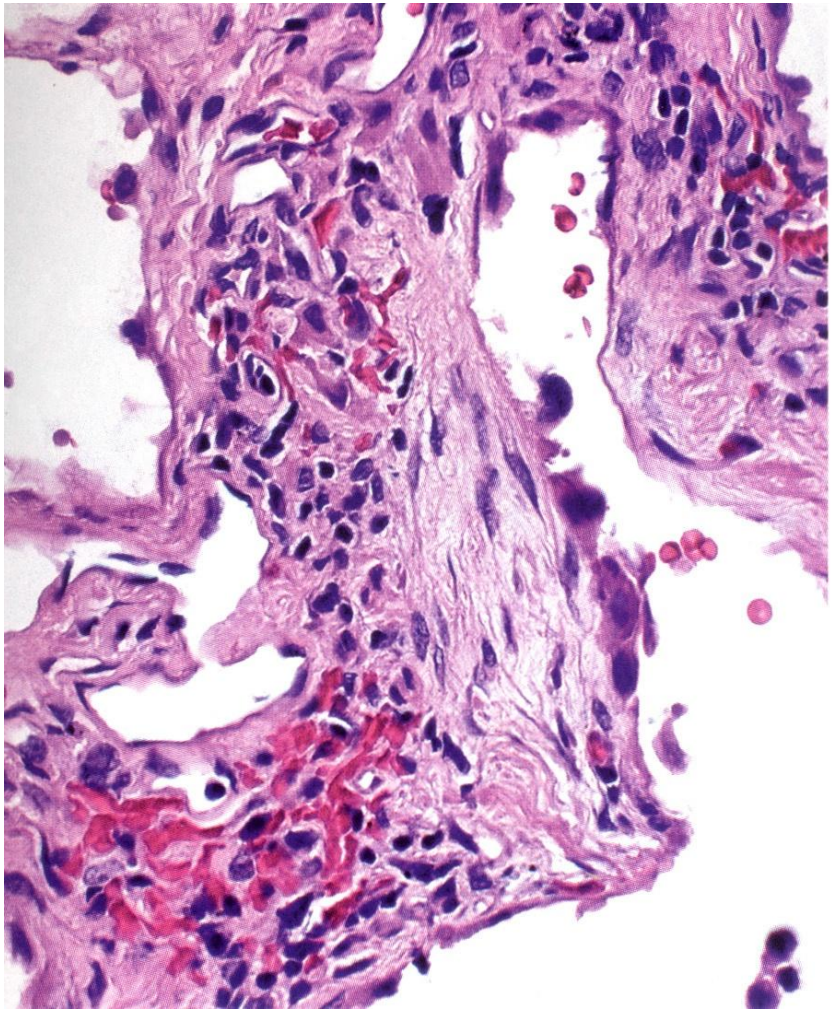
AJRCCM 2011;183:788-824

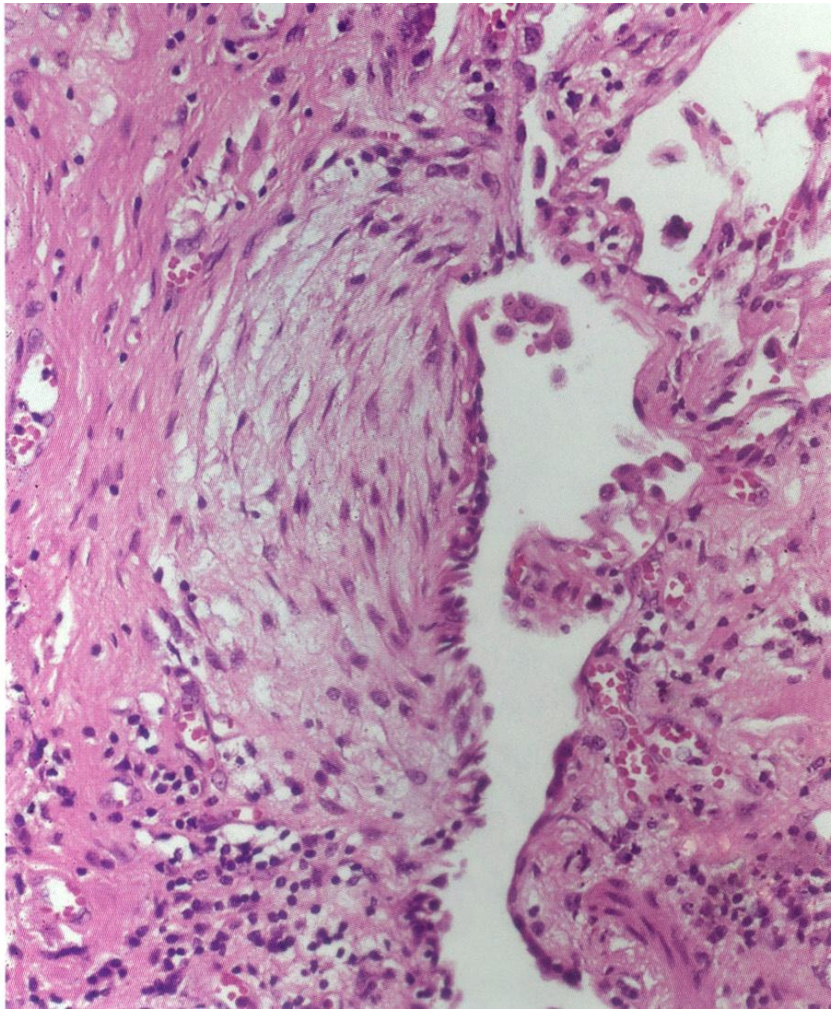
Histologic Usual Interstitial Pneumonia (UIP) pattern



patchwork pattern

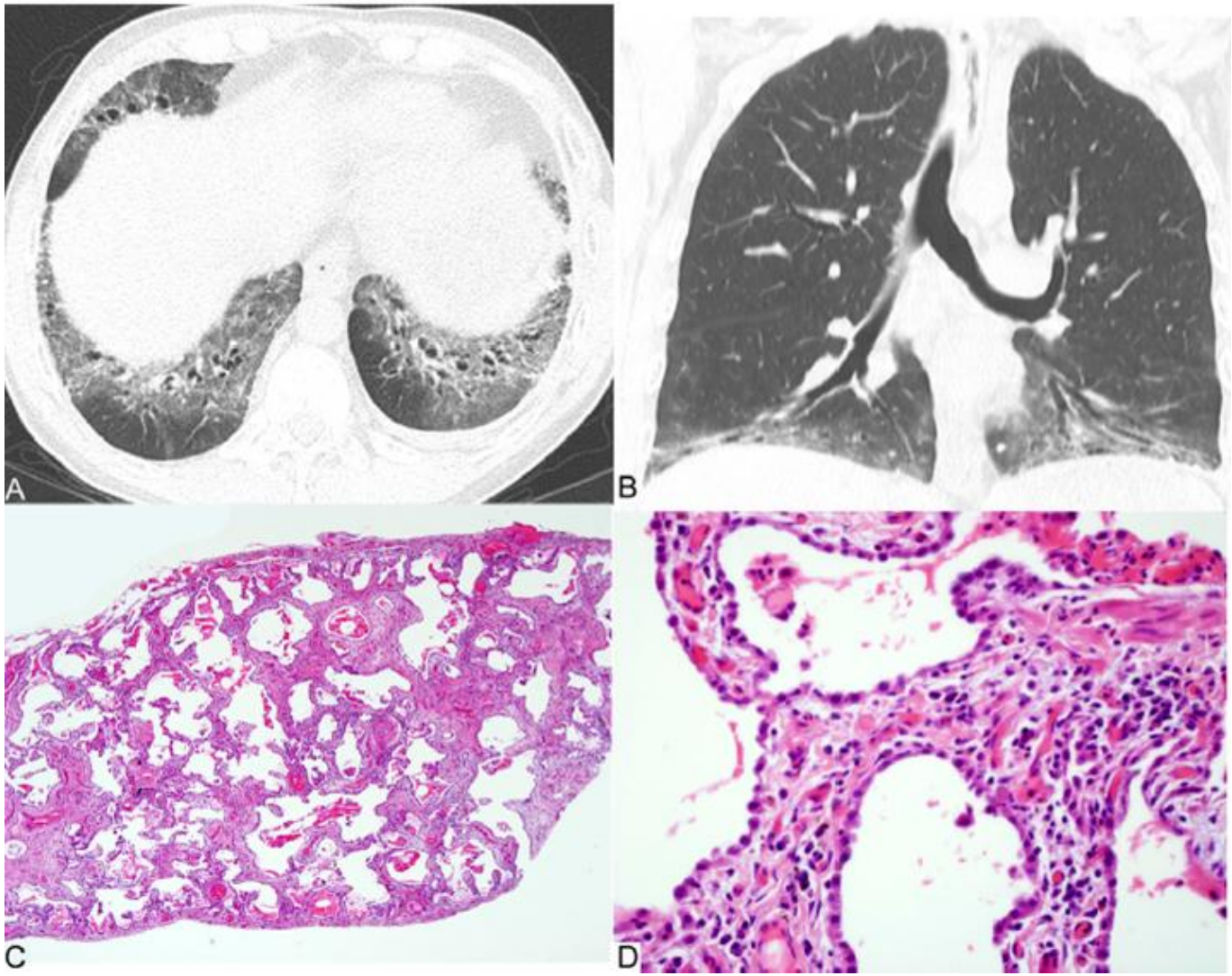
Histologic Usual Interstitial Pneumonia (UIP) pattern





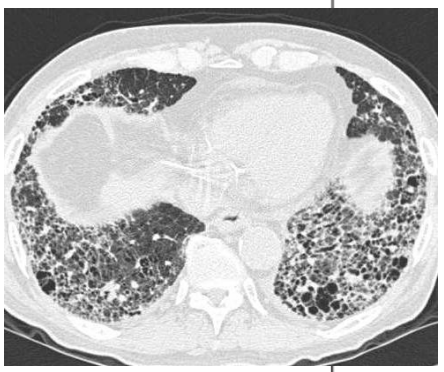
Fibroblast foci

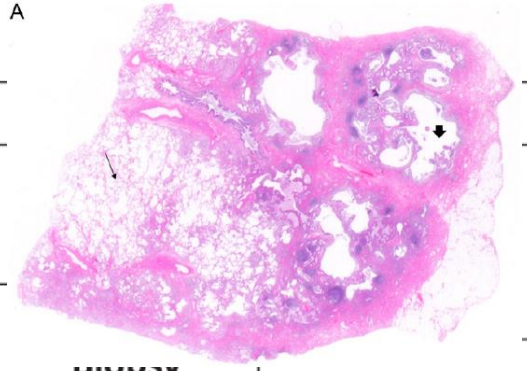
Nonspecific interstitial pneumonia



AJRCCM 2011;183:788-824

Diagnostic algorithm for IPF





Suspected IPF

Identifiable causes for ILD?

Yes

UIP *

Not UIP †

UIP †
Probable UIP † / Possible UIP †
Non-classifiable fibrosis †

MDD

Clinical-Radiologic-Pathologic diagnosis

IPF

IPF/Not IPF per Table 6

Not IPF

HRCT pattern	Surgical lung biopsy Pattern (When performed)	Diagnosis of IPF ?
UIP	UIP	**Yes**
	Probable UIP	
	Possible UIP	
	Nonclassifiable fibrosis	
	Not UIP	No
Possible UIP	UIP	**Yes**
	Probable UIP	
	Possible UIP	Probable
	Nonclassifiable fibrosis	
	Not UIP	No
Inconsistent with UIP	UIP	Possible
	Probable UIP	No
	Possible UIP	
	Nonclassifiable fibrosis	
	Not UIP	

AJRCCM 2011;183:788-824

Combination of HRCT and SLBx

Histopathologic pattern

Radiologic Pattern	Not performed	
UIP	IPF	
Possible UIP	Unknown	
Inconsistent with UIP	Unknown	

HR Collard, ATS 2014 postgraduate course

Combination of HRCT and SLBx

Histopathologic pattern

Radiologic Pattern

		UIP	Probable UIP	Possible UIP	Not UIP
UIP		IPF	IPF	IPF	Not IPF
Possible UIP		IPF	IPF	Some are IPF, some are not	Not IPF
Inconsistent with UIP		Some are IPF, some are not	Not IPF	Not IPF	Not IPF

HR Collard, ATS 2014 postgraduate course

Role of Bronchoalveloar lavage

- Normal cell count of BAL fluid in nonsmokers
  - Macrophages >80%
  - Lymphocytes ≤ 15%
  - Neutrophils ≤ 3%
  - Eosinophils ≤ 0.5%
  - Mast cells ≤ 0.5%

- BAL differential cell count
  - Not pathognomic, but maybe helpful in DDX

Diagnostic Value of BAL in ILD

Condition	Bronchoalveolar Lavage Finding
Sarcoidosis	Lymphocytosis; CD4 : CD8 ratio >3.5 most specific of diagnosis
Hypersensitivity pneumonitis	Marked lymphocytosis (>50%)
Organizing pneumonia	Foamy macrophages; mixed pattern of increased cells characteristic; decreased CD4:CD8 ratio
Eosinophilic lung disease	Eosinophils >25%
Diffuse alveolar bleeding	Hemosiderin-laden macrophages, red blood cells

Diagnostic Value of BAL in ILD

Condition	Bronchoalveolar Lavage Finding
Diffuse alveolar damage, drug toxicity	Atypical hyperplastic type II pneumocytes
Oppirtunistic infections	*Pneumocystis carinii,* fungi, cytomegalovirus-transformed cells
Lymphangitic carcinomatosis, alveolar cell carcinoma, pulmonary lymphoma	Malignant cells
Alveolar proteinosis	Milky effluent, foamy macrophages and lipoproteinaceous Intraalveolar material (periodic acid-Schiff stain-positive)
Lipoid pneumonia	Fat globules in macrophages

Role of surgical lung biopsy

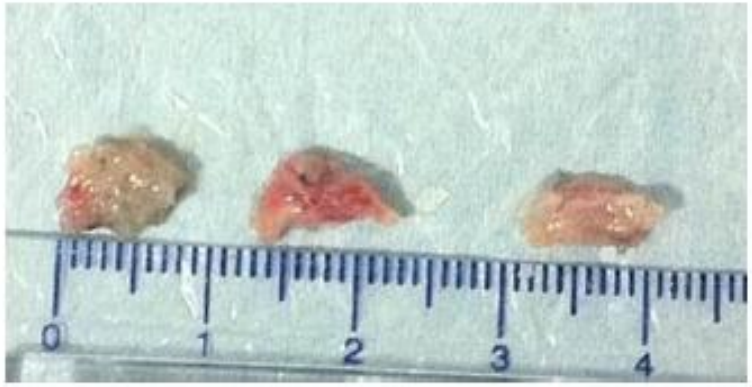
- SLBx
  - Still recommended for diagnostic confirmation in suspected fibrotic ILD
  - Represents only a small sample of the whole lung
  - May be associated with a significant mortality at 90 days
- Pooled post-operative mortality rate
  - 3.6% (95% CI 2.1-5.5)
- Other complications
  - Prolonged air leak
  - Persisting pain
  - Fistula and empyema

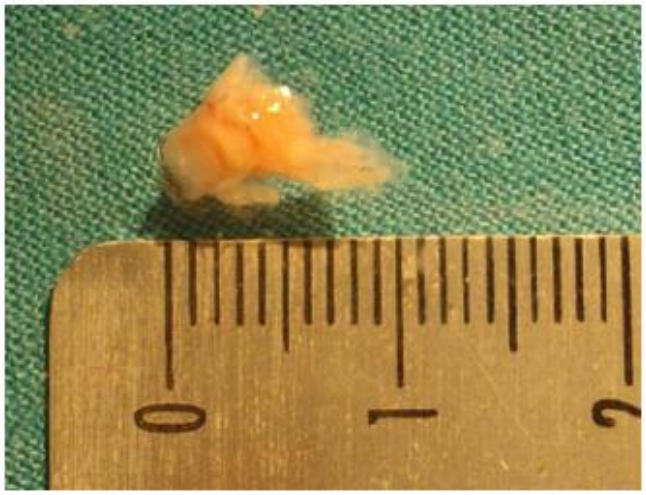
Sarcoidosis Vasc. Diffuse Lung Dis. 2013:30:3
J. Thorac. Cardiovasc. Surg 2015:149:1394

Role of surgical lung biopsy

- Avoid VATS lung biopsy
  - Old age
  - Poor lung function or significant hypoxia
  - On mechanical ventilation
  - Pleural adhesion
  - Bleeding tendency

New technique – Bronchoscopic Cryobiopsy





- 117 fibrotic ILD patients without typical UIP pattern in HRCT
  - 58: bronchoscopic lung cryobiopsy (BLC)
  - 59: Sugical lung biopsy (SLB)
- Increased in diagnostic confidence after addition of BLC, similar to SLB
- Inter-observer agreement in Dx of IPF (BLC κ=0.96 vs. SLB κ=0.93)

AJRCCM 2015. E-pub

질문> 나는 ( )세 이상에서는 ILD진단을 위한 수술적 폐조직 검사를 시행하지 않는다.

1. 70세
2. 80세
3. 90세
4. 나이에 절대적인 제한을 두지 않고 환자의 performance, comorbidity를 고려하여 결정한다.

Survey in Korea

41 University Hospital pulmonologists

- 2011 new guideline 을 ( ).
  - 매우 잘 알고 있다. 42.9%
  - **알고 있다** **54.8%**
  - 보통이다. 2.4%
  - 모른다.

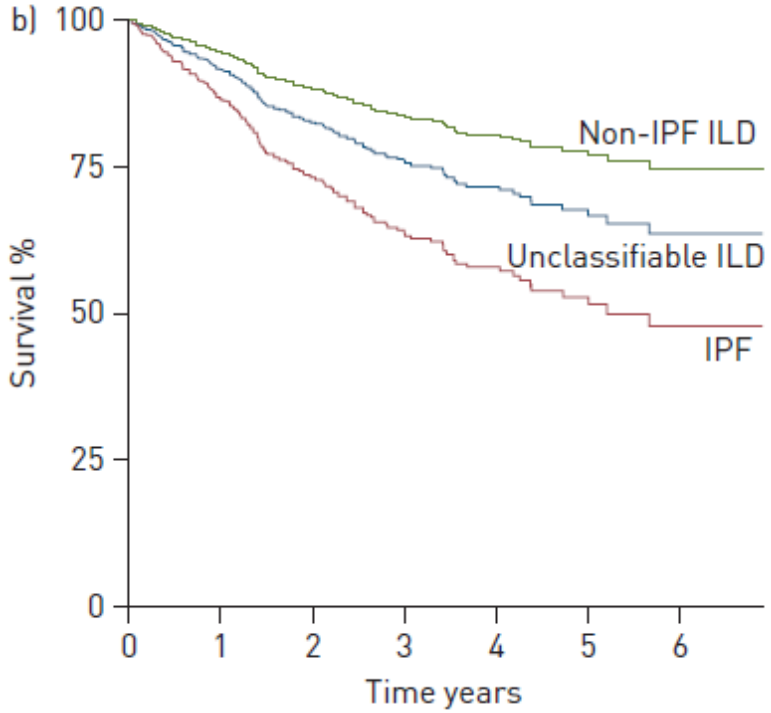
- 2011 new guideline 을 ( ).
  - 매우 신뢰한다. 9.5%
  - **신뢰한다.** **78.6%**
  - 보통이다. 11.9%
  - 신뢰하지 않는다.

- 2011 new guideline 을 실제 임상에서 ( ).
  - 철저히 적용하고 있다. 4.8%
  - **적용하고 있다.** **78.6%**
  - 보통이다. 16.7%
  - 적용하지 않는다.

- 2011년 새로운 guideline 사용 이후 IPF 환자 중 조직 검사 없이 진단한 경우: 81.1 ± 14.6 %

From Prof. Uh, ILD연구회, 2013

Unclassifiable ILD



- Reason for unclassifiable ILD
  - Too old or frail for lung biopsy
  - Conflicting clinical, radiological and pathological data
  - Insufficient tissue on lung biopsy
  - Declined biopsy

- Better survival compared to IPF control (HR 0.62, 95% CI 0.40–0.97; p=0.04)
- No difference compared to non-IPF ILD (HR 1.54, 95% CI 0.89–2.65; p=0.12)

ERJ 2013;42:750

Application of diagnostic procedures in real world practice

	Weight of information (diagnostic confidence)	Need of Semi-invasive procedures	Need of Invasive procedures (Surgical biopsy)
Clinical profile + Lab tests	HIGH	+-- (BAL,EUS/EBUS)	-
+ HRCT features	MEDIUM	+++ (TBB/c-TBB,BAL)	-
+ CLINICAL REASONING	LOW	++- (c-TBB, new surgical procedures)	++/+++*

* Depending greatly from the patient's inclination, age, morbidities and from the therapeutic options available

Respirology, 2016 :21;44

M/85, dyspnea

- Dyspnea & general weakness for 6m

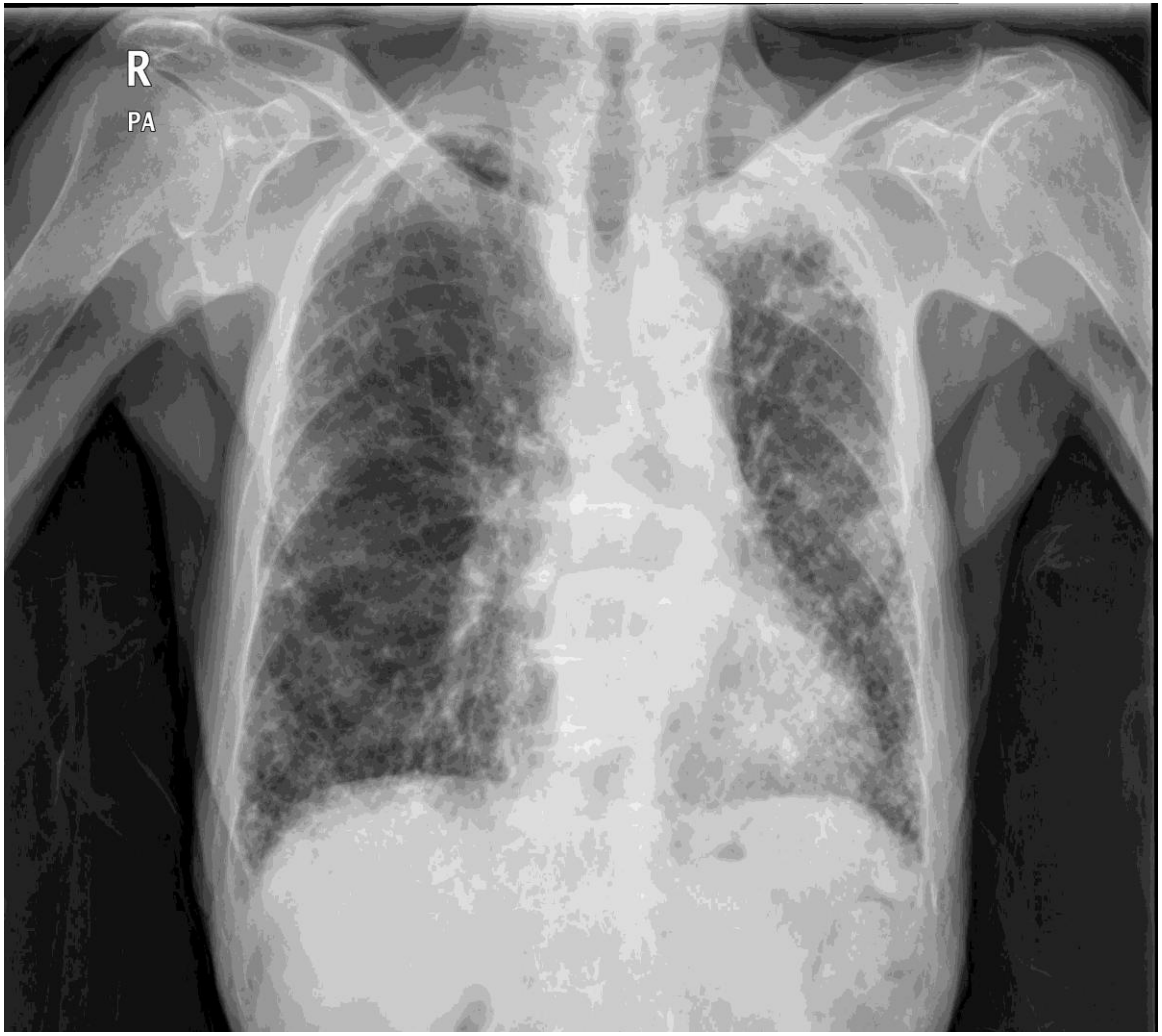
- C/S (+/-) PND (+) Globus (+) Heart burn (+) DOE 2

- Tb hx (-)
- Ex-smoker: 25 PYs, 25YA quit
- SHx> 농사-벼농사
- P/Ex> dry crackle on BLLF

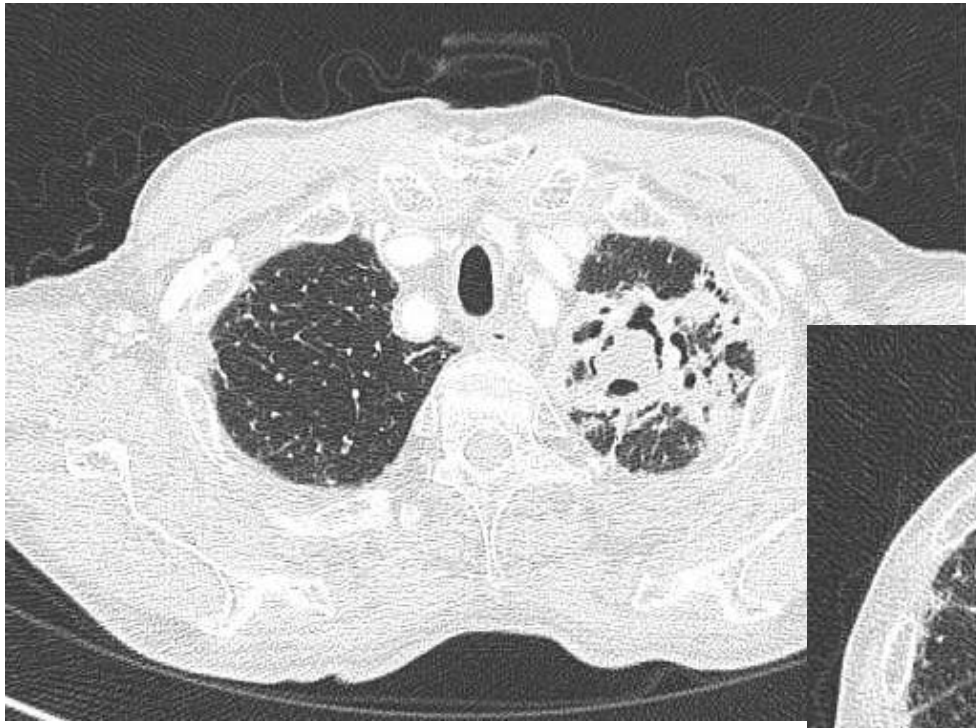
- SaO2 97%

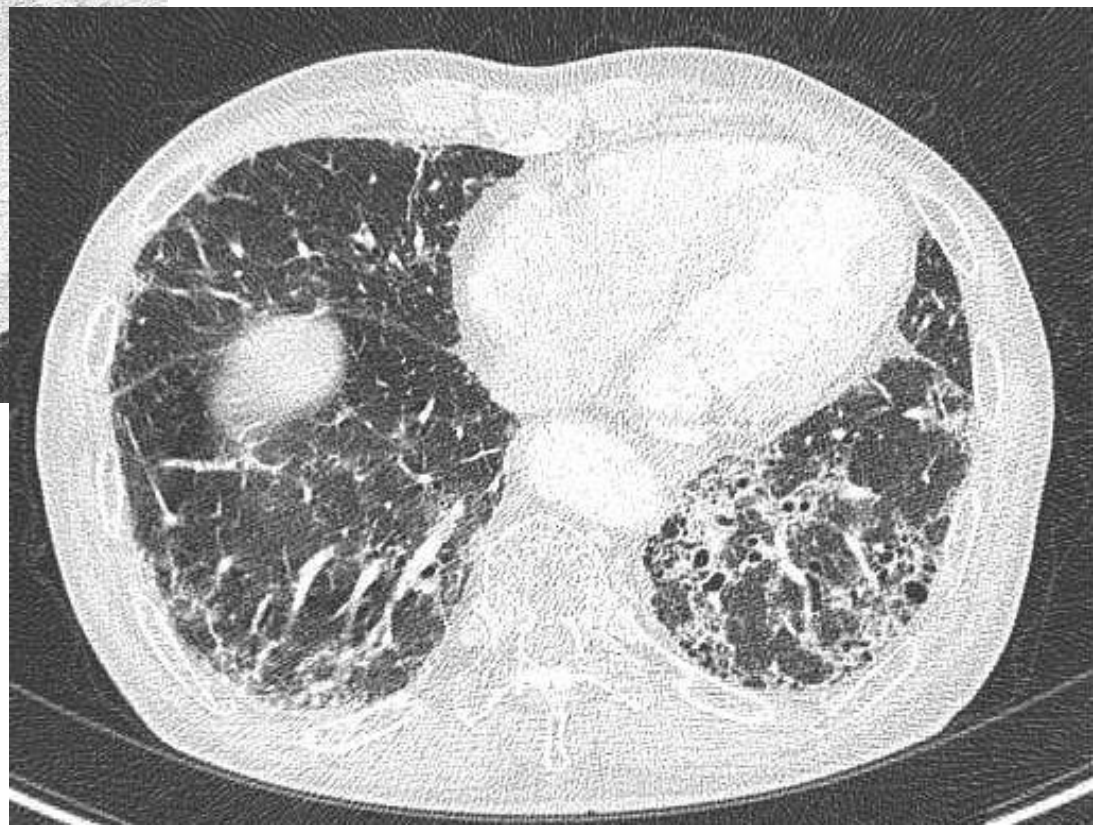
- PFT - fail 함.

M/85, dyspnea



M/85, dyspnea





질문> 다음으로 어떤 검사 또는 치료를 해 보시겠습니까?

1. 입원시켜 BAL을 시행해 본다.
2. 입원시켜 VATS lung biopsy를 시행한다.
3. 외래에서 steroid 치료를 시행해 본다.
4. 외래에서 pirfenidone을 써 본다.
4. 보존적인 치료만 한다.

"Controversy is not a sign of confusion or a breakdown in the scientific process, but a sign of vibrancy and a motor for advance."

Martin Tobin, former Editor-in-Chief,
Am J Respir Crit Care Med 2003

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