Emerging Challenges in Primary Care: 2018

Navigating the Maze of Interstitial Lung Disease: Improving Outcomes through Early Diagnosis

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Disclosures

- Kevin Flaherty, MD, MS serves as a consultant for Boehringer Ingelheim, Veracyte, Roche/Genentech, FibroGen, and Sanofi Genzyme.
- David J. Lederer, MD, MS serves as a consultant for Veracyte.
- Fernando Martinez, MD, MS serves on the advisory boards for AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Sunovion, and Zambon. Dr. Martinez also serves on the study steering committee for AstraZeneca, Boehringer Ingelheim, Bayer, Biogem, Gilead, GSK, Nitto, ProMetic, and Veracyte in addition to the Data and Safety Monitoring Board for Boehringer Ingelheim, Biogen, and Genentech.
- Franck Rahaghi, MD, MHS, FCCP serves as a consultant and speaker for Boehringer Ingelheim and Genentech.
- Arunabh Talwar, MD, FCCP serves as a speaker for Boehringer Ingelheim and on the Advisory Board for Genentech.

Learning Objectives

1. Recognize the importance of early identification of patients with potential idiopathic pulmonary fibrosis (IPF).
2. Utilize appropriate strategies to diagnose a patient with IPF while excluding other potential mimickers.
3. Discuss the available therapeutic options for patients with IPF.
4. Recognize the role of the primary care clinician in managing the multi-morbidities associated with IPF.

PRE-TEST QUESTIONS
Pre-test ARS Question 1

Please rate your confidence in your ability to recognize features consistent with idiopathic pulmonary fibrosis.

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident

Pre-test ARS Question 2

How often do you order full pulmonary function testing, including DLCO, for a patient with unexplained dyspnea on exertion?

1. Never
2. Rarely
3. Sometimes
4. Frequently
5. Always

Pre-test ARS Question 3

On average, about how much time passes between the onset of symptoms of IPF and an accurate diagnosis of IPF?

1. 6-8 weeks
2. 3-6 months
3. 1-2 years
4. >5 years
The Life of a Patient with IPF

- https://youtu.be/U_vGM91Jg2g
- Patient Video courtesy of:
  Canadian Pulmonary Fibrosis Foundation
  http://cpff.ca

Five year survival of IPF is worse than most cancers

![Graph showing 5-year survival rate for IPF and different cancers (%)]

- IPF
- Uterus
- Thyroid
- Skin
- Pancreas
- Prostate
- Lung
- Lymphoma
- Leukemia
- Kidney
- Colon
- Breast
- Bladder

Vancheri et al., Eur Respir J 2010; 35: 496-504

Diagnostic Process

Symptom Onset 1-2 Years (average) → Diagnosis

Patients are often misdiagnosed with bronchitis, asthma, COPD, emphysema, or heart disease as symptoms are common manifestations of many diseases.

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**

**Barriers**
- Nonspecific symptoms easily confused with those of more common conditions.
- Symptoms that can provide clues to underlying etiology are not part of a routine history and require specific questioning.
- Insidious, prolonged development of symptoms often portends diagnosis of more advanced disease.
- Crackles—the major clue on physical exam—are often missed or attributed to heart failure or obesity.
- No specific laboratory tests or characteristic findings for ILD.
- Chest imaging is required.
- Lack of certainty associated with any given finding increases the risk for misdiagnosis and misclassification.

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**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

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**Distinguishing Dyspnea:**

**IPF Prevalence**

- IPF: 128,999
- Heart failure: 5.1 Million
- COPD: 15.7 Million

IPF = idiopathic pulmonary fibrosis

Pre-test ARS Question 4

Which of the following features may suggest the need to evaluate a patient for interstitial lung disease?

1. Hemoptysis
2. Chronic, productive cough
3. Reduced FEV1/FVC ratio on pulmonary function testing
4. Exertional desaturation

What Features Should Trigger Evaluation for ILD?

Key symptoms
- Exertional dyspnea
- Nonproductive cough

Objective findings
- Crackles
- Exertional desaturation
- Spirometry (low FVC) or low DLCO
- Abnormal chest X-ray

Interstitial Lung Diseases - Difficulties

- Diverse group of disorders (130+)
- Similar symptoms, physiology, radiology
- Difficult nomenclature
- Limited treatments
**Diffuse Parenchymal Lung Disease (DPLD)**

- Idiopathic Pulmonary Fibrosis
- Lymphoid Interstitial Pneumonia
- Other forms of DPLD (eg, LAM, HCC, etc)
- Unclassifiable

**Idiopathic Interstitial Pneumonias**

- Desquamative Interstitial Pneumonia
- Lymphoid Interstitial Pneumonia
- Bronchiolitis (cryptogenic)

**Granulomatous DPLD**

- Sarcoidosis

**Acute Interstitial Pneumonia**

**Nonspecific interstitial pneumonia (idiopathic)**

**Cryptogenic Organizing Pneumonia**

**Acute Respiratory Distress Syndrome**


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**Granulomatous DPLD**

- Sarcoidosis

**Acute Interstitial Pneumonia**

**Nonspecific interstitial pneumonia (idiopathic)**

**Cryptogenic Organizing Pneumonia**

**Acute Respiratory Distress Syndrome**


**Rare**

- Lymphoid Interstitial Pneumonia

**Pleuroparenchymal Fibroelastosis**

**Unclassifiable**

**Interstitial Lung Disease Diagnostic Team**

- Clinician
- Radiologist
- Pathologist

Communication among multidisciplinary team members is essential for an accurate diagnosis

**Clinical Tools for Diagnosis**

- History and physical
- PFT
- Lab

- Raise suspicion that ILD is present
- Identify the cause of the disease
  - Infection
  - Systemic disorders
  - Exposures (eg, occupational, environment, hobby)
  - Idiopathic
A 63-year-old man presents with a 6-month history of progressive dyspnea and cough. He is a former smoker (15 pack-years, quit 20 years ago).

Workup identifies:
- PFTs: DLCO 48%, otherwise WNL
- O₂ sat: 98% at rest on RA; 90% while walking 50 meters
- Bilateral crackles in lower lung fields
- Chest x-ray: no infiltrates or masses

Which of the following might be appropriate at this time?
1. Chest MRI
2. Chest high-resolution CT
3. Bronchoscopy with biopsy
4. Test for alpha-1 antitrypsin deficiency

**2011 ATS/ERS Diagnostic Criteria for IPF**

Usual Interstitial Pneumonia (UIP) pattern on High-Resolution Computed Tomography (HRCT) without surgical biopsy
OR
Definite/possible UIP pattern on HRCT with a surgical lung biopsy showing definite/probable UIP

**IPF Diagnosis: Current Approach**
**IPF Becomes Increasingly Likely as the Age of the Patient Increases**

![Graph showing the increase in odds ratio per 5-year increase in age.]

**Radiographic Tools for Diagnosis**

**HRCT**: allows detailed evaluation of the lung parenchyma

**HRCT Features**
- Ground glass attenuation
- Honeycombing/cysts
- Lines/reticular thickening
- Consolidation
- Nodules
- Decreased lung attenuation

**HRCT Distribution**
- Upper
- Lower
- Central
- Peripheral
- Diffuse/bilateral

**HRCT Criteria for UIP Pattern**

Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper

Histologic Tools for Diagnosis

- Bronchoscopy
- Surgical lung biopsy

UIP Pattern
- Marked fibrosis/architectural distortion ± honeycombing, predominantly subpleural/paraseptal
- Patchy fibrosis
- Fibroblastic foci
- Absence of features to suggest alternative diagnosis

Histology

1. Images courtesy of Steven Nathan, MD.

IPF Diagnosis: Current Approach

The role of cryobiopsy evolving

Questions to Consider
ILD Management

- Individualized to patient and type of disease
- Numerous management decisions include:
  - Whether to administer pharmacologic therapy
  - Role of exercise therapy/pulmonary rehab
  - How to best monitor the disease
  - Whether to refer to ILD center
  - Role of lung transplant
  - When to implement supportive, palliative care
  - Preventative care (vaccine, smoking cessation)
  - Potential clinical trials
  - Screen/treat co-morbidity

Engaging in a Shared Decision-Making Process

- Discuss the efficacy and safety of FDA-approved 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.

Pre-test ARS Question 6

Which of the following therapies has been shown to reduce the rate of change in FVC in patients with IPF, without increasing risk for mortality?

1. N-acetylcysteine
2. Sildenafil plus warfarin
3. Nintedanib or pirfenidone
4. N-acetylcysteine, prednisone, and azathioprine
Interim Analysis with 50% data
- Combination n = 77, Placebo n = 78
- Increased Death 8 vs 1, p = 0.01
- Increased Hosp 23 vs 7, p = 0.001
- No physioclinical benefit
- Termination of combination therapy at mean of 32 weeks
- Recommendation against use of pred/azathioprine/N-acetyl cysteine

Termination of combination therapy at mean of 32 weeks

FDA Approval of Nintedanib
- Approved October 15, 2014, for the treatment of IPF
- LFTs required at baseline and at regular intervals during first 3 months of treatment and periodically thereafter
- Dosage and administration
  - 150 mg twice daily with food
  - Take each dose approximately 12 h apart
  - Adverse reactions? Consider temporary dose reduction to 100 mg, temporary interruption, or discontinuation

INPULSIS Primary Endpoint: Adjusted Annual Rate of Decline in FVC
Nintedanib – Safety & Tolerability

<table>
<thead>
<tr>
<th></th>
<th>Nintedanib (n=638)</th>
<th>Placebo (n=423)</th>
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</thead>
<tbody>
<tr>
<td>Dose Reduction*</td>
<td>178 (28%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Treatment Interruptions*</td>
<td>151 (24%)</td>
<td>42 (10%)</td>
</tr>
<tr>
<td>Incidence/Discontinue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>63% / 4.4%</td>
<td>18% / 0.2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>25% / 2.9%</td>
<td>7% / 0%</td>
</tr>
<tr>
<td>Mild/Mod/Severe (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57 / 38 / 5</td>
<td>77 / 20 / 3</td>
</tr>
<tr>
<td>Nausea</td>
<td>74 / 24 / 2</td>
<td>93 / 7 / 0</td>
</tr>
</tbody>
</table>

* No particular time

FDA Approval of Pirfenidone

- Approved October 15, 2014, for the treatment of IPF
- LFTs required at baseline, every month for 6 months, and every 3 months thereafter
- 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

ASCEND: Primary Efficacy Analysis

<table>
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<tr>
<th></th>
<th>Week 13</th>
<th>Week 26</th>
<th>Week 39</th>
<th>Week 52</th>
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</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>48%</td>
<td>46%</td>
<td>42%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Absolute difference: 2.5% 7.9% 12.3% 15.1%
Relative difference: 54.0% 56.0% 57.8% 47.9%
Ranks ANCOVA P: < .001 < .001 < .001 < .001
ASCEND: Treatment-emergent Adverse Events More Common with Pirfenidone

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

Pirfenidone and Nintedanib Attenuate Loss of FVC Across Multiple Patient Subgroups

Pirfenidone

Nintedanib

Pulmonary Fibrosis Foundation

Clinical Trial Finder

The clinical trial finder obtains information directly from ClinicalTrials.gov, a service of the National Institutes of Health, which provides details on publicly and privately supported clinical trials. We strongly recommend that you consult with your healthcare provider about the trials that may interest you and refer to our terms of service below.

We are interested in enhancing this finder to best serve our community. Please consider providing us with your feedback about this tool through this online survey.
### IPF - Acute Exacerbations

- Incidence of 4%-24% / 100 IPF person-years
- Triggers: Infections, mechanical, GERD, other
- Prognosis:
  - 46% of IPF mortality due to AE-IPF
  - Median survival after AE-IPF 3-4 months
- Risk Factors:
  - Advanced disease (primarily FVC)
  - Younger age
  - Comorbid coronary artery disease
  - Increased BMI

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### IPF - Acute Exacerbation Definition

- Acute respiratory deterioration in IPF (typically < 1 month duration)
- Extra-pulmonary cause identified?
  - Yes
  - No acute exacerbation
    - Alternative diagnosis (e.g., infection, sepsis, drug toxicity, congestive heart failure)
  - New, bilateral GGO consolidation on CTP (not fully explained by cardiac failure or fluid overload)
    - Yes
    - Acute exacerbation of IPF
      - Triggered Acute Exacerbation
        - (e.g., infection, post-procedural oxygen, drug toxicity, aspiration)
    - No acute exacerbation
      - Idiopathic Acute Exacerbation
        - No trigger identified

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### IPF - Acute Exacerbation Treatment

- No proven effective therapy
- Weak recommendation for use of steroids
  - High value on anecdotal reports
- Supportive Care – Oxygen, palliation of symptoms
- Recommendation against mechanical ventilation
- Case reports / series of numerous agents
  - Ciclosporin / Tacrolimus
  - Cyclophosphamide
  - Rituximab + Plasma Exchange + IVIG
  - IV Thrombomodulin
  - Polymyxin-B hemoperfusion
Pre-test ARS Question 7
A 68-year-old overweight woman with a history of IPF and gastroesophageal reflux disease (GERD) presents complaining of daytime fatigue and poor sleep quality. Workup identifies obstructive sleep apnea (OSA).

Which of the following might be an appropriate approach to managing her comorbidities?
1. Initiate CPAP for OSA; avoid treatment for GERD
2. Refer to surgery for GERD and recommend CPAP for OSA
3. Recommend antacid therapy for GERD and CPAP for OSA
4. Prescribe antacid therapy for GERD but avoid CPAP for OSA

Comorbidities are Common in IPF
- Contribute to decreased quality of life
- May be related to the pathobiology of ILD/IPF
- May be more common in IPF
- Common comorbidities include:
  - Cardiovascular disease (3%-68%)
  - Gastroesophageal reflux disease (0%-94%)
  - Obstructive sleep apnea/sleep disorders (6%-91%)
  - Pulmonary hypertension (3%-86%)
  - COPD (6%-67%)
  - Lung cancer (3%-48%)

Comorbidities Increase Mortality Risk
Impact of IPF and comorbidities on mortality

1. Other cancers
2. Lung cancer
3. Coronary artery disease
4. Diastolic dysfunction
5. Diabetes
6. Anxiety
7. Depression
8. GERD
9. Other cardiac diseases
10. VTE
11. Arteriosclerosis
12. COPD
13. Arterial hypertension
Comorbidities Increase Mortality Risk

Managing Comorbidities in IPF

<table>
<thead>
<tr>
<th>Condition</th>
<th>Management in IPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>Same as non-IPF</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Same as non-IPF</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Same as non-IPF</td>
</tr>
<tr>
<td>GERD</td>
<td>Potential benefit to antacid therapy in IPF</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>CPAP can improve QoL, sleep quality in IPF</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Possible role for sildenafil (under investigation)</td>
</tr>
<tr>
<td>Depression/anxiety</td>
<td>CBT, antidepressants, Possible benefits of pulmonary rehabilitation</td>
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</table>

Summary
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- IPF is rare but deadly interstitial lung disease
- Current therapies slow progression so early diagnosis is essential to preserve lung function
- Suspect IPF in patient with cough/dyspnea and crackles on exam
- Key investigations include H/P, PFTs, and HRCT
- Diagnostic tools in development include cryobiopsy and bronchoscopic techniques
- Nintedanib and pirfenidone are approved to treat IPF
- Multiple clinical trials are ongoing
- Comorbidities are common and can further impede quality of life and in some cases may relate to IPF pathobiology

POST-TEST QUESTIONS

Post-test ARS Question 1

After completing this activity, how confident are you now in your ability to recognize features consistent with idiopathic pulmonary fibrosis.

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Post-test ARS Question 2
After completing this activity, how often do you intend to order full pulmonary function testing, including DLCO, for a patient with unexplained dyspnea on exertion?

1. Never
2. Rarely
3. Sometimes
4. Frequently
5. Always

Post-test ARS Question 3
On average, about how much time passes between the onset of symptoms of IPF and an accurate diagnosis of IPF?

1. 6-8 weeks
2. 3-6 months
3. 1-2 years
4. >5 years

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Which of the following features may suggest the need to evaluate a patient for interstitial lung disease?

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