Idiopathic Pulmonary Fibrosis: Making Sense of Diagnostic and Therapeutic Options in Primary Care
Faculty

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Disclosures

- **Kevin Flaherty, MD, MS** serves as a consultant for Boehringer Ingleheim and Genentech. Dr. Flaherty also serves on the advisory board for Fibrogen.

- **Franck Rahaghi, MD, MHS, FCCP** serves as a consultant/speaker/researcher for Boehringer Ingleheim. Dr. Rahaghi also serves as a researcher for Merck.
Learning Objectives

1. Implement an appropriate strategy for diagnosing a patient with idiopathic pulmonary fibrosis

2. Discuss and contrast the available pharmacotherapeutic options for patients with IPF

3. Describe the non-pharmacotherapeutic options for IPF patients

4. Establish the clear role for the primary care clinician in diagnosing and managing disease in IPF patients
PRE-TEST QUESTIONS
Pre-test Question 1

All of the following features have been associated with risk for idiopathic pulmonary fibrosis, EXCEPT:

1. Older age
2. Female gender
3. >20 pack-year smoking history
4. Gastroesophageal reflux disease
Pre-test Question 2

Which of the following therapies recommended for idiopathic pulmonary fibrosis was associated with high rates of diarrhea in clinical trials?

1. Antacid therapy
2. Nintedanib
3. Pirfenidone
4. Both nintedanib and pirfenidone
Pre-test Question 3

A 67-year-old man with a 9-month history of progressive dyspnea on exertion and dry cough presents for evaluation. He is a former smoker (30 pack-years) and has a history of dyslipidemia and GERD. Workup identifies bibasilar crackles, BP 122/74 mmHg, normal sinus rhythm, and no fever. Spirometry identifies a restrictive pattern with no reversibility. Current medications include atorvastatin 80 mg qd and omeprazole 20 mg as needed.

What should his primary care provider do at this time?

1. Refer to pulmonologist immediately
2. Prescribe two-week trial of bronchodilator
3. Initiate short course of oral corticosteroids
4. Continue workup with chest imaging and pulse oximetry
Which of the following non-pharmacologic therapies has been shown to improve survival in patients with idiopathic pulmonary fibrosis?

1. Lung transplantation
2. Pulmonary rehabilitation
3. Supplemental oxygen therapy
4. Cognitive behavioral therapy
Pre-test Question 5

Please rate your confidence in your ability to recognize features consistent with idiopathic pulmonary fibrosis (based on a scale of 1 to 5, with 1= “Not at all confident” and 5= “Very confident”).

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Patient Case: Michael

- 66-year-old man with 3 year history of dyspnea on exertion and a dry cough over the last month

- History
  - Hypertension, 10 years
  - Gastroesophageal reflux disease, 5 years
  - Chronic low back pain, 8 years
  - Retired construction foreman
  - Former smoker (25 pack-years, quit 15 years ago)

- Medications
  - Hydrochlorothiazide 25 mg qd
  - Esomeprazole prn
  - Naproxen prn
Michael (cont’d)

Physical examination:
- Vitals:
  - BP: 126/82 mmHg
  - HR: 74 bpm
  - RR: 19 bpm
  - Temp: 98.8 F
- Crackles in lower lung fields bilaterally
- Normal cardiac exam
- No jugular venous distention

Plain radiography
- No masses, infiltrates, or cardiomegaly
- Diffuse interstitial lung markings

Treatment:
- Doctor prescribes 7 days of oral antibiotics
At follow-up, Michael reports no improvement in symptoms

- **Additional tests:**
  - PFTs: restrictive pattern, reduced DLCO
  - Pulse oximetry (sitting): 94% \( O_2 \)Sat

- **Treatment:**
  - Doctor prescribes trial of bronchodilator
  - Recommends daily use of esomeprazole
Michael (cont’d)

2 years later after being treated for recurrent bronchitis, Michael reports cough and DOE are getting worse

- **Treatment:**
  - Oral corticosteroids while awaiting test results

- **Additional tests:**
  - CT for pulmonary embolism: diffuse scarring in lower lung fields; no PE

Prior to his follow up visit in 2 weeks his dyspnea continued to increase, and he was seen at a local ER where a PE-CT shows no PE but additional diffuse ground glass infiltrates. He is admitted, treated with empiric antibiotics and steroids but dies from progressive respiratory failure. Post-mortem exam revealed Idiopathic Pulmonary Fibrosis exacerbation.

*What did we miss?*
Interstitial Lung Diseases - Difficulties

- Diverse group of disorders (130+)
- Similar symptoms, physiology, radiology
- Difficult nomenclature
- Limited, often toxic, treatments
The Family of ILD

**Known etiology**
- Connective tissue disease
- Drugs
- Occupational exposures

**Granulomatous**
- Sarcoidosis
- Hyper-sensitivity pneumonitis

**Idiopathic interstitial pneumonias (IIP)**

**Non-IPF IIP**
- non-specific interstitial pneumonia
- cryptogenic organizing pneumonia
- respiratory bronchiolitis ILD
- desquamative interstitial pneumonia
- acute interstitial pneumonia
- lymphocytic interstitial pneumonia
- idiopathic pleuroparenchymal fibroelastosis

**Miscellaneous**
- LAM
- Histiocytosis X
Idiopathic Pulmonary Fibrosis

A specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs.

It is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis.
Five year survival of IPF is worse than most cancers

Vancheri et al., Eur Respir J 2010; 35: 496-504
Symptoms that should trigger consideration of IPF

Initial symptoms of IPF are **cough (typically nonproductive) and dyspnea**. Over time, the cough may become paroxysmal and dyspnea and exercise limitation worsen.
Potential Risk Factors

- Smoking, current or former, esp. >20 pack-years
- Older age
- Male gender
- Environmental exposures
  - Certain dusts (wood, metal, agricultural)
  - Certain microbes (cytomegalovirus, Epstein-Barr)
- Gastroesophageal reflux
Diagnosis
Updated Consensus Statement for Diagnosis of IPF

The diagnosis of IPF requires answering *three* key questions:

1. Exclusion of known causes of interstitial lung disease
2. Presence of Usual Interstitial Pneumonia (UIP) pattern on HRCT (in patients without surgical biopsy)
3. A HRCT pattern of definite/possible UIP with a surgical lung biopsy showing Definite/Probable UIP

Raghu et al., *Am J Respir Crit Care Med* 2011; 183:788
Velcro Crackles

- Inspiratory crackles that sound like Velcro being pulled apart:

- Bibasilar predominance – listen to all lung fields

- Characteristic of IPF
Pulmonary Function Testing

- **Pulmonary Mechanics** – FEV$_1$, FVC, FEV$_1$/FVC
  - Obstructive Lung Disease → Decreased FEV$_1$/FVC ratio
  - Restrictive Lung Disease → Normal/Increased FEV$_1$/FVC ratio
  - Muscle weakness → Normal/Increased FEV$_1$/FVC ratio
  - Percent predicted grades severity of FEV$_1$ and FVC

- **Lung Volumes**
  - True measure of size of lung
  - Total lung capacity (TLC), residual volume (RV)

- **Diffusion capacity for carbon monoxide (DL$_{CO}$)**
  - Decreased in many diseases such as emphysema, interstitial lung diseases, pulmonary vascular disease, pulmonary emboli
IPF diagnosis: current approach

Suspected ILD

Identifiable cause?

Chest HRCT

Possible UIP
Inconsistent with UIP

Surgical lung biopsy

UIP
Probable UIP
Possible UIP

MDD*

*MDD – Multidisciplinary Diagnosis

IPF
IPF / Not IPF
Not IPF

1. Raise suspicion that ILD is present
2. Identify a cause of the disease
   a. Infection
   b. Systemic Disorders
   c. Exposures (inhaled or oral)
   d. Idiopathic
Imaging Tools
IPF diagnosis: current approach

Suspected ILD

Identifiable cause?

Chest HRCT

Possible UIP
Inconsistent with UIP

Surgical lung biopsy

UIP
Probable UIP
Possible UIP

MDD

IPF
IPF / Not IPF

Not UIP

YES

Not UIP

IPF

Not IPF

Male presents with progressive dyspnea and cough for THREE years
High Resolution Computed Tomography

Allows detailed evaluation of the *lung parenchyma*

Optimal for *interstitial lung disease*, infection, emphysema, bronchiectasis

**Technique**

Does NOT use contrast

Thin collimation with approximately 1mm slice thickness

Reconstruction with specific Windows

Inspiration, Expiration, and prone images

*Regular CT or PE CT for everything else*
UIP features

- Upper lobes
  - Irregular Lines
  - Peripheral/Subpleural

- Lower lobes
  - Honeycomb
  - Lower lobe predominant
Usual Interstitial Pneumonia is lower lobe predominant
Early HRCT Findings in IPF

Courtesy of David A. Lynch, MD.
IPF diagnosis: current approach

Suspected ILD

Identifiable cause?

Chest HRCT

Possible UIP
Inconsistent with UIP

Surgical lung biopsy

UIP
Probable UIP
Possible UIP

MDD

IPF
IPF / Not IPF

Not UIP

Not IPF

Prognosis and Treatment
DISEASE PROGRESSION IN IPF IS VARIABLE AND OFTEN UNPREDICTABLE


Remember Michael...
Prognosis - Summary

- **Baseline factors** associated with ↑ risk for mortality
  - Age older than 60
  - Decreased FVC, DL_{CO}, 6 minute walk distance, VO_{2} max
  - Impaired oxygenation (rest and with exercise)
  - Presence of pulmonary hypertension
  - Failure of heart rate to recover after 6-minute walk test
  - Cough

- **Longitudinal factors** associated with ↑ risk for mortality
  - Acute Exacerbation/Respiratory Hospitalization
  - Decline in FVC of 5 - 10%
  - Decline in DL_{CO}
  - Increase in dyspnea
  - Decrease in walk distance/development of desaturation

- In many patients the course is still unpredictable
### Table: Treatment of Idiopathic Pulmonary Fibrosis: Executive Summary

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Strong For</th>
<th>Conditional For</th>
<th>Conditional Against</th>
<th>Strong Against</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan/Macitentan</td>
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<tr>
<td>Ambrisentan</td>
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<td></td>
<td>X</td>
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<tr>
<td>Imatinib</td>
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<tr>
<td>Anticoagulation</td>
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<tr>
<td>Pirfenidone</td>
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<tr>
<td>Nintedanib</td>
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<tr>
<td>Antacid therapy</td>
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<td></td>
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<tr>
<td>Sildenafil</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Decrease in Percent Predicted FVC by $\geq 10\%$

- Pirfenidone vs placebo: 0.52 (0.41-0.67)
- Nintedanib vs placebo: 0.61 (0.48-0.78)
- Pirfenidone vs nintedanib: 0.86 (0.60-1.20)

Network meta-analysis suggests little difference between pirfenidone and nintedanib in preserving lung function

Canestaro et al; *Chest* 2016; 149: 756-66
## Pirfenidone Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pirfenidone (%) (N = 278)</th>
<th>Placebo (%) (N = 277)</th>
<th>Δ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>36</td>
<td>13.4</td>
<td>22.6</td>
</tr>
<tr>
<td>Rash</td>
<td>28.1</td>
<td>8.7</td>
<td>19.4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>17.6</td>
<td>6.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Anorexia</td>
<td>15.8</td>
<td>6.5</td>
<td>9.3</td>
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<tr>
<td>GERD</td>
<td>11.9</td>
<td>6.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>12.6</td>
<td>7.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11.2</td>
<td>6.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17.6</td>
<td>13</td>
<td>4.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.9</td>
<td>8.7</td>
<td>4.2</td>
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</tbody>
</table>
# Common Nintedanib Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>INPULSIS-1</th>
<th></th>
<th>INPULSIS-2</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Nintedanib (n = 309)</td>
<td>Placebo (n = 204)</td>
<td>Nintedanib (n = 329)</td>
<td>Placebo (n = 219)</td>
</tr>
<tr>
<td>Any (%)</td>
<td>96</td>
<td>89</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>62</td>
<td>19</td>
<td>63</td>
<td>18</td>
</tr>
<tr>
<td>Nausea(%)</td>
<td>23</td>
<td>6</td>
<td>26</td>
<td>7</td>
</tr>
</tbody>
</table>
SUMMARY OF RECOMMENDATIONS FOR NON-PHARMACOLOGIC TREATMENT

- **Strong recommendation for use:**
  - Oxygen therapy
  - Lung transplantation

Raghu et al., *Am J Respir Crit Care Med* 2011; 183:788-24
DELAYED ACCESS TO TERTIARY CARE AMONG IPF PATIENTS IS ASSOCIATED WITH INCREASED MORTALITY

Summary
IPF: SUMMARY FOR PRIMARY CARE

- Typical symptoms are **progressive dyspnea on exertion, dry cough**
- Increased risk with **smoking history, male sex, age >50 years**
- Physical examination: **Bibasilar crackles** – evaluate lower lung fields

**Workup:**
- PFTs: often **restrictive pattern**, no reversibility, **reduced DLCO**
- Oximetry: desaturation with activity or at rest in advanced disease
- Plain radiography: may be normal in early IPF
- HRCT: **gold-standard imaging study for UIP pattern**
- Blood tests: used for differential diagnosis of interstitial lung diseases

**Refer early!**
- Referral delays are common
- Refer patients with no clear etiology for symptoms

**DO NOT IGNORE CRACKLES OR CHRONIC CHANGES ON CXR!**
POST-TEST QUESTIONS
Post-test Question 1

All of the following features have been associated with risk for idiopathic pulmonary fibrosis, EXCEPT:

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Post-test Question 2

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Post-test Question 4

Which of the following non-pharmacologic therapies has been shown to improve survival in patients with idiopathic pulmonary fibrosis?

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