Fibrotic lung diseases: Basic Principles, Common Problems, and Reporting

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Disclosures

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None

Off-label usage:
None
Learning Objectives

At the end of this course, the participant should be able to do the following:

• Explain the prognostic and therapeutic implications of a diagnosis of IPF versus other fibrotic ILDs
• Describe the international consensus criteria for the diagnosis of IPF, and explain when and how the surgical lung biopsy is used to establish this diagnosis
• Explain the histologic similarities and differences among diseases that produce a UIP pattern
• Explain how to formulate a clinically useful pathology report for fibrotic ILDs

Lecture Outline

• Basic Principles
• Diagnostic Approach to Common Fibrotic ILDs
• Formulating a Clinically Useful Report
Medical Training

**Biology:**
- "Disease"
  - Pathology pattern
  - Clinical pattern

**Medicine:**
- Clinical pattern
  - Pathology pattern
  - "Disease"

Harsh Reality

**Biology:**
- "Disease"
  - Path patterns A, B, or C
  - Clinical patterns X, Y, or Z

**Medicine:**
- Clinical pattern Y
  - Pathology pattern C
  - "Disease" R, S, or T
Diffuse Interstitial Lung Disease: Patterns change over time

Part I: Basic Principles
Diffuse Parenchymal Lung Disease (DPLD)

- DPLD of known cause or association
- Idiopathic Interstitial Pneumonias (IIPs)
- Granulomatous DPLD: Sarcoidosis, HP
- Others: PLCH, CEP

Connective Tissue Diseases
  - RA, SS, lupus, DM/PM, etc.
Vasculitic Syndromes
  - Iatrogenic
    - Drug Reactions
    - Radiation
Infections / Aspiration / Sepsis
Environmental
  - Toxic Exposures
  - Pneumoconioses
Miscellaneous

Idiopathic Pulmonary Fibrosis (IPF)
Idiopathic Nonspecific Interstitial Pneumonia (NSIP)
Respiratory Bronchiolitis-Interstitial Lung Disease (RB-ILD)
Desquamative Interstitial Pneumonia (DIP)
Cryptogenic Organizing Pneumonia (COP)
Acute Interstitial Pneumonia (AIP)
Idiopathic Lymphoid Interstitial Pneumonia (LIP)
Idiopathic Pleuroparenchymal Fibroelastosis (PPFE)
Unclassifiable IIPs

Basic principles of lung injury and repair

Mild diffuse fibrosis

alveoli

lobule

mild to moderate injury

Alveoli

Airways

normal
Basic principles of lung injury and repair

- Airways
- Lobule
- Alveoli
- Alveoli

Severe injury

- Normal
- Honeycombing

Inhalational injury: central

- Normal
- Airway-centered fibrosis
Basic principles of lung injury and repair

autoimmune injury: peripheral, diffuse, irregular

Peripheral, irreg. fibrosis

Prognostic significance of histologic patterns of ILD

Idiopathic
- IPF
Non-idiopathic
- Chr HP
- CTD
- Asbestosis
- Chr drug rxn
- Etc.

**Prognostic significance of etiology of ILD**

Unadjusted Kaplan-Meier figure stratified by ILD subtype: CT-ILD = connective tissue disease-associated interstitial lung disease; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia.

**Diagnosis based on MDD**

<table>
<thead>
<tr>
<th>Mortality (%)</th>
<th>Years</th>
<th>IPF</th>
<th>Unclassifiable ILD</th>
<th>CT-ILD/idiopathic NSIP</th>
<th>Chronic HP</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0</td>
<td>307</td>
<td>218</td>
<td>150</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>265</td>
<td>137</td>
<td>90</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>216</td>
<td>64</td>
<td>64</td>
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<td></td>
<td>3</td>
<td>169</td>
<td>174</td>
<td>128</td>
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<td>4</td>
<td>130</td>
<td>22</td>
<td>14</td>
<td>51</td>
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<td></td>
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<td>96</td>
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<td>71</td>
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<td>7</td>
<td>71</td>
<td>24</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>71</td>
<td>24</td>
<td>14</td>
<td>7</td>
</tr>
</tbody>
</table>

**Number at risk**

- IPF: 307
- Unclassifiable ILD: 173
- CT-ILD/idiopathic NSIP: 256
- Chronic HP: 206

**Time to Death or Hospitalization**

- **Combination therapy**
  - Weeks since Randomization: 0, 15, 30, 45, 60
  - Probability: 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0
- **Placebo**
  - Weeks since Randomization: 0, 15, 30, 45, 60
  - Probability: 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0

**No. at Risk**

- **Combination therapy**
  - 77 at risk
  - 40 at risk
  - 29 at risk
  - 23 at risk
  - 10 at risk
- **Placebo**
  - 78 at risk
  - 55 at risk
  - 42 at risk
  - 26 at risk
  - 18 at risk
Treatment Differences in 2018

- **IPF**
  - Anti-fibrotic agents (perfenidone, nintedanib)
  - PPI
  - AVOID immunosuppression

- **CTD-ILD**
  - Prednisone
  - Azathioprine
  - Mycophenolate
  - Methotrexate
  - Cyclophosphamide
  - Rituximab

- **Chr HP**
  - Removal of offending antigen
  - Steroids
  - Rituximab?

- **Pattern matters**
- **Etiology matters**
Part II: Diagnostic Approach to Fibrotic ILDs

Algorithmic approach to Fibrotic ILD

Don’t panic. → Fibrosis?
Algorithmic approach to Fibrotic ILD

Don’t panic. ➔ Fibrosis? ➔ yes ➔ UIP? ➔ yes ➔ “UIP” ➔ UIP of IPF? (multidisciplinary discussion)

- Connective tissue disease
  - Idiopathic NSIP
  - DIP / SRIF
  - Pneumoconiosis
  - Sarcoidosis / berylliosis
  - Small airway disease
  - PLCH
  - Malignancy
  - IgG4-related disease
  - Erdheim-Chester
  - Hermansky-Pudlak
  - PPFE
  - Misc.

- Acute lung injury
  - MAB, PF, infection, drug rxn, CTD, infarct, vasculitic syndrome, LP, idiop. etc.

- Cellular infiltrates
  - Infection, HP, drug rxn, CTD, LP, OP, vasculitic syndrome, LIP, etc.

- Alveolar filling
  - OP, DAD, IB, infarct, TAP, etc.

- Nodules
  - Neoplasia, nodular LH, granulomas, fibrosis, PLCH, pneumoconiosis, etc.

- Small airway disease
  - Constrictive bronchiolitis, chronic aspiration, immunodeficiency, BB, etc.

- Vascular disease
  - IPF, BOS, FEP, PCP, thrombosis, thromboembolic disease, vasculitis syndromes, etc.

- Misc.

UIP/IPF

yes ➔ maybe

no ➔ no

- Chronic HP?
- Advanced PLCH?
- End-stage sarcoidosis?
- Erdheim-Chester?
- Hermansky-Pudlak?
- Other?
Idiopathic pulmonary fibrosis

- Idiopathic (dx of exclusion!)
- Most common in elderly (usu. >60 yrs)
- Strongly associated with smoking
- Relentlessly progressive
- Median survival <3 yrs
- UIP pattern on imaging
- UIP pattern on histology
Usual Interstitial Pneumonia

- UIP is a pathologic PATTERN, not a disease!
- Spatially heterogeneous fibrosis
  - Patchy
  - Architectural distortion (honeycombing)
  - Subpleural / peripheral
  - Lower lung zones
- Temporally heterogeneous fibrosis
  - Old fibrosis
  - Young fibrosis – fibroblast foci

Normal

UIP pattern
Radiologic UIP pattern in IPF

- Reticular abnormalities (i.e. fibrosis)
- Subpleural, basal predominance
- Honeycombing ± traction bronchiectasis
- No features inconsistent with UIP pattern

Raghu G et al., Am J Respir Crit Care Med. 2011;183:788-824
UIP pattern in IPF

UIP pattern in IPF
Histologic UIP pattern in IPF

**TABLE 3. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN**

<table>
<thead>
<tr>
<th>UIP Pattern (All Four Criteria)</th>
<th>Probable UIP Pattern</th>
<th>Possible UIP Pattern</th>
<th>Not UIP Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution</td>
<td>- Evidence of marked fibrosis/ architectural distortion, ± honeycombing</td>
<td>- Presence of patchy involvement of lung parenchyma by fibrosis</td>
<td>- Honeycombing</td>
</tr>
<tr>
<td>- Presence of patchy involvement of lung parenchyma by fibrosis</td>
<td>- Absence of either patchy involvement or fibroblastic foci, but not both</td>
<td>- Presence of fibroblast foci</td>
<td>- Organizing pneumonia</td>
</tr>
<tr>
<td>- Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
<td>- OR</td>
<td>- Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
<td>- Granuloma</td>
</tr>
</tbody>
</table>

Definition of abbreviations: HRCT = high-resolution computed tomography; UIP = usual interstitial pneumonia.

* Can be associated with acute exacerbation of idiopathic pulmonary fibrosis.

* An isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be consistent in lung biopsies with an otherwise UIP pattern.

* This scenario usually represents end-stage idiopathic lung disease where honeycombed segments have been sampled but where a UIP pattern might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided by pre-operative targeting of biopsy sites away from these areas using HRCT.
## Dx of IPF: ATS/ERS/JRS/ALAT Guidelines

### Table 6. Combination of High-Resolution Computed Tomography and Surgical Lung Biopsy for the Diagnosis of IPF (Requires Multidisciplinary Discussion)

<table>
<thead>
<tr>
<th>HRCT Pattern</th>
<th>Surgical Lung Biopsy Pattern* (When Performed)</th>
<th>Diagnosis of IPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP</td>
<td>UIP</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>Probable UIP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Possible UIP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonclassifiable fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not UIP</td>
<td>NO</td>
</tr>
<tr>
<td>Possible UIP</td>
<td>Probable UIP</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>Possible UIP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonclassifiable fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not UIP</td>
<td>NO</td>
</tr>
<tr>
<td>Inconsistent with UIP</td>
<td>Probable UIP</td>
<td>Probable</td>
</tr>
<tr>
<td>Inconsistent with UIP</td>
<td>Possible UIP</td>
<td>Possible</td>
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</tr>
<tr>
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<td>Not</td>
</tr>
</tbody>
</table>

* Patterns as described in Tables 4 and 5.

**Connective tissue disease-associated ILD**
CTD-associated ILD

- Lung fibrosis due to CTD
- Most common: RA, PSS, SLE, PM/DM, SS
- Significant ILD ~15%, subclinical nearly 50%
- ~10% present initially with ILD!
- UIP histology: usually RA (others usually NSIP)
- Imaging: UIP or NSIP
- Treatment: Steroids, immunosuppression, LTx

Rheumatoid arthritis – radiologic UIP
RA with radiologic NSIP pattern

RA-ILD
Chronic hypersensitivity pneumonitis

Chronic HP

- Lung fibrosis due to exaggerated immune response to inhaled organic antigen
- Antigens: Avian, fungal, bacterial, protozoal proteins, or LMW organic compounds
- Usually NOT smokers
- Treatment: Removal of antigen, steroids, LTx
Chronic HP

- Air trapping (airway obstruction)
- Central predominance
- Upper lobe predominance
Part III: Formulating a Clinically Useful Pathology Report
Pathology Reporting: Clinician Expectations

• What do you see?
• How bad is it?
• What is causing it?
• How do I treat it?

Pathology Reporting: Clinician Expectations

• What do you see?  
• How bad is it?  
• What is causing it?  
• How do I treat it?

Lymph node, left supraclavicular, core biopsy:
  Metastatic adenocarcinoma, poorly differentiated, most likely from the lung (see Comment).

Comment: Immunostaining for TTF-1 is positive, indicating that the tumor most likely arose in the lung. Material will be sent to an outside lab for molecular testing for potential targetable mutations, and will be reported separately.
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Lung, left upper and lower lobes, wedge biopsies: Usual interstitial pneumonia.

Pathology Reporting: Clinician Expectations

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Pathology Reporting: Clinician Expectations

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- How bad is it?
- What is causing it?
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Lung, left upper and lower lobes, wedge biopsies: Usual interstitial pneumonia.

Clinician Toolbox for ILD

1. Antibiotics
2. Bronchodilators and anti-tussives
3. Immunosuppression
4. Small molecule therapy for IPF (perfenidone and nintedanib)
5. PPIs for GERD and microaspiration
6. Pulm HTN disease-modifying agents
7. Transplantation
Lung, left upper and lower lobes, wedge biopsies:
Advanced fibrosing interstitial pneumonia (see Comment).

Comment: Although the pattern of fibrosis is most consistent with UIP, it is also accompanied by lymphoid hyperplasia and chronic pleuritis, which would not be expected in IPF. Instead, this pattern is most suggestive of connective tissue disease, and hopefully this will be at least partially responsive to steroids. Correlation with clinical, imaging, and serologic findings is recommended.
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Take-home messages

• UIP is a pattern, NOT a disease!
• Not all UIP is idiopathic
  • Prognosis
  • Treatment
  • Family members
  • Research (future treatment)
• Pay attention to sub-characteristics
• Clinical history, imaging often provides clues
• Multidisciplinary discussion often required

QUESTIONS?