The Changing Landscape of Interstitial Lung Disease

A Visiting Faculty Grand Rounds
Interstitial Lung Disease (ILD)

- ILD comprises more than 130 distinct disorders
  - Characterized by cellular proliferation, cellular infiltration, and/or fibrosis of the lung parenchyma not due to infection or neoplasia
- Incidence and prevalence of ILD believed to be higher than previously estimated
- Similar symptoms, physiology, radiology
- Difficult nomenclature
- Limited, often toxic, treatments

Interstitial Lung Diseases

**ILD of Known Cause or Association**
- Medications
- Radiation
- Connective tissue disease
- Vasculitis
- Hypersensitivity pneumonitis
- Pneumoconioses

**Idiopathic Interstitial Pneumonias**
- Idiopathic pulmonary fibrosis
- Idiopathic nonspecific interstitial pneumonia
- Respiratory bronchiolitis–ILD
- Desquamative interstitial pneumonia
- Cryptogenic organizing pneumonia
- Acute interstitial pneumonia
- Rare IIPs (LIP, IPPFE)
- Unclassifiable IIP

**Sarcoidosis**

**“Other” ILD**
- Pulmonary LCH
- LAM
- Eosinophilic pneumonias
- Alveolar proteinosis
- Genetic syndromes

**Definitions**
- IIP = idiopathic interstitial pneumonia
- LIP = lymphoid interstitial pneumonia
- IPPFE = idiopathic pleuroparenchymal fibroelastosis
- LCH = Langerhans cell histiocytosis
- LAM = lymphangioleiomyomatosis

Early and accurate diagnosis of ILD and its specific type is vital to directing therapy and monitoring disease course and therapeutic response.

Barriers to Timely Diagnosis of ILD

<table>
<thead>
<tr>
<th>Barriers</th>
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<tbody>
<tr>
<td>• Nonspecific symptoms easily confused with those of more common conditions.</td>
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<tr>
<td>• Symptoms that can provide clues to underlying etiology are not part of a routine history and require specific questioning.</td>
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<tr>
<td>• Insidious, prolonged development of symptoms often portends diagnosis of more advanced disease.</td>
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<td>• Crackles—the major clue on physical exam—are often missed or attributed to heart failure or obesity.</td>
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<td>• No specific laboratory tests or characteristic findings for ILD.</td>
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<td>• Chest imaging is required.</td>
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<td>• Lack of certainty associated with any given finding increases the risk for misdiagnosis and misclassification.</td>
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Case: 67-year-old man with persistent dry cough (4 years) and exertional dyspnea (1 year)

History of Present Illness
- Recently seen in the ED for symptoms and treated with antibiotics for “walking pneumonia”; symptoms did not resolve
- No hemoptysis or wheeze
- Reports exertional dyspnea has increased over the past 6 months
- Denies fever/chills, URI symptoms, chest pain or pressure, orthopnea, paroxysmal nocturnal dyspnea, pedal edema, and weight loss

Physical Exam
- BP 120/70; pulse 71 beats/minute, respirations 18/minute, RA SpO2 98%
- Chest with mild bibasilar inspiratory and expiratory dry crackles

ED = emergency department; URI = upper respiratory infection.
## Differential Diagnosis

### Cough
- Asthma
- “Upper airway cough syndrome”
- Gastroesophageal reflux disease (GERD)
- ACE inhibitor
- COPD
- ILD
- Bronchiectasis
- Lung cancer
- Chronic bronchopulmonary infection

### Dyspnea
- Cardiac
  - Heart failure
  - Angina
- Pulmonary
  - COPD
  - Asthma
  - ILD
  - Bronchiectasis
  - Airway obstruction (eg, lung cancer)
- Anemia
- Obesity/Deconditioning
Distinguishing Dyspnea: IPF Prevalence

IPF = idiopathic pulmonary fibrosis

What additional information/testing would you pursue at this time?

- Additional history
- Pulmonary function tests (PFTs)
- Chest X-ray
- Echocardiogram
- Serologic testing
- High-resolution computed tomography (HRCT)
- Surgical biopsy
Case, cont’d.: Additional History

• GERD – symptoms controlled with medication
• No sleep apnea, no joint/muscle pain, no skin changes, no dry eyes/mouth, no Raynaud’s symptoms
• Vietnam veteran – exposure to agent orange; remodeled a home ~30 years ago that was eventually condemned due to mold; for past 4 years has worked in airline hydraulic assembly with possible exposure to aerosolized lubricants
• Former 20 pack-year smoker

GERD = gastroesophageal reflux disease.
Case, cont’d.: Additional Testing

- Pulmonary function testing
  - FEV1 = 2.74 L (89% predicted)
  - FVC = 3.40 L (79% predicted)
  - FEV1/FVC = .81
  - DLCO = 18.85 (68% predicted)

- Echocardiogram
  - Unremarkable

- Chest X-ray
What Features of the Case Should Trigger Further Evaluation for ILD?

Key symptoms
• Exertional dyspnea
• Nonproductive cough

Objective findings
• Crackles
• Exertional desaturation
• Spirometry (low FVC) or low DLCO
• Abnormal chest X-ray
What additional information/testing would you pursue at this time?

- Serologic testing
- HRCT
- Surgical biopsy
HRCT Plays Key Role in the Diagnosis of ILD, Particularly IPF

- Does NOT use contrast
- Thin collimation
  - HRCT, approximately 1-mm slice thickness
  - MDCT (contiguous slices) preferred
    - Close tracking of subtle parenchymal and airway abnormalities
    - Avoids missing small/subtle abnormalities
- Should use low dose (~80 mA)
- Reconstruction with specific windows; high kernel reconstruction
- Inspiration, expiration, and prone images

MDCT = multidetector computed tomography.
HRCT, cont’d.

- Examines the **entire lungs**
  - Avoids sampling error (like surgical biopsy)
  - Can visualize mixed disease patterns
- Expiratory images add physiologic element
- Key limitation is resolution
  - Ground glass may be inflammation, fibrosis, infection, water, blood, etc
  - Microscopic honeycomb change
  - Histopathologic features
Impact of Thickness and Algorithm

CT
10-mm standard algorithm

HRCT
1.5-mm high-resolution algorithm

Slide courtesy of Ella Kazerooni.
Case, cont’d.: HRCT
### Criteria for UIP Pattern in HRCT

<table>
<thead>
<tr>
<th>UIP Pattern (All 4 Features)</th>
<th>Possible UIP (All 3 Features)</th>
<th>Inconsistent with UIP (Any)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Subpleural, basal predominance</td>
<td>• Subpleural, basal predominance</td>
<td>• Upper or mid-lung predominance</td>
</tr>
<tr>
<td>• Reticular abnormality</td>
<td>• Reticular abnormality</td>
<td>• Peribronchovascular predominance</td>
</tr>
<tr>
<td>• Honeycombing with/without traction bronchiectasis</td>
<td>• Absence of features listed as inconsistent with UIP (column 3)</td>
<td>• Extensive ground glass abnormality (extent &gt; reticular abnormality)</td>
</tr>
<tr>
<td>• Absence of features listed as inconsistent with UIP (column 3)</td>
<td></td>
<td>• Profuse micronodules (bilateral, predominantly upper lobe)</td>
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<td></td>
<td></td>
<td>• Discrete cysts (multiple, bilateral, away from areas of honeycombing)</td>
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<td></td>
<td></td>
<td>• Diffuse mosaic attenuation/air-trapping (bilateral, in ≥3 lobes)</td>
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<td>• Consolidation in bronchopulmonary segment(s)/lobe(s)</td>
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UIP = usual interstitial pneumonia.
Case, cont’d.: Summary of Current Findings

- Exertional dyspnea
- Nonproductive cough
- Crackles
- Exertional desaturation
- Low FVC
- Low DLCO
- Normal echocardiogram
- Chest X-ray revealed interstitial changes
- HRCT reveals possible UIP pattern
- ANA, RF, CCP, and other serologies unremarkable
Diagnosis and Multidisciplinary Evaluation

• Accurately identifying ILD requires a comprehensive approach:
  – Detailed history and physical examination
  – PFTs (every 3-4 months to determine if there is lung function decline)
  – Chest X-ray
  – Echocardiogram
  – Serologic testing
  – HRCT
  – Surgical biopsy (in some cases)

• Multidisciplinary evaluation may allow for more accurate disease classification, diagnosis, and prognosis and a more informed application of therapeutic advances.
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Diagnosis requires:

1. Exclusion of other known causes of ILD.
3. Specific combinations of HRCT and surgical lung biopsy patterns in patients subject to surgical lung biopsy.

The Major and Minor Criteria proposed in the 2000 ATS/ERS Consensus Statement were eliminated.

ATS/ERS = American Thoracic Society/European Respiratory Society.
Is surgical lung biopsy appropriate in this patient?

- Yes
- No
Considerations Before Surgical Lung Biopsy

• Is it safe?
  – ~12,000 surgical lung biopsies performed annually for ILD in the United States (2/3 elective)
  – In-hospital mortality ~1.7% for elective procedures but significantly higher for nonelective procedures (~16.0%)
  – Risk factors for mortality: male sex, increasing age, increasing comorbidity, open surgery, suspected provisional diagnosis of IPF-CS or CTD-ILD

• Additional risk factors
  – Extensive honeycombing
  – Pulmonary hypertension
  – Oxygen requirements
  – Active progression of disease
  – DLCO < ~35% or FVC < ~50%

• Can you confirm the diagnosis without a biopsy?

Case cont’d.: Surgical Lung Biopsy

• Surgical lung biopsy reveals UIP pattern
  - Patchwork fibrosis, left, and fibroblast foci, right

• Diagnosis of IPF
IPF

• Peripheral lobular fibrosis of unknown cause
• More common than previously thought
• Disease of older adults
  – 0.5% of US adults >65 years old have IPF
  – 1 new case diagnosed per 1,000 adults >65 years old each year
• “High impact” disease
  – Disabling exertional dyspnea and cough
  – Severe functional limitation
  – Impaired quality of life
  – Median survival time 3.8 years
• Until recently, no FDA-approved therapies in the US

What would be the next thing you would do to manage this patient?

- Start pharmacotherapy
- Start oxygen
- Refer to an ILD center
- Refer for evaluation for lung transplantation
- Do a sleep study
- Send for pulmonary rehabilitation
- Refer to a clinical trial
ILD Management

• There is no universal treatment strategy for ILD. Approaches are tailored to ILD subtype and other factors.

• Numerous management decisions include:
  – Whether to administer pharmacologic therapy
  – How to best monitor the disease and assess indicators of stabilization improvement, and progression
  – Whether to refer to ILD center
  – Whether the patient should be referred for lung transplantation evaluation
  – When to implement supportive, palliative care for patients with end-stage disease

• Guideline recommendations for some subsets of ILD rely on insufficient evidence

• Treatment of ILD remains a challenge
ILD Management Checklist

• Address comorbidities
• Consider pharmacologic therapy
• Establish follow-up plan, including PFTs every 3-4 months
• Smoking cessation
• Supplemental oxygen
• Home SpO₂ monitoring
• Sleep study or nocturnal oximetry
• Pulmonary rehabilitation
• Lung transplant evaluation
• Age-appropriate vaccination
• Weight management
• Clinical trial enrollment
• ILD support groups and education
• Advocacy group involvement
ILD and Comorbidities

• Comorbidities impair quality of life, impact respiratory status, and can lead to disease progression and death

• Early detection and accurate management of comorbidity are essential

• Comorbidities include:
  – Acute and chronic infection
  – Gastroesophageal reflux disease
  – Obstructive sleep apnea/sleep disorders
  – Pulmonary hypertension
  – Cardiovascular disease

What pharmacotherapy would you consider to manage a patient with IPF?

- Pirfenidone
- Nintedanib
- Imatinib
- Sildenafil
Approved Pharmacologic Therapies for IPF

- **Pirfenidone**
  - Small non-peptide molecule
  - Inhibits release of pro-inflammatory cytokines
    - TNF-α, IL-12, IFN-γ
  - Attenuates fibroblast proliferation
  - Inhibits release of TGF-β1
  - Inhibits collagen synthesis

- **Nintedanib**
  - Tyrosine kinase inhibitor
    - VEGF
    - PDGF
    - FGF
  - Anti-angiogenic effects
  - Anti-tumor effects
  - Anti-fibrotic effects

Both have shown efficacy to slow functional decline and disease progression.

Nintedanib: INPULSIS-1 and INPULSIS-2 Trial Design

Inclusion Criteria
- Age ≥40
- IPF ≤5 y
- ≥50% FVC pred
- 30%-79% DLCO pred
- HRCT within 1 y

Endpoints
1º: Δ FVC
2º: Time to first AE Δ SGRQ

1,066 Patients

Nintedanib 300 mg daily

Placebo

52 Weeks
INPULSIS Primary Endpoint: Adjusted Annual Rate of Decline in FVC

**INPULSIS-1**

- **Nintedanib, 150 mg Twice Daily (N = 309)**
  - Adjusted Annual Rate of Change in FVC, mL/y: -114.7
  - Difference: 125.3 (95% CI, 77.7-172.8)  
  - P < .001

- **Placebo (N = 204)**
  - Adjusted Annual Rate of Change in FVC, mL/y: -239.9

**INPULSIS-2**

- **Nintedanib, 150 mg Twice Daily (N = 329)**
  - Adjusted Annual Rate of Change in FVC, mL/y: -113.6
  - Difference: 93.7 (95% CI, 44.8-142.7)  
  - P < .001

- **Placebo (N = 219)**
  - Adjusted Annual Rate of Change in FVC, mL/y: -207.3

Nintedanib – Safety and Tolerability

<table>
<thead>
<tr>
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<th>Nintedanib (N = 638)</th>
<th>Placebo (N = 423)</th>
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<tbody>
<tr>
<td><strong>Dose Reduction</strong>*</td>
<td>178 (28%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td><strong>Treatment Interruptions</strong>*</td>
<td>151 (24%)</td>
<td>42 (10%)</td>
</tr>
<tr>
<td></td>
<td>Incidence/Discontinue</td>
<td>Incidence/Discontinue</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>63% / 4.4%</td>
<td>18% / 0.2%</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>25% / 2.0%</td>
<td>7% / 0%</td>
</tr>
<tr>
<td></td>
<td>Mild/Mod/Severe (%)</td>
<td>Mild/Mod/Severe (%)</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>57 / 38 / 5</td>
<td>77 / 20 / 3</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>74 / 24 / 2</td>
<td>93 / 7 / 0</td>
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</table>

* No particular time
FDA Approval of Nintedanib

- Approved October 2014 for the treatment of IPF
- Liver function tests are required prior to treatment and should be evaluated every 3 months in first year
- Dosage and administration
  - 150 mg twice daily with food
  - Take each dose approximately 12 hours apart
  - Adverse reactions? Consider temporary dose reduction to 100 mg, temporary interruption, or discontinuation
Pirfenidone: ASCEND Trial Design

**Inclusion Criteria**
- Age 40-80 y
- Confirmed IPF
- 50%-90% FVC pred
- 30%-90% DLCO pred
- FEV₁/FVC ≥0.80
- 6MWD ≥150 m

**Endpoints**
1. Δ FVC or death
2. 6MWD
   - PFS
   - Dyspnea
   - Death

**555 Patients**

ASCEND: Primary Efficacy Analysis

<table>
<thead>
<tr>
<th>Week</th>
<th>Patients With ≥10% Decline in FVC or Death, %</th>
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<tbody>
<tr>
<td>13</td>
<td>4% (Pirfenidone) 7% (Placebo)</td>
</tr>
<tr>
<td>26</td>
<td>13% (Pirfenidone) 15% (Placebo)</td>
</tr>
<tr>
<td>39</td>
<td>20% (Pirfenidone) 23% (Placebo)</td>
</tr>
<tr>
<td>52</td>
<td>35% (Pirfenidone) 40% (Placebo)</td>
</tr>
</tbody>
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Absolute difference: 2.5%, 7.9%, 12.3%, 15.3%
Relative difference: 54.0%, 58.0%, 57.8%, 47.9%
Rank ANCOVA P: < .001, < .001, < .001, < .001

ANCOVA = analysis of covariance.
ASCEND: Treatment-Emergent Adverse Events More Common in Pirfenidone Group

- Nausea (36% vs 13%)
- Rash (28% vs 9%)
- AEs generally mild-to-moderate severity, reversible, and without clinically significant sequelae

AEs = adverse events.
FDA Approval of Pirfenidone

• Approved October 15, 2014, for the treatment of IPF
• Liver function tests are required prior to treatment and should be evaluated every 3 months in first year
• Dosage and administration
  – 801 mg 3x daily with food (three 267-mg capsules per dose)
  – Take each dose at the same time each day
  – Initiate with titration
    ▪ Days 1-7: one capsule 3x daily
    ▪ Days 8-14: two capsules 3x daily
    ▪ Days 15 onward: three capsules 3x daily
  – Adverse reactions? Consider temporary dosage reduction, treatment interruption, or discontinuation
2015 Update to the ATS/ERS/JRS/ALAT Clinical Practice Guidelines for IPF

- **STRONG recommendations FOR use**
  - Oxygen use (when medically indicated by low oxygen levels)
  - Lung transplantation (when medically indicated)

- **CONDITIONAL recommendations FOR use**
  - Pirfenidone (new)
  - Nintedanib (new)
  - Antacid therapy, even in the absence of symptoms
  - Pulmonary rehabilitation

2015 Update to the ATS/ERS/JRS/ALAT Clinical Practice Guidelines for IPF, cont’d.

- **STRONG recommendations AGAINST use**
  - Anticoagulation (warfarin)
  - Combination prednisone/azathioprine/N-acetylcysteine
  - Ambrisentan
  - Imatinib

- **CONDITIONAL recommendations AGAINST use**
  - N-acetylcysteine monotherapy
  - Macitentan (new)
  - Bosentan (new)
  - Sildenafil (new)
Importance of a Shared Decision-Making Process

• Discuss the efficacy and safety of available therapies
• Listen to patient’s preferences and concerns
• Focus on symptom control and management of comorbidities
• Set treatment expectations
• Look at the option of lung transplantation
Lung Transplantation for IPF: Current Referral Guidelines

• Histopathologic or radiographic evidence of UIP
• Abnormal lung function: FVC <80% predicted or DLCO <40% predicted
• Any dyspnea or functional limitation attributable to lung disease
• Any supplemental oxygen requirement, even if only during exertion
Case, cont’d.

• Patient initiated on therapy
• Oxygen titration study on a treadmill
  - 1.8 mph with 5% grade: desaturation to 88% after 1 minute
  - 1.8 mph with 5% grade + 2L NC → maintained 97%
• Six-minute walk test 380 meters, end-walk 90% on 2L NC
• Prescribed oxygen 2L with exertion and sleep
• Given PCV13 pneumococcal vaccination
• Joined ILD support group
• Referred for pulmonary rehabilitation
• Referred for lung transplant evaluation
Conclusion

• Don’t forget about ILD
  - Exertional dyspnea or cough with crackles → think ILD
  - Attaining an accurate diagnosis is crucial: treatment implications
• History/Physical Exam/Serologies/HRCT BEFORE biopsy
• HRCT is a key diagnostic test; SLB if needed
• Nonpharmacologic approaches improve quality of life
• Never too early to consider/discuss treatment options
  - Pirfenidone and nintedanib slow IPF progression
  - Lung transplantation
• Holistic approach is important
  - Shared decision making
  - Comorbidities
  - Pulmonary rehabilitation
  - End-of-life discussion
Question 1:
When should pharmacologic therapy be started in patients with IPF?
Question 2:
How can you tell when an exposure is really causing the disease when you're taking a history?
Question 3:
How can we get input from expert radiologists in reading ILD CT scans (ie, how to get a second opinion if local radiologist is inexperienced)?
Question 4: Why shouldn't every patient be biopsied?
Question 5: Is most mortality after lung biopsy due to exacerbations?