New Therapeutic Options in Idiopathic Pulmonary Fibrosis

The Path to Improved Diagnosis and Patient Outcomes

Learning Objectives

At the conclusion of this activity, participants should be able to demonstrate the ability to:

• Screen patients presenting with shortness of breath and other risk factors for pulmonary fibrosis and differentiate idiopathic from non-idiopathic forms by applying appropriate diagnostic testing, such as high-resolution CT scanning, to characterize distribution of fibrosis and inflammation
• Incorporate current guidelines and new clinical evidence to develop an appropriate management plan for patients with IPF
• Describe strategies to engage patients and facilitate a multidisciplinary approach to the management of IPF and associated comorbidities

An Exciting Time in IPF

• Guidelines to standardize the definitions
• Networks developing across the US
• Patient support resources expanding
• Registries established
• New treatment options

A Challenging Time in IPF

• Making the right diagnosis of IPF is more critical than ever
• Patients often see multiple doctors prior to diagnosis
• Delayed referral to tertiary care center associated with mortality

Making the IPF Diagnosis is Hard

• There are more than 200 recognized types of diffuse parenchymal lung diseases
• While IPF is the most common, there are many “look alike” diseases
• History, symptoms, physical exam, imaging, and sometimes histology are required to make the IPF diagnosis

Screening Patients for IPF

• Common first symptoms: dyspnea on exertion, cough
  – Symptoms may be present years before diagnosis
    • Registry data suggest 3.9 ± 4.4 years
• Age >50
• Male predominance
• Consider occupational, environmental, and drug exposures, along with autoimmune disease symptoms that may point to another diagnosis
• Consider risk factors associated with IPF
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Risk Factors Associated with IPF

- History of cigarette smoking
- Environmental exposures
  - Recent registry report with 27% of IPF patients reporting an environmental exposure
- Gastroesophageal reflux disease (GERD)
- Genetics
- Infections

Patient 1 Case Study

- CC: Shortness of Breath (SOB), Post-hospital Discharge Evaluation
- HPI: Patient 1 is a 63-year-old man who presents for outpatient pulmonary evaluation of an abnormal chest x-ray found during recent hospitalization.
  - One week prior to his office visit, patient 1 was admitted to a local hospital with a diagnosis of atypical community acquired pneumonia, treated with 7 days of levofloxacin therapy, and discharged to home with supplemental oxygen. Patient notes admissions for pneumonia 2 previous times over the past 3 years and has noticed increasing dyspnea with exertion.
  - Other concerns during evaluation are nonproductive cough (which he attributes to sinus congestion), general fatigue, and heart burn.

Case 1 (continued)

PMH: Osteoarthritis, GERD, and macular degeneration
Medications: Ranitidine OTC and levofloxacin 500 mg daily for one week
Allergies: NKDA
FH: No history of lung disease, no heart disease, no malignancies
Social History: Patient 1 is a previous smoker (1/2 ppd for 18 years) and stopped smoking after he left the Navy. He served in the Navy for 12 years. No overseas tours of duty noted.
  - He worked at an office and does not recall any exposures. He is married with one daughter. He was originally from Chicago, IL and moved to Florida in his 30s. He has a family dog. No recent travel noted.

Case 1 (continued)

Physical Exam
T: 97.6   P: 82   BP: 116/60   RR: 16   Sat: 98% on 2L   Ht: 65 in   Wt: 165 lbs
Gen: Well developed, well nourished, not in distress
CV: RRR, no murmur, rubs, no gallops
Lungs: Clear anteriorly without wheeze, basilar inspiratory and expiratory dry crackles
    - Abd: soft/non-tender
    - Ext: No clubbing noted and no cyanosis noted, mild edema at ankles
Neuro: Alert and oriented x3, non-focal; ambulating with portable oxygen E tank today
Labs:
  - Normal chemistries and renal function
  - CBC WNL without eosinophilia, normal diff
  - Serologies normal rheum panel, normal immunoglobulins

Case 1 (continued)

- CXRs: bibasilar interstitial infiltrates (R>L), no effusions, no pulmonary edema, no adenopathy; review of exams (back 3 years) with progressive interstitial changes mid-lung and basilar
- Echo: EF 50%, normal valves, PA est. 60 mmHg
- HRCT: bilateral ground-glass opacities and reticular changes with subpleural and lower lobe predominance
- Select PFT Data 2 weeks after initial visit:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>59%</td>
</tr>
<tr>
<td>TLC</td>
<td>81%</td>
</tr>
<tr>
<td>DLco</td>
<td>40%</td>
</tr>
</tbody>
</table>

Diagnostic Tools

- Symptoms
- Exam: inspiratory basilar “velcro” crackles, clubbing
- Serologies for connective tissue disorders
- Pulmonary function testing with restrictive pattern, though may be normal in early stages
- HRCT
- Histology of lung biopsy (not always needed)
Follow Up on Case 1

- Patient 1 had rapid progressive course after routine follow up. Hospitalized 2 more times during the year with worsening hypoxemia and increased oxygen needs requiring 5L continuous to maintain saturations of 92% at rest.
- A referral was placed to the lung transplant service and patient 1 started on prednisone 60 mg daily during the first hospitalization and titrated down to a daily dose of 15 mg daily.
- Hospitalized again within 3 months due to chest pain; during second hospitalization a right- and left-heart catheterization confirmed secondary PH and no coronary disease. Started on nintedanib 100 mg, twice daily at discharge. Seen by transplant team 2 weeks after discharge and awaiting completion of work up.
- One week after transplant service evaluation, family took patient 1 to the hospital due to an inability to obtain oxygen saturations above 86% on 6L. He was intubated and hospitalized for 2 weeks on a ventilator with an inability to wean from support due to persistent hypoxemia. He expired in hospice care due to hypoxic respiratory failure.

Histology

<table>
<thead>
<tr>
<th>UIP Pattern (Six Criteria)</th>
<th>Probable UIP Pattern (Any of the Six Criteria)</th>
<th>Possible UIP Pattern (Any of the Four Criteria)</th>
<th>Not UIP Pattern (Any of the Six Criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of marked fibrosis and architectural distortion, a honeycombing in a predominantly subpleural/paraseptal distribution</td>
<td>Evidence of widespread involvement of lung parenchyma by fibrosis, a honeycombing</td>
<td>Evidence of either patchy involvement of the honeycomb, or an occipital distribution</td>
<td>Evidence of honeycomb changes only</td>
</tr>
<tr>
<td>Presence of patchy or diffuse inflammation. Presence of fibroblast foci</td>
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UIP = usual interstitial pneumonia

HRCT = high-resolution computed tomography

Organizing pneumonia*†
Granulomas†
Marked interstitial inflammation suggestive of infection
Predominant artery centred changes
Other features suggestive of an alternate diagnosis

* Can be associated with acute exacerbation of idiopathic pulmonary fibrosis.
† Air inhaled or occasional granulomas and/or a mild component of organizing pneumonia pattern may rarely be coincident in lung biopsies with an otherwise UIP pattern.
‡ This scenario usually represents end-stage fibrotic 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.

HRCT Heterogeneous Fibrotic and Normal Lung Tissue

HRCT of the Chest

High-Resolution Computed Tomography Criteria for UIP Pattern

<table>
<thead>
<tr>
<th>UIP Pattern (Six Features)</th>
<th>Possible UIP Pattern (Any of the Seven Features)</th>
<th>Inconsistent with UIP Pattern (Any of the Seven Features)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subpleural, basal Predominance</td>
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<tr>
<td>Reticular abnormality</td>
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</tr>
<tr>
<td>Honeycombing with or without traction bronchiolectasis</td>
<td>Absence of features listed as inconsistent with UIP pattern (see third column)</td>
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UIP = usual interstitial pneumonia

Follow Up on Case 1

- Patient 2 Case Study

Follow Up on Case 1

- HPI: Patient 2 is a 74-year-old woman with 2 episodes of pneumonia treated by antibiotic in the past 6 months. First chest x-ray diagnosed RLL pneumonia; treated with azithromycin for 5 days and she felt better after the course of treatment.
- Two months later, had recurrent fever and cough. Chest CT demonstrated atypical infiltration of the RLL, and she was treated for 10 days with levofloxacin 750 mg. In her presentation she denied muscle or joint pain. Increased lethargy and fatigue, progressively worse since the first pneumonia. No chest pain or discomfort noted. She did still complain of productive cough without wheezing.

Making a Differential Diagnosis: Patient 2 Case Study

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Case 2 (continued)

PMH: GERD, hypercholesterolemia, and hypertension
Medications: Amlodipine 10 mg daily, HctZ 12.5 mg daily, simvastatin 40 mg at bedtime, and esomeprazole 20 mg daily
Allergies: none reported
FH: CAD
Social History: She is a previous smoker (40 pack years) and stopped 10 years prior to visit. When asked about work or exposure, she notes she is a retired administrator without specific exposures.
ROS: negative
Gen: Healthy appearing
CV: RRR, no G
Chest: Clear bilaterally without wheeze or crackle
Abd: Soft +6S wrt
Ext: No cyanosis, no clubbing
Neuro: Alert and oriented x3

Radiology: HRCT with mild subpleural cystic changes bilaterally in the mid-lung to lower lung fields with diffuse ground glass opacities noted bibasilarly
Course: Patient 2 was treated with prednisone at 40 mg daily for 2 weeks and tapered off over an additional 2 weeks; HRCT was repeated 2 months after completion of her steroid taper.
CT scan demonstrated mild basilar fibrotic changes without ground glass opacities and stability in the previously seen subpleural cystic changes.
Her repeat PFTs one year after initial evaluation demonstrates stability in her FVC with only a 7% change from initial presentation spirometry. She remains with minimal cough as her primary complaint and no longer has limiting shortness of breath on exertion. No exposures were found after careful review of her environment and travel history and UIP is not believed to be the diagnosis of fibrosing lung pathology.

MH First PFT Second PFT
FEV1 1.70 (81%) 1.40 (67%)
FVC 2.17 (78%) 1.97 (71%)
FEV1/FVC 0.78 0.71

When To Do A Lung Biopsy?
Histologic confirmation should be obtained in all patients with atypical imaging findings, such as extensive ground-glass opacities, nodules, consolidation, or a predominantly peribronchovascular distribution

When NOT To Do A Lung Biopsy?
Surgical lung biopsy is the gold standard method of diagnosing IPF, but carries risks that should be discussed prior to the procedure. Risks include infection, bleeding, pneumothorax, persistent air leak into the chest cavity, and as with all surgical procedures, risk of death in 3%-4% of cases within 30 days of biopsy

Histology-IPF vs NSIP

Putting It All Together

Comorbidities of Idiopathic Pulmonary Fibrosis
Comorbidities in IPF

- GERD
- CAD
- OSA
- Pulmonary hypertension
- Pulmonary embolism
- Emphysema
- Obesity
- Diabetes mellitus
- Osteoporosis
- Cachexia
- Depression and anxiety

Aging

- Loss of 20-30 mL vital capacity per year
  - Loss of 1900 mL by age 85
- Other causes of reduced lung volumes in an aging population
  - Kyphosis/scoliosis
  - CHF with an enlarged heart
  - Deconditioning
  - Neuromuscular disease
  - Metabolic disease
  - Obesity


Obesity

Physiologic Effects:
- Restriction
- Decreased airway size
- Compromised chest muscle function
  - reduced respiratory muscle and diaphragm endurance
- Altered lung perfusion and VQ mismatch at bases
- Upper airway narrowing

Endocrine Effects:
- Adipose tissue
- Hormonal effects
  - *Leptin: promotes visceral fat deposition
- Proinflammatory
  - *TNF alpha: promotes
- Pharyngeal neuromuscular dysfunction


GERD in IPF

Prevalence of GERD

- Normal prevalence: 10%-20%
- Prevalence of GERD in COPD: 60%
- Prevalence of GERD in cystic fibrosis: 35%-81%
- Prevalence of GERD in asthma: 63%
- Prevalence in IPF: 90%

Therapy for GERD is Associated with Improved Survival


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IPF With Severe PH

Prevalence of PH in IPF

ATS/ERS Recommendation

- PH should not be treated in the majority of patients with IPF, but treatment may be a reasonable choice in a minority (weak recommendation, very low-quality evidence).
- In patients with moderate to severe PH (mPAP >35 mmHg) documented by right heart catheterization, a trial of vasomodulatory therapy may be indicated.
- It is not clear if IPF with PH represents a distinct clinical phenotype (IPFs-PH).

Why Refer Early to an ILD Center?

- Diagnostic expertise
  - Standardized assessment
  - Confirmation of diagnosis
- Management expertise
  - Choice of an appropriate therapy
  - Oxygen prescription
  - Pulmonary rehabilitation
  - Attention to obesity and sarcopenia/frailty
  - Potential enrollment in a clinical trial
  - Transplant evaluation

Maintain Recreational Activities

- Normalcy should be maintained as much as possible
- Regular activities give rhythm to life
- Low intensity activities enhance pleasure and social contact
  - Socializing
  - Cultural activities
  - Family events
  - Sexual activity
  - Exercise

Pulmonary Rehabilitation

- Program originally designed for COPD
- Education, exercise, support/counseling
- Run by PT/RT
- Goals:
  - Improve self-management
  - Reduce symptoms
  - Optimize functional capacity
  - Increase social participation

Monitoring for Disease Progression

- Every 3 to 6 months:
  - PFTs
  - 6MWT (distance/nadir saturation)
  - O₂ requirement
  - Comorbidities
  - Consider dyspnea questionnaire (UCSD)
- HRCT
  - Annually or when suspicion for clinical worsening

Lung Transplantation for IPF: 2014 Referral Guidelines

- Histopathologic or radiographic evidence of usual interstitial pneumonitis (UIP)
- Abnormal lung function: FVC <80% predicted or DLCO <40% predicted
- Any dyspnea or functional limitation attributable to lung disease
- Any oxygen requirement, even if only during exertion

Oxygen Therapy

- Goal: Maintain SpO₂ >89%
  - Rest, activity, sleep
- Give patients control over their disease
- Make sure patients are using O₂ correctly
- Regular assessment
  - Yearly (or with change in status), nocturnal oximetry, exercise oximetry (q3 months)
- Pulse oxygen does not generally supply enough O₂ in IPF patients to fulfill their exertional O₂ needs

Risk Factor Reduction

- Smoking cessation
- Weight management
- Sleep study
- Exercise training/pulmonary rehab
- Screen and address comorbidities
  - GERD
  - OSA
  - Heart disease (diastolic dysfunction/PH/CAD)
  - Thromboembolic disease

Patient Care Summary

- Educate patients
  - Refer to reliable sources
- Prescribe O₂
  - (screen for resting/nocturnal/exertional requirement)
- Prescribe medication
- Look for treatable comorbid conditions
- Refer
  - Pulmonary rehab
  - ILD center
  - Lung transplantation evaluation
- Monitor for disease progression

Patient Resources

- INSPIRE support groups
  - https://www.inspire.com/conditions/pulmonary-fibrosis
- Pulmonary Fibrosis Physician Blogs
  - Jeff Swigris: www.pulmonaryfibrosisresearch.org/blog
  - David Lederer: PFDoc.org
- Local support groups
- Online resources
  - www.patientslikeme.com
  - www.coalitionforpf.org
  - www.pulmonaryfibrosis.org
  - www.lungsandyou.com
  - www.knowIPFnow.com
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New Therapeutic Options in Idiopathic Pulmonary Fibrosis

New Agents for the Management of IPF

Pirfenidone

- Pirfenidone is an orally-available small molecule that exerts systemic antifibrotic effects
- Pirfenidone is active in several animal models of fibrosis
  - Including lung, liver, heart, and kidney
  - Active at clinically relevant exposures
- The molecular target of pirfenidone is not known; however, preclinical evidence of antifibrotic activity exists
  - Both antifibrotic and anti-inflammatory activities in vivo and in vitro
  - Modulates extracellular matrix deposition, production of cytokines and growth factors, and fibroblast proliferation

Past Negative Clinical Trials in IPF

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Primary Endpoint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon-beta (1999)</td>
<td>167</td>
<td>Progression-free survival</td>
<td>Negative</td>
</tr>
<tr>
<td>Interferon-gamma (GIPF-001)</td>
<td>330</td>
<td>Progression-free survival</td>
<td>Negative</td>
</tr>
<tr>
<td>Interferon-gamma (Inspire)</td>
<td>826</td>
<td>Survival time</td>
<td>Negative</td>
</tr>
<tr>
<td>Pirfenidone (CAPACITY I)</td>
<td>344</td>
<td>Change in FVC</td>
<td>Negative</td>
</tr>
<tr>
<td>Silvestrol</td>
<td>118</td>
<td>Change in 6MW distance</td>
<td>Negative</td>
</tr>
<tr>
<td>Interferon-gamma (Inspire)</td>
<td>130</td>
<td>Progression-free survival</td>
<td>Negative</td>
</tr>
<tr>
<td>Silvestrol (BUILD 1 and 2)</td>
<td>130</td>
<td>Change in 6MW distance</td>
<td>Negative</td>
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<tr>
<td>Silvestrol (BUILD 3)</td>
<td>380</td>
<td>Progression-free survival time</td>
<td>Negative</td>
</tr>
<tr>
<td>Ambrisentan (Artemis-IPF)</td>
<td>295</td>
<td>Change in 6MW distance</td>
<td>Negative</td>
</tr>
<tr>
<td>Ambrisentan (Artemis-PH)</td>
<td>50</td>
<td>6MWD</td>
<td>Stopped –</td>
</tr>
<tr>
<td>Everolimus</td>
<td>478</td>
<td>Progression-free survival</td>
<td>Stopped –</td>
</tr>
</tbody>
</table>

Inclusion Criteria

- Age 40-80 years
- Confident diagnosis of IPF based on central review of HRCT +/- SLB
- Percent predicted FVC ≥50% and ≤90%
- Percent predicted DLco ≥30% and ≤90%
- FEV1/FVC ratio ≥0.80
- 6MWD ≥150 m

Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone (n=279)</th>
<th>Placebo (n=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.0</td>
<td>68.0</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>79.9</td>
<td>76.9</td>
</tr>
<tr>
<td>US enrollment (%)</td>
<td>67.3</td>
<td>66.4</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>68.1</td>
<td>68.0</td>
</tr>
<tr>
<td>DLco (% predicted)</td>
<td>47.5</td>
<td>43.0</td>
</tr>
<tr>
<td>6MWT distance (m)</td>
<td>418.3</td>
<td>432.0</td>
</tr>
<tr>
<td>FEV1/FVC ratio</td>
<td>0.84</td>
<td>0.84</td>
</tr>
<tr>
<td>Supplemented O2 use (%)</td>
<td>26.1</td>
<td>27.4</td>
</tr>
<tr>
<td>Time since IPF diagnosis (years)</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Former Smoker (%)</td>
<td>66.2</td>
<td>61.0</td>
</tr>
<tr>
<td>HRCT - Definite IPF (%)</td>
<td>95.7</td>
<td>94.6</td>
</tr>
<tr>
<td>Surgical lung biopsy (%)</td>
<td>30.9</td>
<td>26.5</td>
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Decreased FVC or Death with Pirfenidone

![Decreased FVC or Death with Pirfenidone](image_url)
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Program Slides

Pirfenidone Reduces Loss of FVC

Increased Progression Free Survival with Pirfenidone

Conclusions

• Pirfenidone decreases the decline in breathing tests over 52 weeks
• Pirfenidone appears to have a benefit in terms of risk of death
• Pirfenidone appears to be well tolerated

Pirfenidone Patients Maintain Walk Distance or Survive

Increased Progression Free Survival with Pirfenidone

Pirfenidone Associated with Less Mortality

Nintedanib

• Nintedanib is an orally-available intracellular inhibitor that targets multiple tyrosine kinases, including:
  – VEGF receptors
  – FGF receptors
  – PDGF receptors

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**Inclusion Criteria**

- Age ≥40 years
- Diagnosis of IPF within previous 5 years
- IPF diagnosis based on central review of HCRT and lung biopsy, if available
- Percent predicted FVC ≥50%
- Percent predicted DLco 30%–79%

**Baseline Patient Characteristics**

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<th>Characteristic</th>
<th>Impulsis-1</th>
<th>Impulsis-2</th>
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<tbody>
<tr>
<td>Number of Patients</td>
<td>718</td>
<td>794</td>
</tr>
<tr>
<td>Randomized</td>
<td>616</td>
<td>551</td>
</tr>
<tr>
<td>Treated</td>
<td>513</td>
<td>548</td>
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**Nintedanib Reduces Loss of FVC**

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<td>Difference in FVC loss (L/month)</td>
<td>-1.74</td>
<td>-0.94</td>
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<tr>
<td>Time to first AE</td>
<td>20 weeks</td>
<td>52 weeks</td>
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**Time to Acute Exacerbations Delayed with Nintedanib**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Impulsis-1</th>
<th>Impulsis-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in time to first AE (weeks)</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

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**Conclusions**

- Nintedanib decreases the decline in breathing tests over 52 weeks
- There was no detectable difference in mortality over 52 weeks
- Nintedanib appears to be well tolerated

**Future Therapies**

- Better stratification of IPF patients
  - CCL 18 data and risk for death
  - Loxyl-2 and composite endpoint
  - HSP 80 and acute exacerbation
- Combination therapy?
- IPF registries and further research