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

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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

Pre-test Question 4
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
Michael (cont’d)

At follow-up, Michael reports no improvement in symptoms

**Additional tests:**
- PFTs: restrictive pattern, reduced DLco
- Pulse oximetry (sitting): 94% O₂ Sat

**Treatment:**
- Doctor prescribes trial of bronchodilator
- Recommends daily use of esomeprazole

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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?*

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Interstitial Lung Diseases - Difficulties

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

Idiopathic Interstitial Pneumonias (IIP)
- IPF
- Non-IPF IIP

Know etiology
- Connective tissue disease
- Drugs
- Occupational exposures

Granulomatous
- Sarcoidosis
- Hyper-sensitivity pneumonitis

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

Five year survival rate for IPF and different cancers (%)
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 – FEV₁, FVC, FEV₁/FVC
- Obstructive Lung Disease → Decreased FEV₁/FVC ratio
- Restrictive Lung Disease → Normal/Increased FEV₁/FVC ratio
- Muscle weakness → Normal/Increased FEV₁/FVC ratio
- Percent predicted grades severity of FEV₁ and FVC
- Lung Volumes
  - True measure of size of lung
  - Total lung capacity (TLC), residual volume (RV)
- Diffusion capacity for carbon monoxide (DL₅₀₂)
  - Decreased in many diseases such as emphysema, interstitial lung diseases, pulmonary vascular disease, pulmonary emboli
**IPF diagnosis: current approach**

- Suspected ILD
- Identifiable cause?
  - NO
  - Check HRCT
  - Possible UIP inconsistent with UIP
  - Surgical lung biopsy
  - Probable UIP
  - Possible UIP

**Diagnostic “Tools”**

1. History & Physical, PFT, Lab

   1. Raise suspicion that ILD is present
   2. Identify a cause of the disease
      - Infection
      - Systemic Disorders
      - Exposures (inhaled or oral)
      - Idiopathic

**Imaging Tools**
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
Usual Interstitial Pneumonia is lower lobe predominant

Early HRCT Findings in IPF
**IPF diagnosis: current approach**

- **Suspected ILD**
  - **Identifiable cause?**
    - **NO**
      - Chest HRCT
      - Surgical lung biopsy
    - **YES**
      - Possible UIP
      - Inconsistent with UIP
      - Not UIP

**IPF / Not IPF**

**Prognosis and Treatment**

**DISEASE PROGRESSION IN IPF IS VARIABLE AND OFTEN UNPREDICTABLE**

- Minimal Symptoms
- Hypoxemia
- Increased Disability
- Pulmonary HTN
- Death

Remember Michael...

Prognosis - Summary

- **Baseline factors** associated with ↑ risk for mortality
  - Age older than 60
  - Decreased FVC, DLCO, 6 minute walk distance, VO2 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 DLCO
  - Increase in dyspnea
  - Decrease in walk distance/development of desaturation
  - In many patients the course is still unpredictable

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis: Executive Summary


### Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Strong For</th>
<th>Conditional For</th>
<th>Conditional Against</th>
<th>Strong Against</th>
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<tbody>
<tr>
<td>Bosentan/Macitentan</td>
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<tr>
<td>Ambrisentan</td>
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<td></td>
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<tr>
<td>Pirfenidone</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>NAC/Azathioprine/ Prednisone</td>
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<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Nintedanib</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>NAC</td>
<td></td>
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<tr>
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<tr>
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<td></td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
<td></td>
<td></td>
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</table>

### Decrease in Percent Predicted FVC by ≥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

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### 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>Depression</td>
<td>17.6</td>
<td>6.1</td>
<td>11.5</td>
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<tr>
<td>Anorexia</td>
<td>15.8</td>
<td>6.5</td>
<td>9.3</td>
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<tr>
<td>Gastroesophageal reflux (GERD)</td>
<td>11.9</td>
<td>6.5</td>
<td>5.4</td>
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<tr>
<td>Weight Loss</td>
<td>12.8</td>
<td>7.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11.2</td>
<td>6.9</td>
<td>4.3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17.6</td>
<td>13</td>
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</tr>
<tr>
<td>Vomiting</td>
<td>12.8</td>
<td>8.7</td>
<td>4.2</td>
</tr>
</tbody>
</table>

### Common Nintedanib Adverse Events

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

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

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