Lung Biopsy in the Diagnosis of ILD

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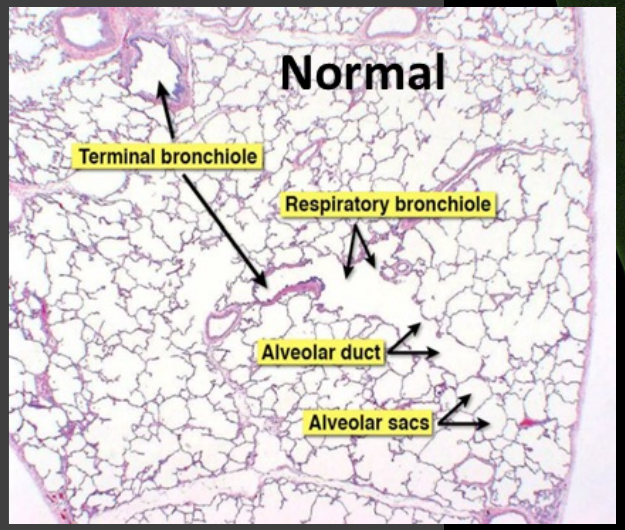
Importance of establishing a diagnosis in ILD

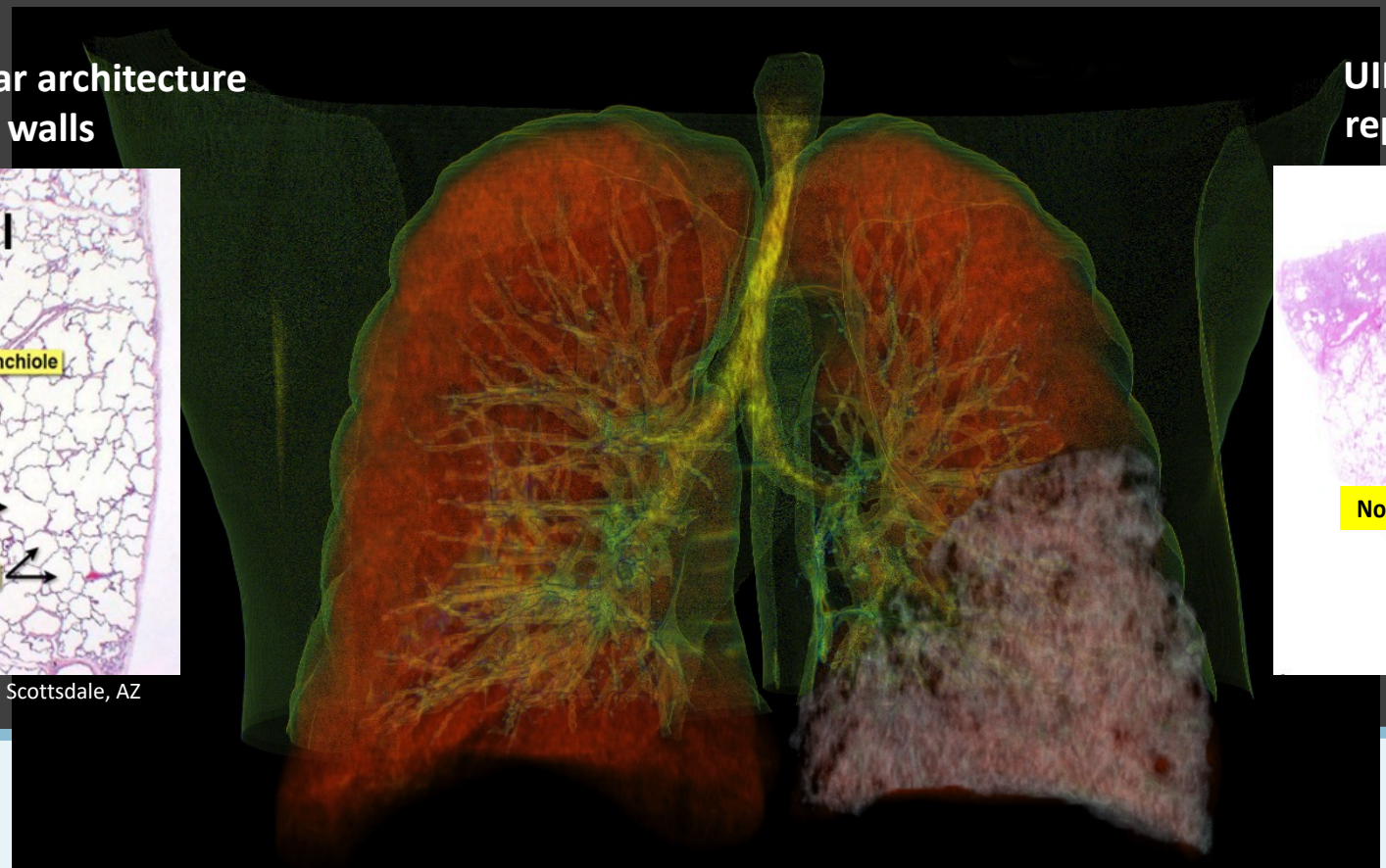
Important to distinguish various ILDs for the following reasons:

- Establish a high-confidence diagnosis
- Make informed decisions about therapeutic strategy
- Provide information about prognostic implications

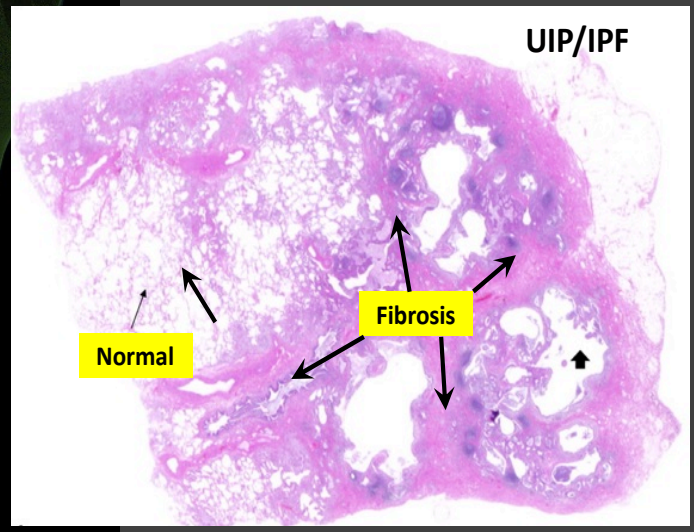
Normal lung: Intact alveolar architecture with thin delicate walls



Slide courtesy of Dr. H. Tazelaar, Mayo Clinic, Scottsdale, AZ

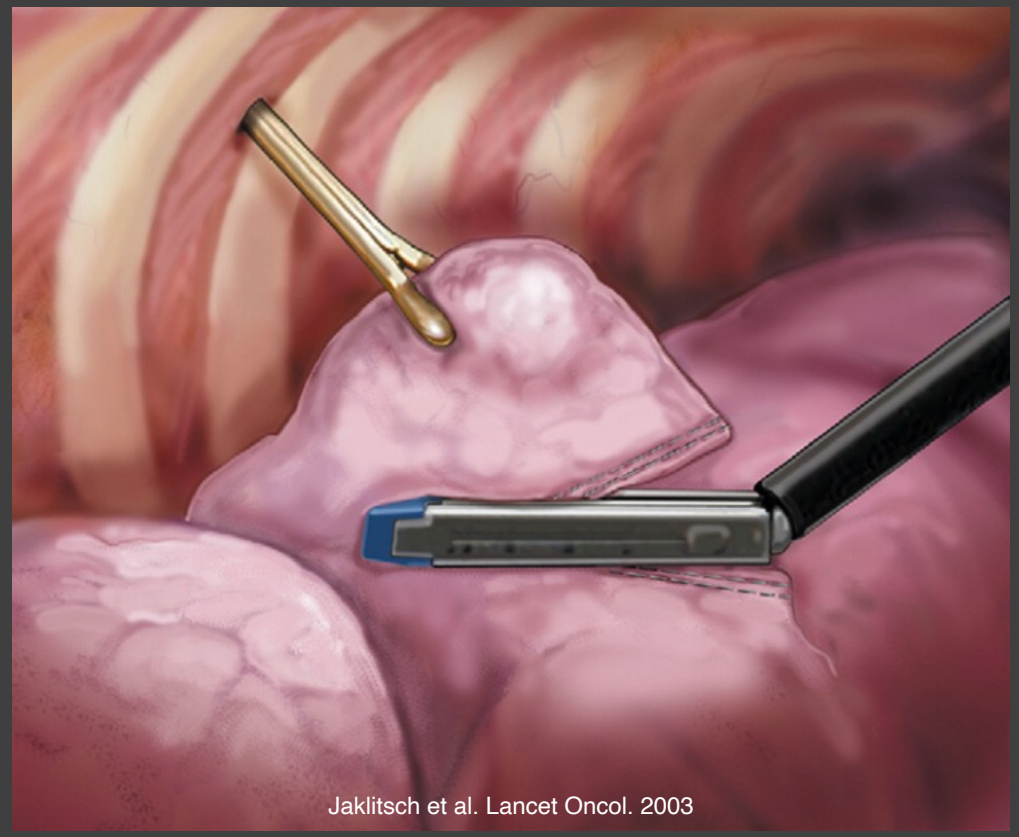


UIP/IPF: Fibrosis destroys and replaces normal alveolar lung



Raghu et al. AJRCCM. 2018

Surgical Lung Wedge Biopsy



Surgical procedure where a walnut-sized piece of lung removed for microscopic pathology assessment

Typically, biopsies taken from 3 sites (Upper, Middle, and Lower Lobe) to assess disease distribution and heterogeneity

Risk of perioperative morbidity

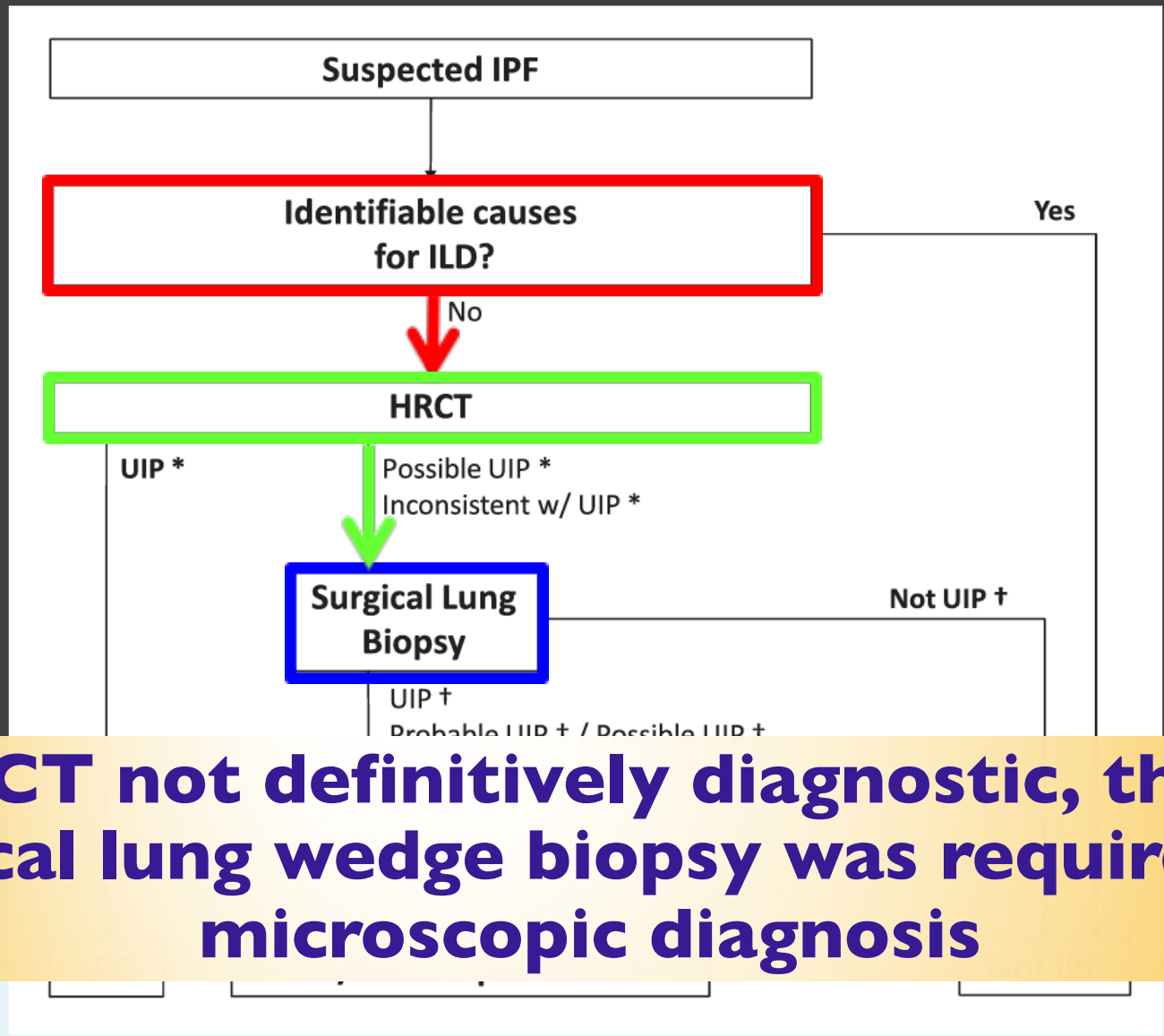
Prolonged hospitalization, pneumonia, acceleration of disease

Risk of Mortality

Elective: 1-2% mortality

Non-elective: 4-20% mortality

2011 ATS Diagnostic Work Flow



If CT not definitively diagnostic, then surgical lung wedge biopsy was required for microscopic diagnosis

Raghu et al. ATS/ERS/JRS/ALAT IPF Diagnostic Guidelines. AJRCCM 2011.

HRCT: Diagnostic Requirements in 2011

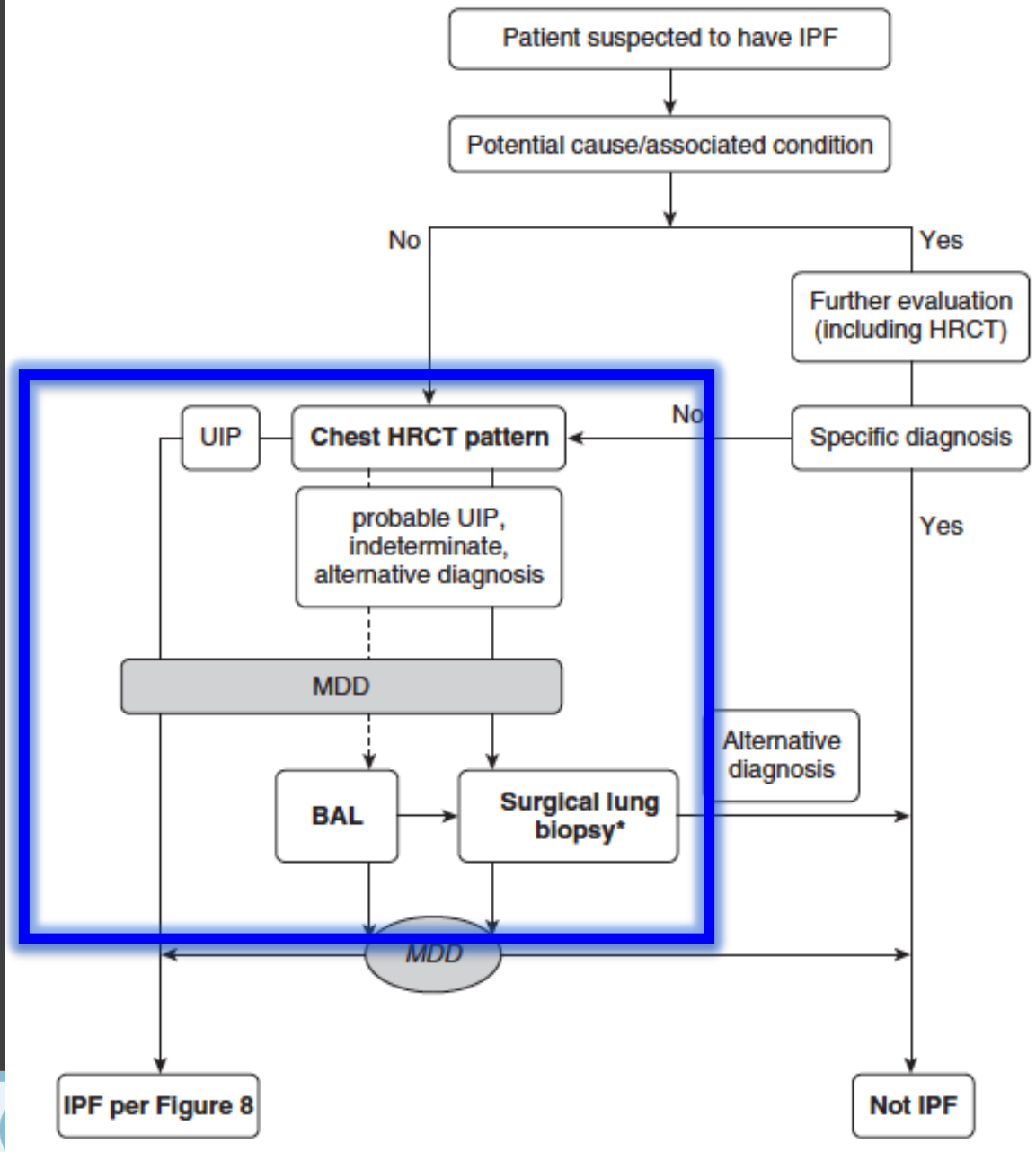
UIP Pattern (all 4 features)
Subpleural, basal predominance
Reticular abnormality
Honeycombing With Or without Traction bronchiectasis
Absence of Inconsistent features

Possible UIP (all 3 features)
Subpleural, basal predominance
Reticular abnormality
Absence of Inconsistent features

Inconsistent with UIP (Any of 7 features)
Upper or mid-lung predominance
Peribronchovascular predominance
Extensive ground-glass abnormality
Profuse micronodules
Discrete cysts
Mosaic attenuation or air-trapping
Consolidation in bronchopulmonary segments(s) or lobe(s)

Raghu et al. ATS/ERS/JRS/ALAT IPF Diagnostic Guidelines. AJRCCM 2011.

ATS 2018 Guidelines



Raghu et al. ATS/ERS/JRS/ALAT IPF Diagnostic Guidelines. AJRCCM 2018.

Fleischner Guidelines

Panel 3: Pathways to a confident working multidisciplinary diagnosis of IPF

When can one make a confident diagnosis of IPF without biopsy?

- Clinical context of IPF*, with CT pattern of typical or probable UIP

When is a diagnostic biopsy necessary to make a confident diagnosis of IPF?

- Clinical context of IPF* with CT pattern either indeterminate or suggestive of an alternative diagnosis
- Clinical context indeterminate for IPF† with any CT pattern

When is multidisciplinary diagnosis necessary in the context of suspected IPF?

- When the clinical context or the CT pattern, or both, are indeterminate; the outcome of multidisciplinary discussion will be a decision whether to perform an additional clinical evaluation, bronchoalveolar lavage, or diagnostic biopsy, or some combination of these procedures
- After biopsy, to integrate the clinical, imaging, and histological features
- To re-review patients in whom the longitudinal course of disease is discordant with the previously established multidisciplinary diagnosis
- When diagnostic tissue is not available, to consider a working diagnosis of IPF

What should be done when diagnostic tissue is not available?

- Multidisciplinary diagnosis with consideration of the patient's age, sex, smoking status, findings on bronchoalveolar lavage, and longitudinal disease behaviour
- In this context, a working diagnosis of IPF can be made in the presence of a progressive fibrosing interstitial pneumonia, and in the absence of an alternative explanation; the level of diagnostic confidence of such a working diagnosis should be recorded, and the diagnosis should be reviewed at regular intervals, since it might change over time

IPF=idiopathic pulmonary fibrosis. UIP=usual interstitial pneumonia. *Clinical context of IPF includes all of the following: older than 60 years, absence of clinically significant environmental or medication exposure, no evidence of connective tissue disease. †Clinical context indeterminate for IPF includes any of the following: aged 60 years or younger, potentially significant environmental or medication exposure, or evidence of connective tissue disease.

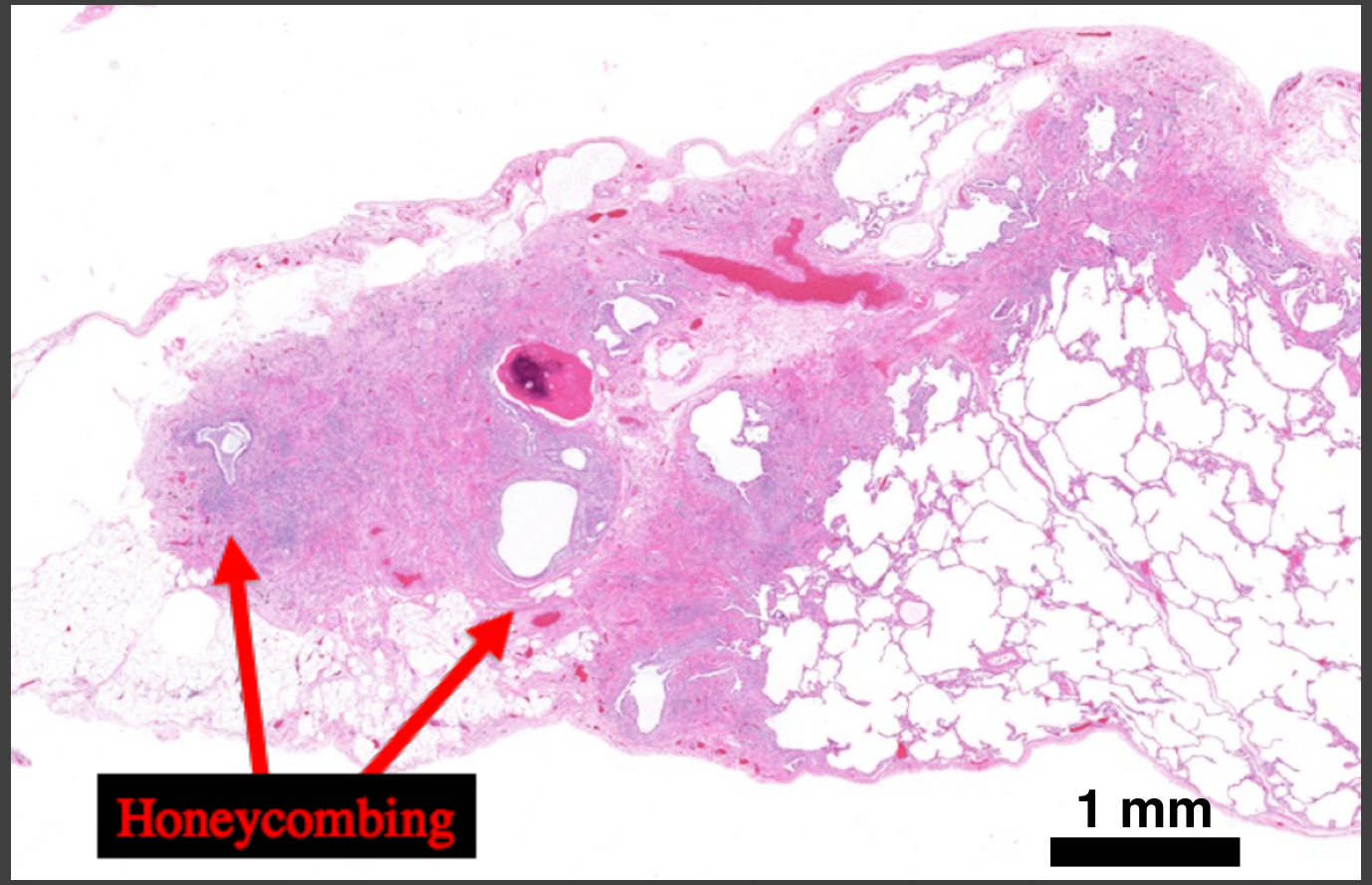
Lynch et al. Fleischner IPF Diagnostic Guidelines. Lancet Respir Med 2017.

HRCT: Diagnostic Requirements in 2018

UIP Pattern	Probable UIP (all 4 features)	Indeterminate	Alternate Diagnosis
Subpleural, basal predominance	Subpleural, basal predominance	Subpleural, basal predominance	Upper or mid-lung predominance
Reticular abnormality	Reticular abnormality	Reticular abnormality	Peribronchovascular predominance
Honeycombing With Or without Traction bronchiectasis	Peripheral traction bronchiectasis	Absence of Inconsistent features	Extensive ground-glass abnormality
Absence of Inconsistent features	Absence of Inconsistent features		Profuse micronodules
			Discrete cysts
			Mosaic attenuation or air-trapping
			Consolidation in bronchopulmonary segments(s) or lobe(s)
>95 % PPV	~80% PPV	~50% PPV	

Lynch et al. Fleischner IPF Diagnostic Guidelines. Lancet Respir Med 2017.
Raghu et al. ATS/ERS/JRS/ALAT IPF Diagnostic Guidelines. AJRCCM 2018.

HRCT resolution is ~ 2mm



- Challenging to visualize “microscopic” honeycombing < 2-3 mm diameter
- Difficult to distinguish true honeycombing from traction bronchiectasis (TB)

UIP can have TB, but not all ILD with TB is UIP

Histology Criteria for UIP Pattern: ATS / ERS / JRS / ALAT 2018 Statement

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
• Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing) • Predominant subpleural and/or paraseptal distribution of fibrosis • Patchy involvement of lung parenchyma by fibrosis • Fibroblast foci • Absence of features to suggest an alternate diagnosis	• Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF *And* • Absence of features to suggest an alternative diagnosis *Or* • Honeycombing only	• Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause* • Some histologic features from column 1, but with other features suggesting an alternative diagnosis†	• Features of other histologic patterns of IIPs (e.g., absence of fibroblast foci or loose fibrosis) in all biopsies • Histologic findings indicative of other diseases (e.g., hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)

Lynch et al. Fleischner IPF Diagnostic Guidelines. Lancet Respir Med 2017.
Raghu et al. ATS/ERS/JRS/ALAT IPF Diagnostic Guidelines. AJRCCM 2018.

Usual Interstitial Pneumonitis (UIP)

Spatial heterogeneity

Alternating areas of:

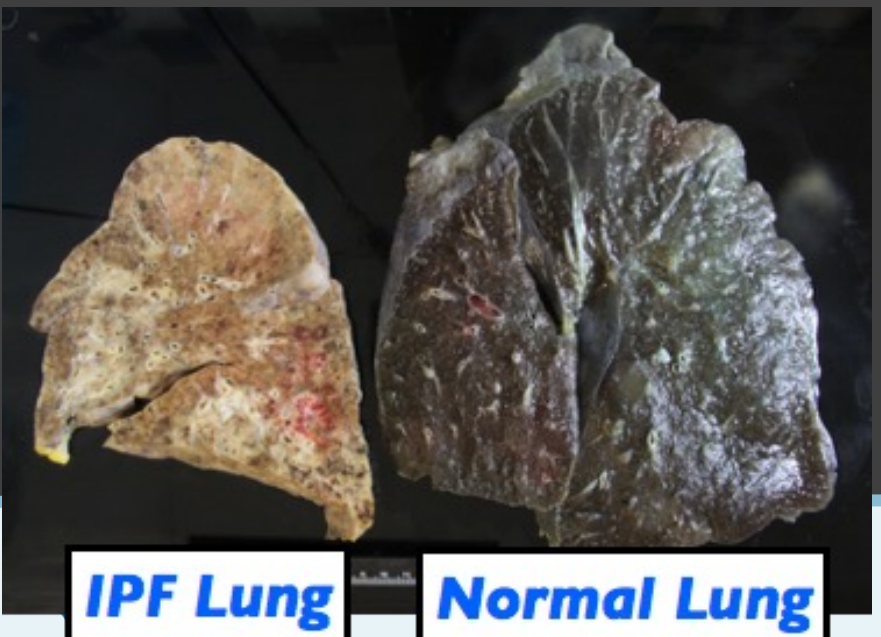
- Honeycomb change
- Fibrosis / distorted architecture
- Normal lung

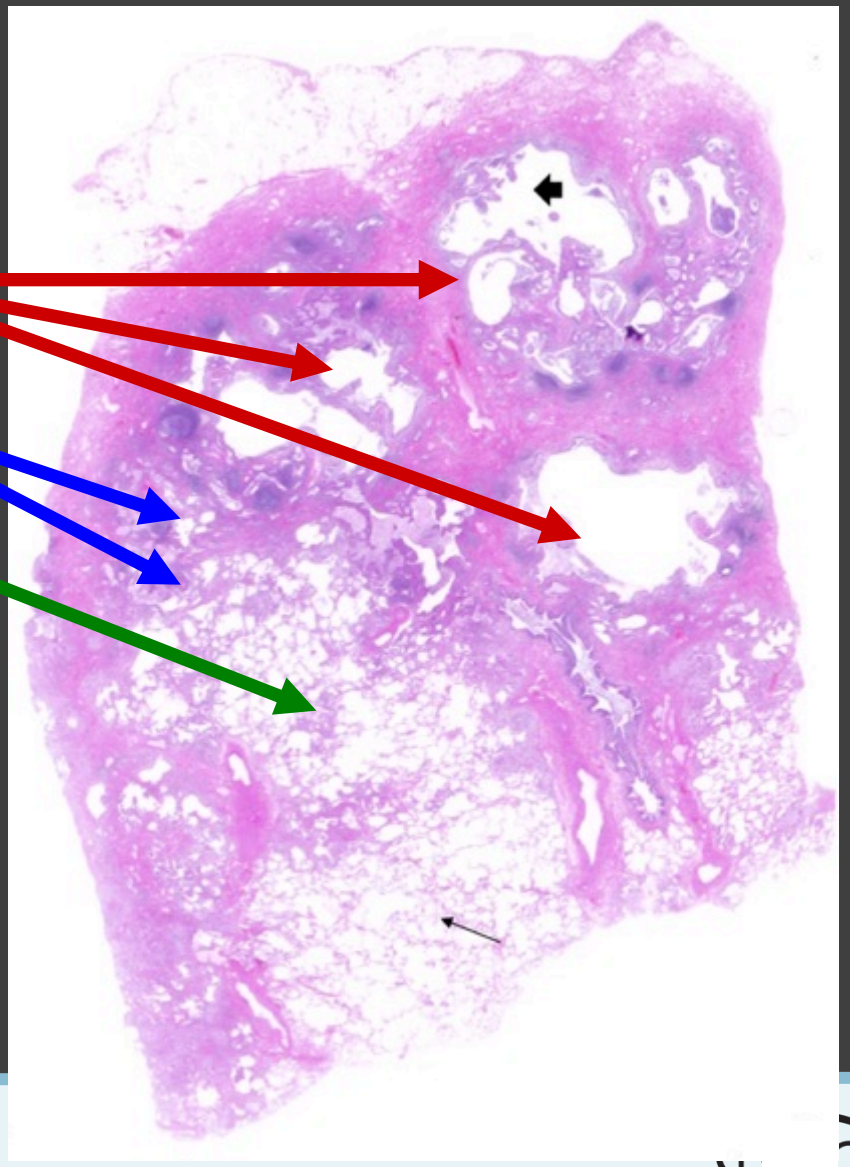
Subpleural / paraseptal Predominance

Lower Lobe Predominant

Temporal heterogeneity

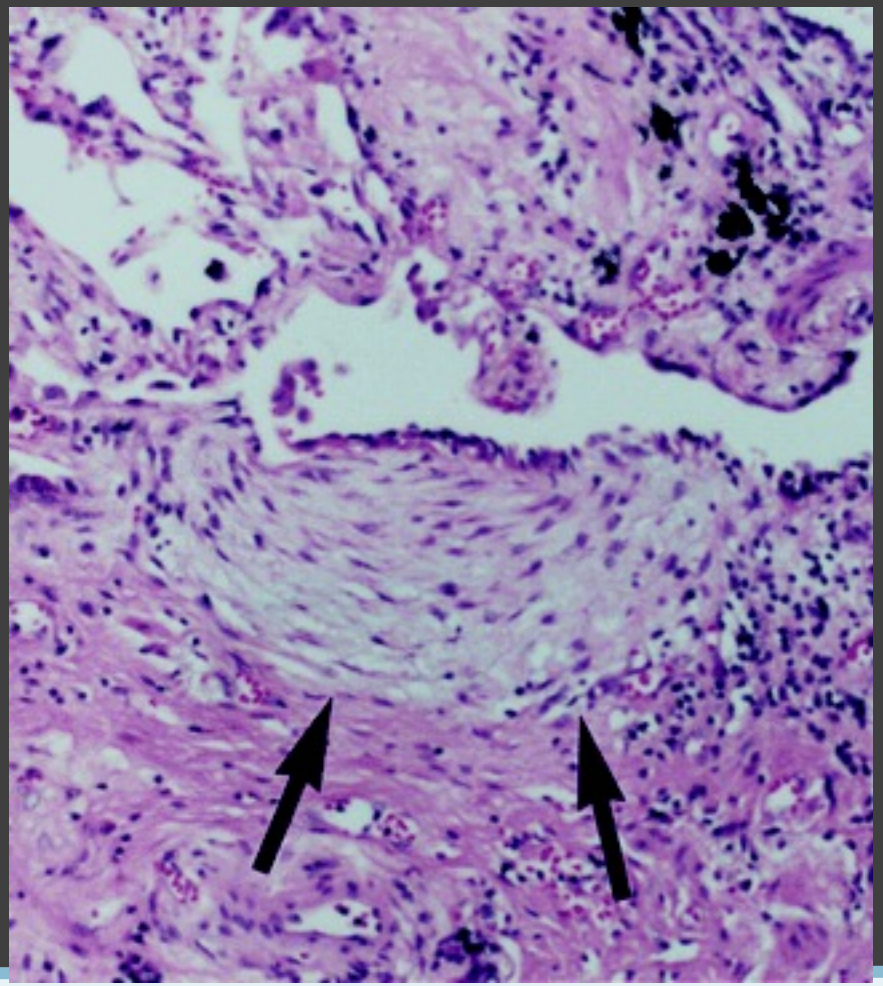
Fibroblastic foci





Raghu et al. ATS/ERS/JRS/ALAT IPF Diagnostic Guidelines. AJRCCM 2011.

Pathology Criteria for UIP Pattern: Fibroblastic Foci



- Small aggregates of actively proliferating fibroblasts/myofibroblasts
- Sites of active collagen synthesis
- Not pathognomonic for UIP, but necessary for the diagnosis
- Number of fibroblastic foci inversely correlates with survival

Raghu et al. ATS/ERS/JRS/ALAT IPF Diagnostic Guidelines. AJRCCM 2011.

Histology Criteria for UIP Pattern: ATS / ERS / JRS / ALAT 2018 Statement

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
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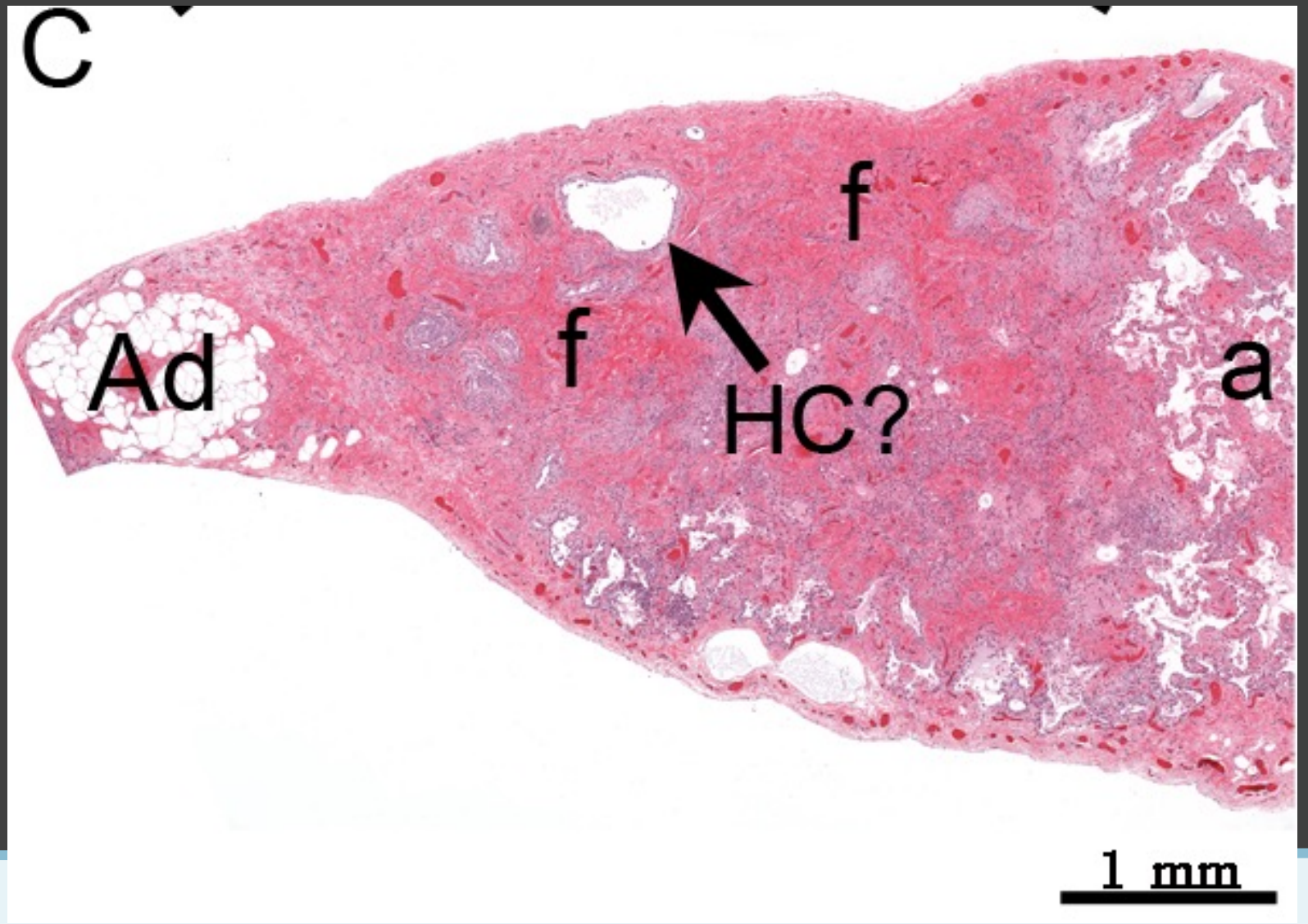
Probable UIP



Histology Criteria for UIP Pattern: ATS / ERS / JRS / ALAT 2018 Statement

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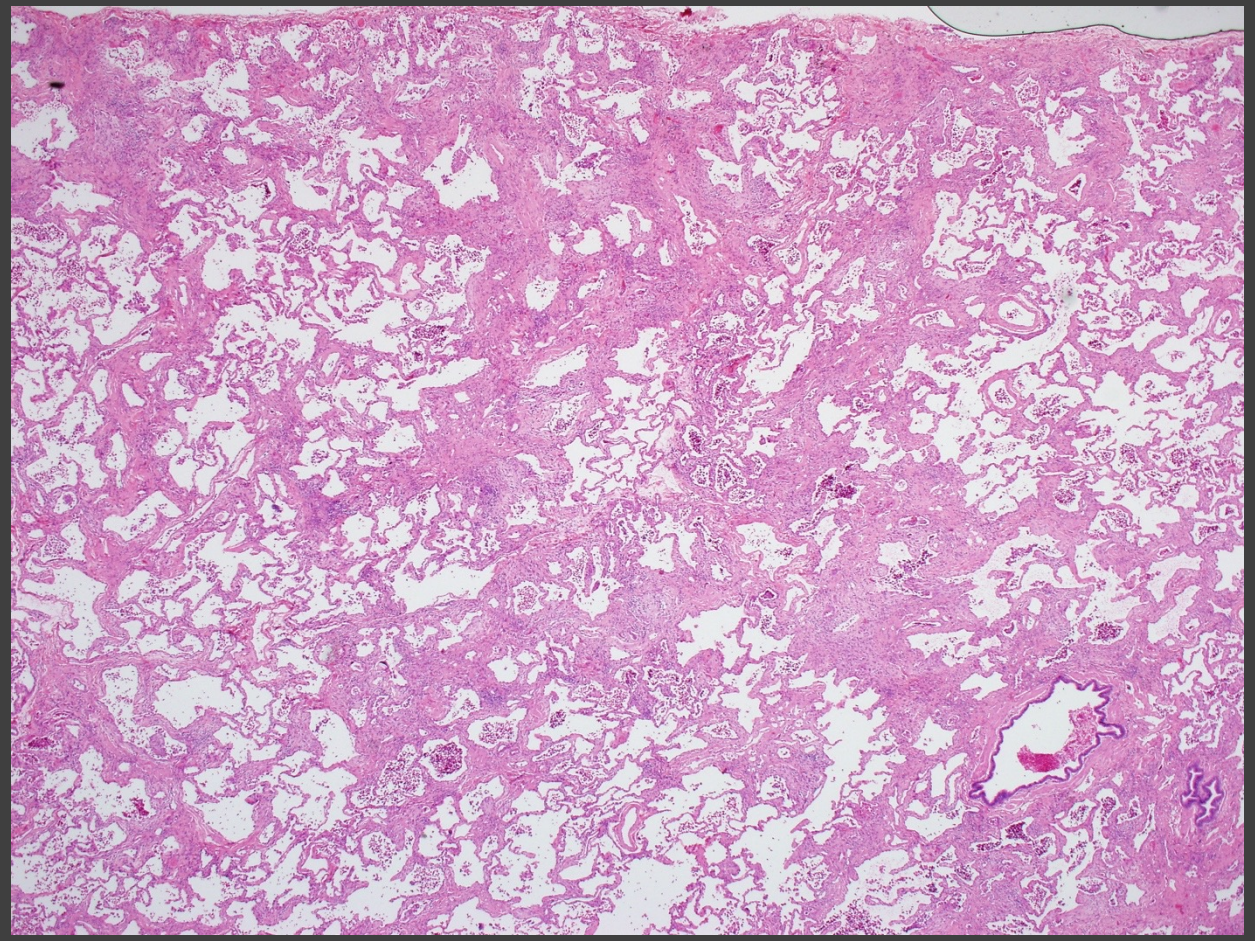
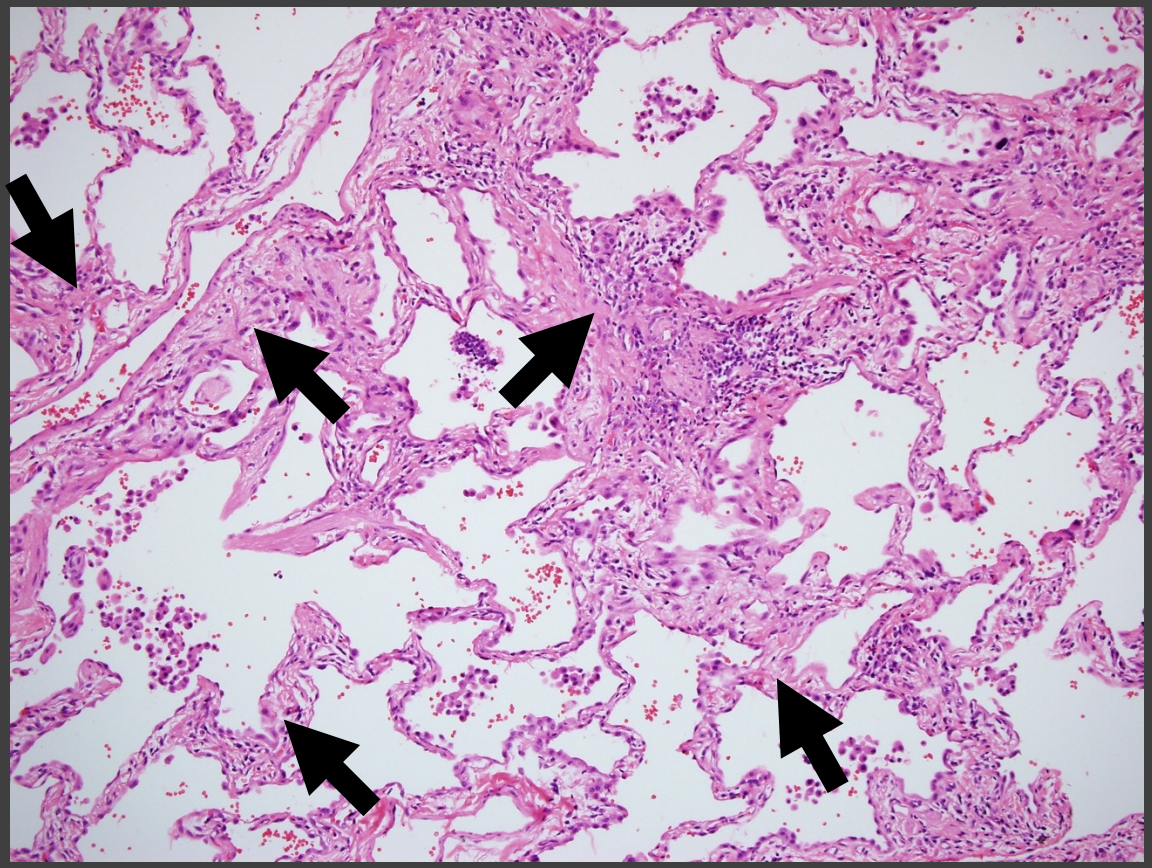
Lynch et al. Fleischner IPF Diagnostic Guidelines. Lancet Respir Med 2017.
Raghu et al. ATS/ERS/JRS/ALAT IPF Diagnostic Guidelines. AJRCCM 2018.

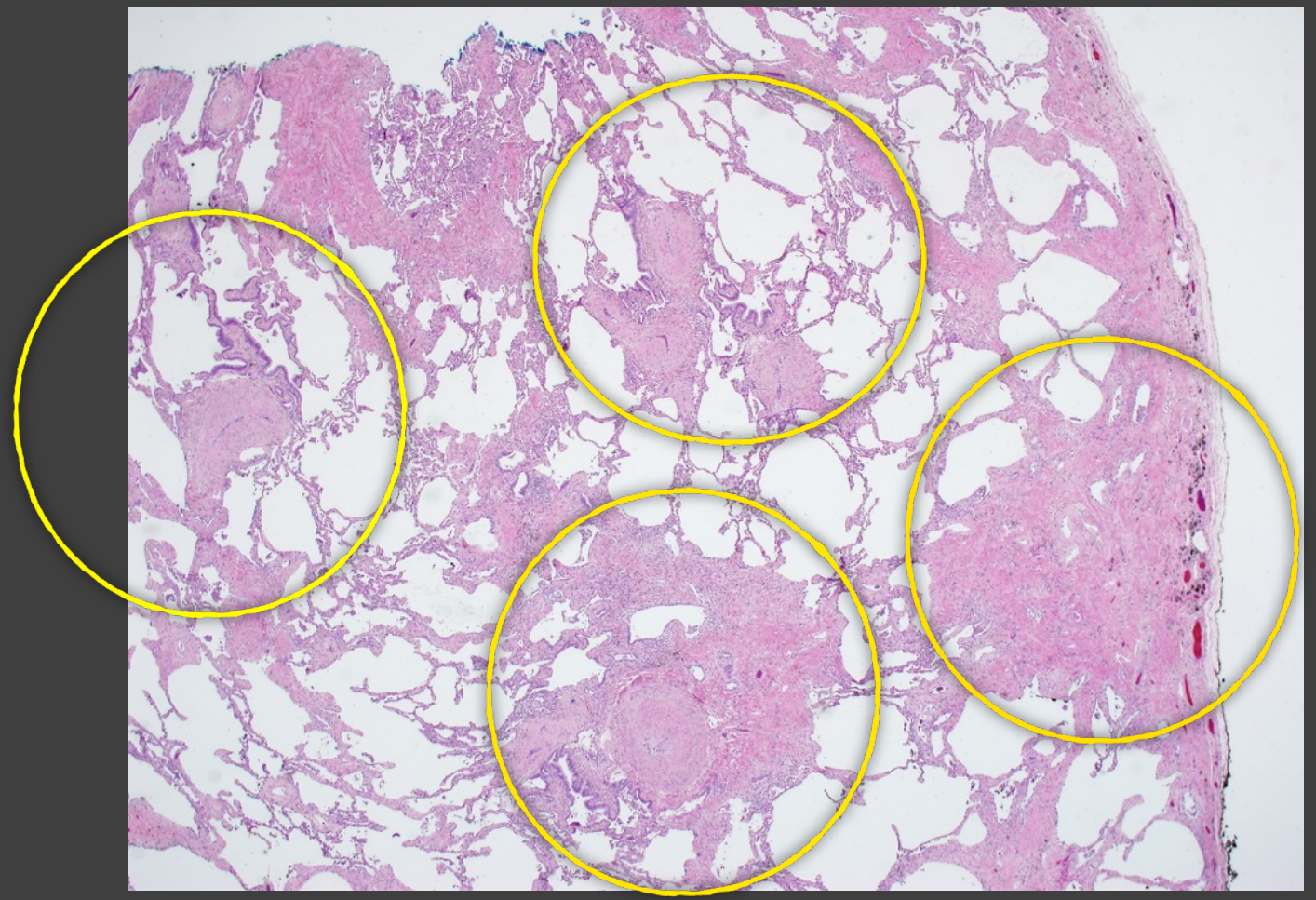
Pattern: Non-Specific Interstitial Pneumonitis (NSIP)





Homogenous diffuse fibrotic thickening of alveolar walls
No destructive fibrosis, spatial heterogeneity, or honeycomb change
<u>Etiology</u>: Can be idiopathic or secondary to chronic HP or autoimmune related ILD

Pattern: Airway-Centered Fibrosis



<u>Etiology</u>: Chronic exposure to inhaled allergen (Chronic Hypersensitivity Pneumonitis)
Autoimmune related interstitial lung disease
May see this pattern is familial ILD

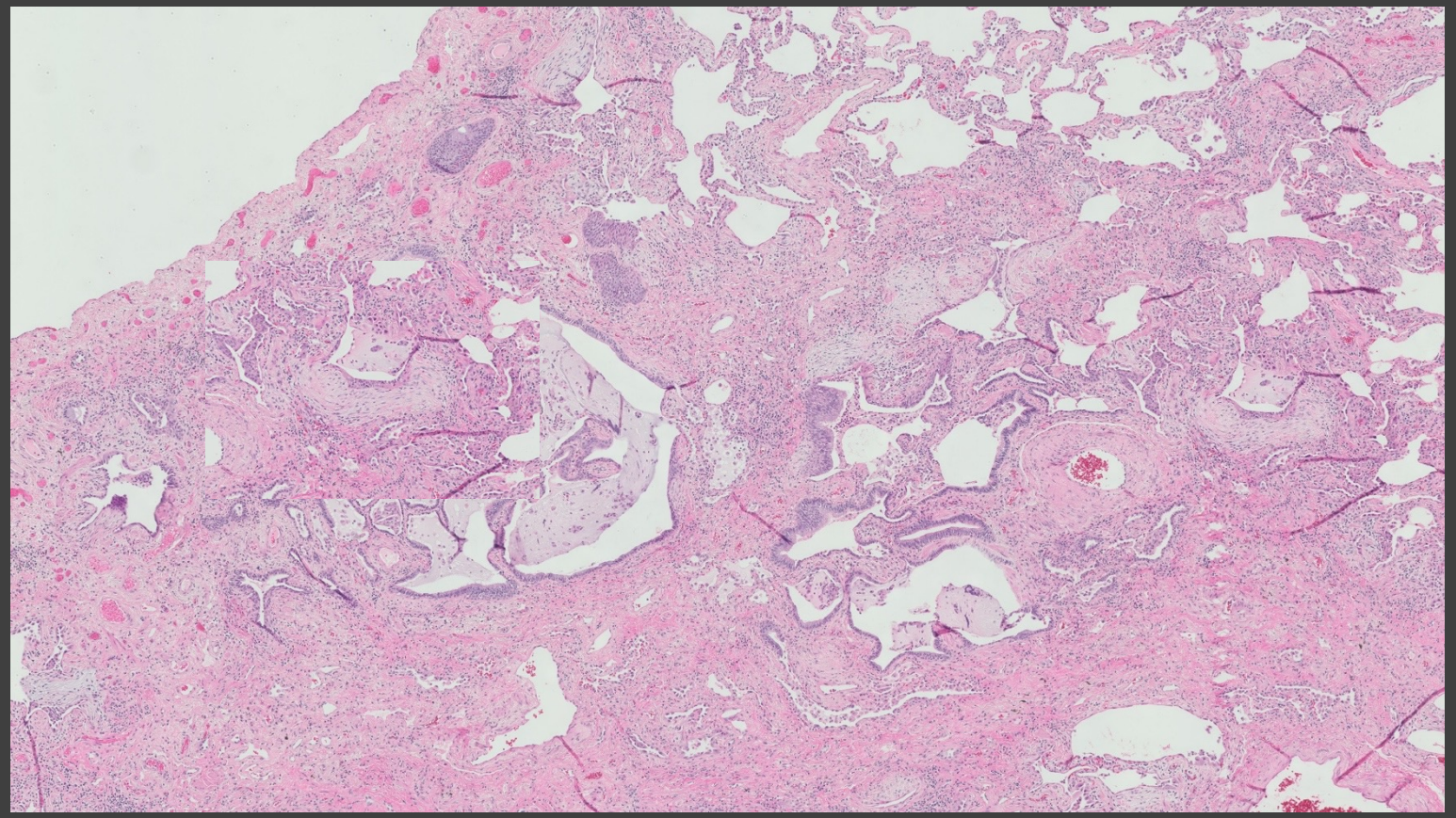
Idiopathic (No identifiable underlying cause)

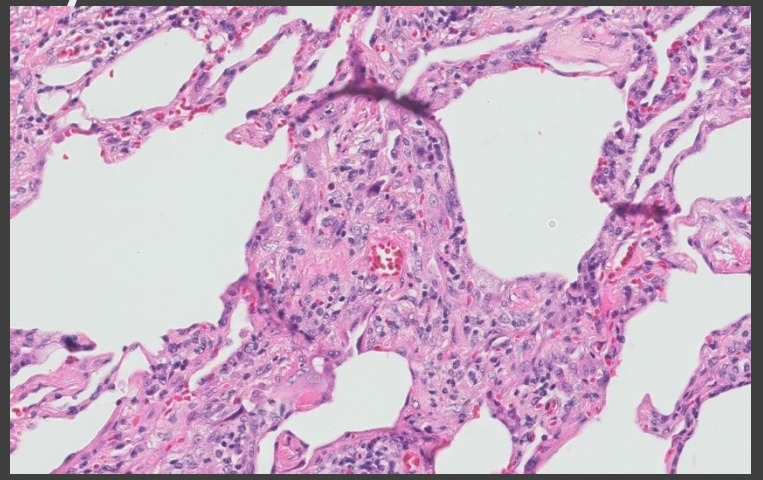
- Idiopathic pulmonary fibrosis: UIP with no known underlying cause
- Idiopathic fibrotic NSIP: NSIP with no known underlying cause

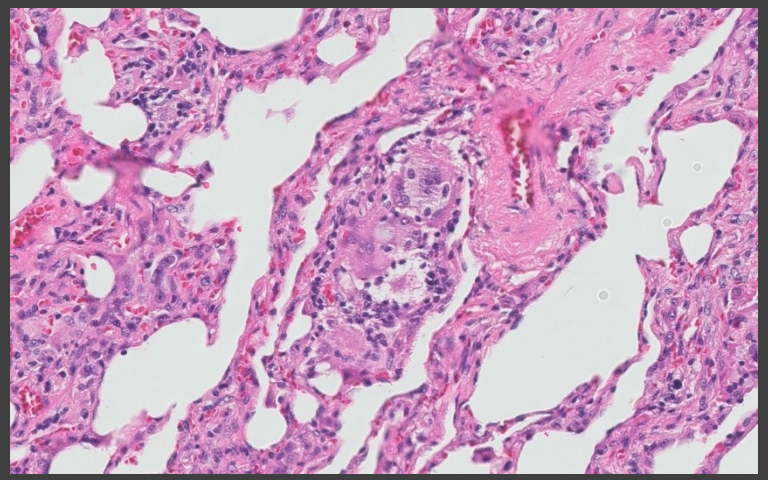
Secondary (Identifiable underlying cause)

- Chronic Hypersensitivity Pneumonitis
- Connective tissue disease (CTD) ILD

Diagnosis: Chronic Hypersensitivity Pneumonitis





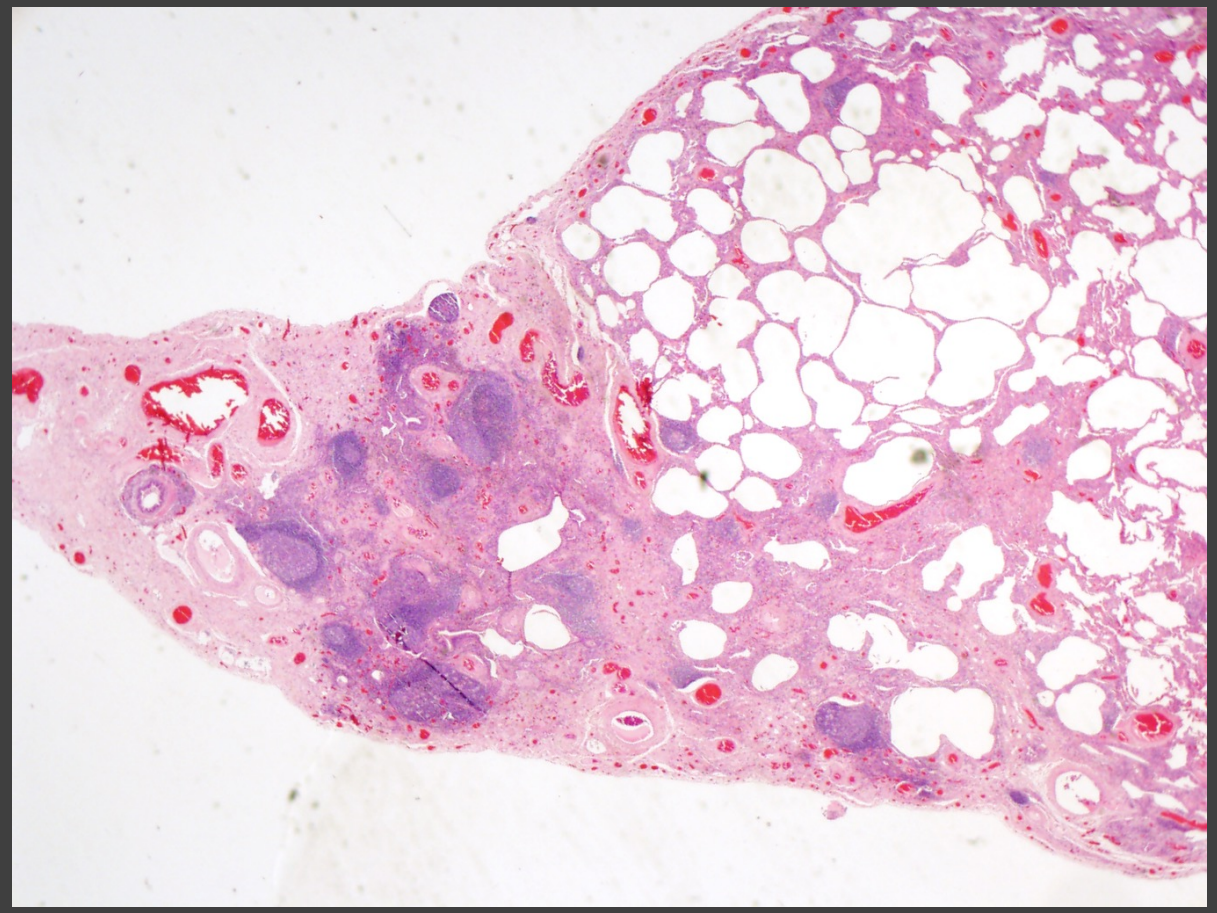


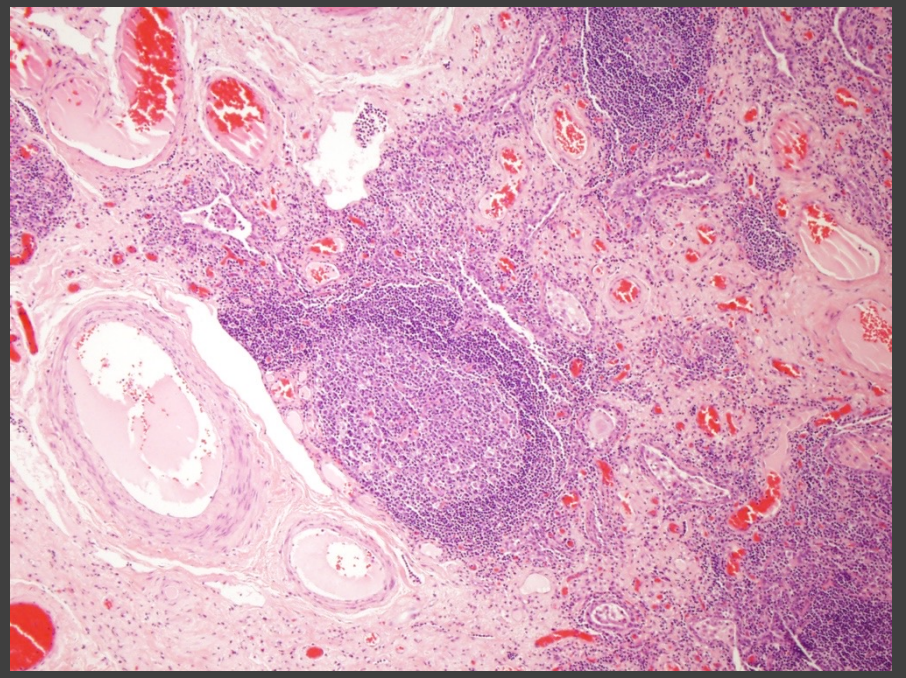
Chronic exposure to inhaled allergen: Mold, bird dander, some thermophilic bacteria

Classically has patchy peribronchiolar granulomatous inflammation

Chronic form can have UIP pattern, NSIP pattern, Airway centered fibrosis, or a mix

Diagnosis: Connective Tissue Disease Related ILD

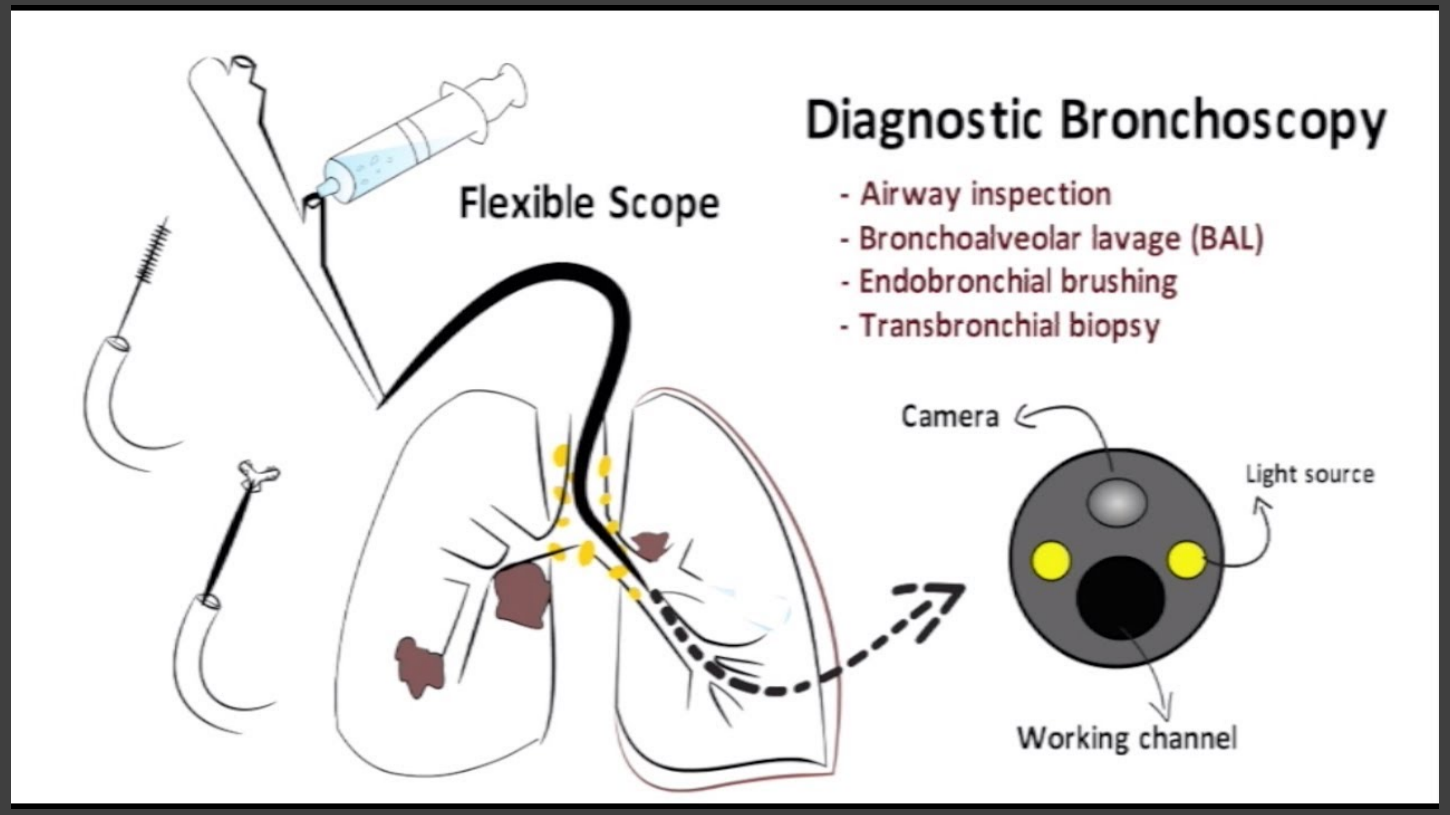




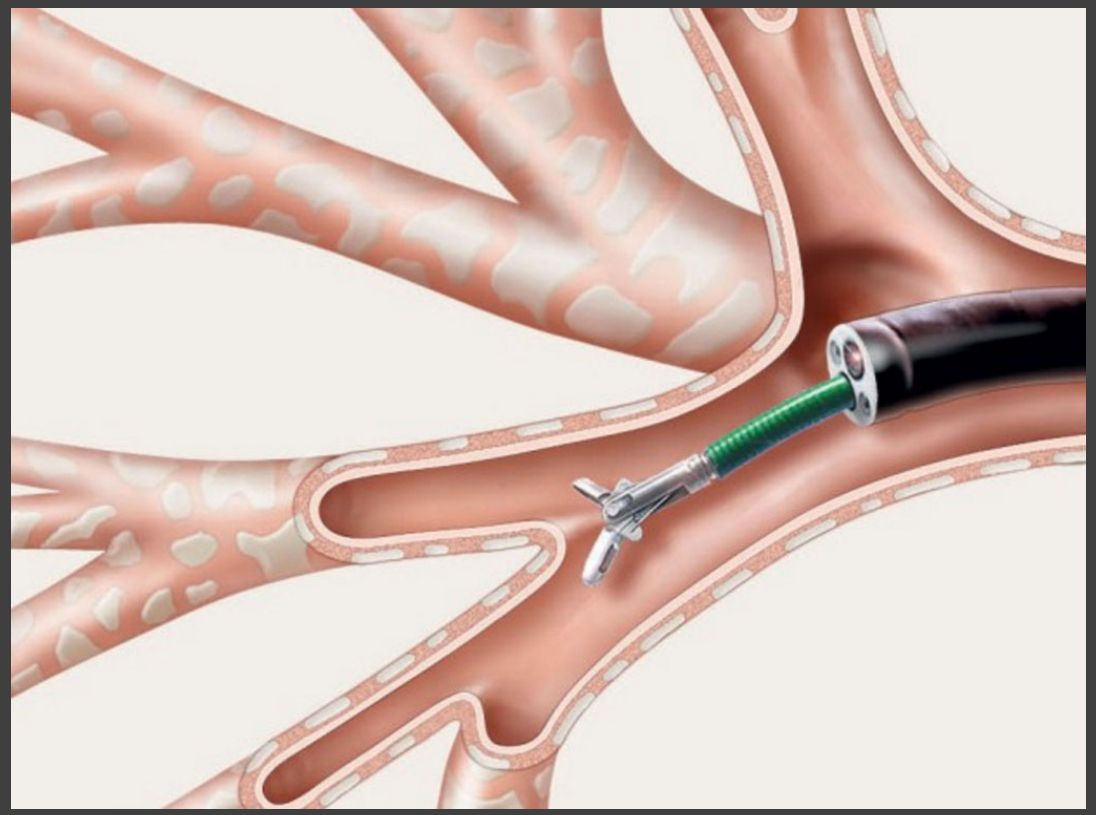
Can have UIP pattern, NSIP pattern, Airway centered fibrosis, or a mix
Presence of a mixed fibrosis pattern, or lymphoid aggregates can be histological clues
Sometimes lung manifestations are the initial presenting symptom, and can even precede serology

Other types of biopsy in ILD

Transbronchial Biopsy
Insufficient for diagnosis in most ILDs



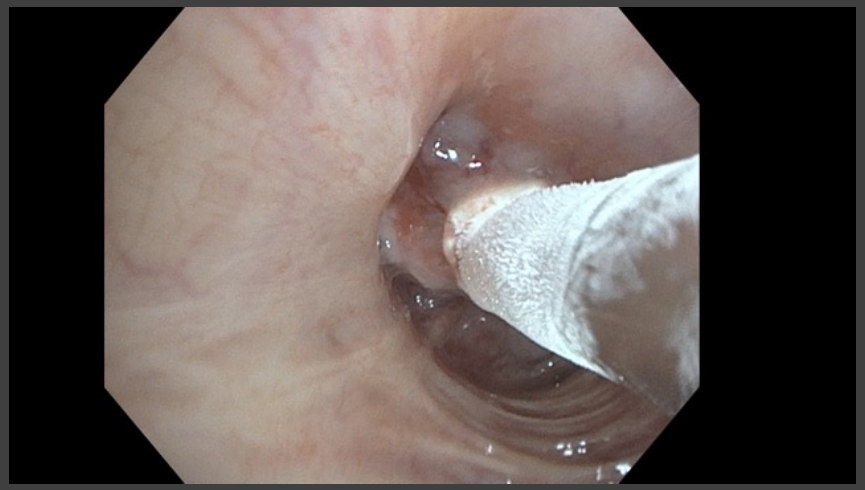
Best of ATS Video Lecture



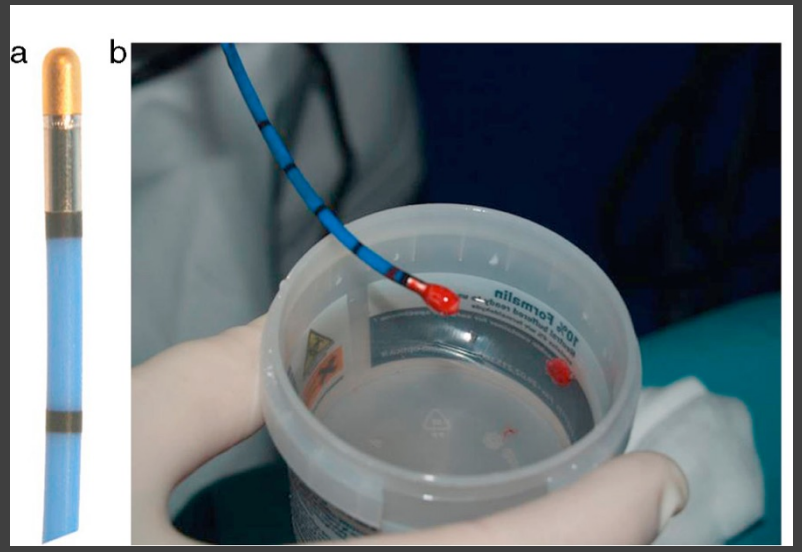
https://www.pedilung.com

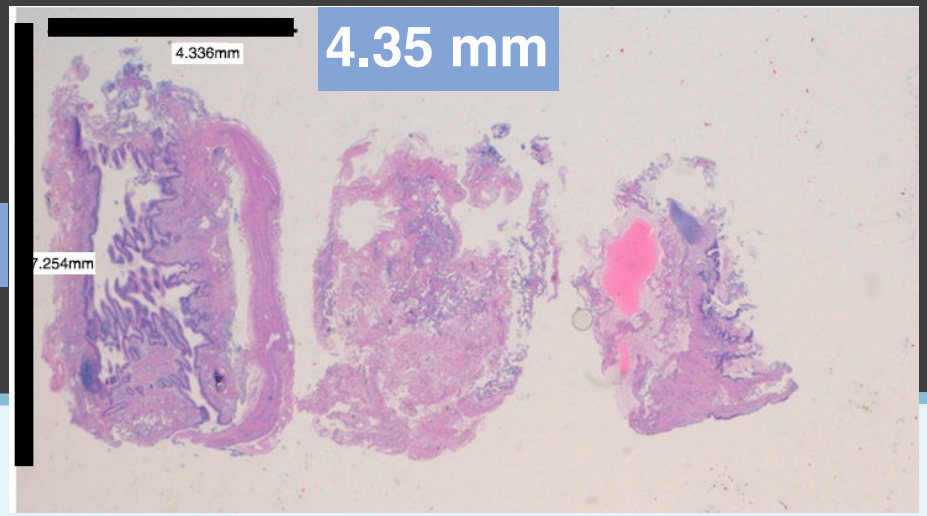
Bronchoscopic Cryobiopsy

Uses a freezing probe to adhere and remove lung tissue



http://www.erbe-med.com





Casoni GL et al. Rev Port Pneumol. 2012.

Cryobiopsy vs Surgical Lung Biopsy

Romagnoli et al. 2019 (N=21)

Comparison	% Agreement (95% CI)	K (95% CI)
TBLC versus SLB	38% (18%-62%)	0.22 (0.01-0.44)
TBLC versus MDA2	48% (26%-70%)	0.31 (0.06-0.56)
SLB versus MDA2	62% (38%-82%)	0.51 (0.27-0.75)

COLDICE Trial (N=65)

- Histopathological agreement between TBCB and SLB was 70.8%, with diagnostic agreement at MDD at 76.9% (κ 0.62, 0.47–0.78).
- 60% of cases TBCB with MDD was felt to provide high confidence in the diagnosis, and in those cases concordance between TBCB and SLB diagnosis was high (95%).
- 40% of cases where TBCB with MDD did not provide a high confidence diagnosis, concordance with SLB was low.

Romagnoli M. et al. Poor concordance between sequential TBLC and SLBX in the diagnosis of ILD. AJRCCM 2019.
Troy LK et al. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. Lancet Respir Med. 2019.

What biopsy type to use in ILD and when?

- **Surgical Lung Biopsy (SLB)**
  - Patients with low confidence ILD diagnosis
  - SLB is likely to alter treatment decisions (immunosuppresssion vs anti-fibrotics vs dual therapy)
  - Patient not at excessively increased risk for post-operative complication

- **Transbronchial Cryobiopsy (TBCB)**
  - ATS 2022: Conditional recommendation was made to regard transbronchial lung cryobiopsy as an acceptable alternative to surgical lung biopsy in centers with appropriate expertise. (conditional recommendation, very low quality evidence).
  - Lack of standardization in procedure performance, number/size of specimens, and locations of sampling
  - May be considered as an alternative to SLB in some circumstances

- **Transbronchial Biopsy (TBB)**
  - NOT recommended in ILDs that do not have a peribronchial component due to insufficient tissue size and sampling error
  - i.e. sarcoidosis, HP, eosinophilic pneumonia, organizing pneumonia