Evaluation and Treatment of Idiopathic Pulmonary Fibrosis

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Case

- 57 yo WM
- SOB over the past 6 months
- Throat clearing, dry cough for 3 years
- DOE at work, difficulty climbing steps
- Not feeling better after cath/PTCA 2 months prior
- Abnormal CXR showing fibrosis
- PMHx: CAD, GERD
- Meds: ASA, Plavix, metoprolol, PPI
- PSHx: 15PY tob, quit 20 years ago

Exam
- Bibasilar dry crackles
- Mild clubbing

PFTs:
- Normal spirometry
- Lung volumes restriction TLC 68% predicted
- DLCO 55% predicted
- 6 minute walk: 2100 feet, 97% at rest, 84% with walk on room air

Labs:
- ANA (+) 1:80
- RF (+), ANCA (-), ENA (-)

CXR shows interstitial lung disease

Interstitial Lung Diseases

- Groups of disorders characterized by varying degrees of inflammation and fibrosis
- Response to a known tissue injury or part of unknown process
- Dysregulated repair process
- Effect the interstitial space
  - Between the alveolar epithelial cell membrane-pulmonary capillary endothelial cell membrane
  - Site of initial injury, early effects on gas transfer
Interstitial Lung Diseases

• Can also effect areas outside the alveoli, such as the bronchioles, larger airways and pulmonary vasculature
  • Diffuse parenchymal lung diseases

Interstitial Lung Disease

• Over 150 etiologies
• Symptoms nonspecific
  • SOB/DOE and cough
• Diagnosis requires combination of:
  • Clinical presentation
  • Radiology (high resolution chest CT)
  • Pathology
• Prognosis and treatment dependent on diagnosis

Interstitial Lung Disease

• Desquamative Interstitial Pneumonitis
• Lymphocytic Interstitial Pneumonitis
• Alveolar Proteinosis
• Amyloidosis
• Lymphangitic Carcinomatosis
• Radiation Pneumonitis
• Langerhan's Cell Granulomatosis
• Lymphangioleiomyomatosis
• Tuberous Sclerosis
• Neurofibromatosis
• Sarcoidosis
• Berylliosis
• Ankylosing Spondylitis
• Rheumatoid Arthritis
• Silicosis
• Asbestosis
• Lymphoma

Interstitial Lung Disease

• Hemorrhagesis
• Wegener's Granulomatosis
• Drug-Induced Fibrosis
• Systemic Sclerosis
• Systemic Lupus
• Erythematous
• Sjogren's Syndrome
• Mycobacterial infection
• Histoplasmosis
• Aspiration
• Lipoid Pneumonia
• Polymyositis
• Mixed Connective Tissue Disease
• Microthiasis
• Churg-Strauss Syndrome
• Pneumocystis carinii
• Oxygen Toxicity
• Cryptogenic Organizing Pneumonia
• Non-Specific Interstitial Pneumonitis
• Usual Interstitial Pneumonitis
• Bleomycin

Interstitial Lung Disease

• IgG4 disease
• Hard metal disease
• Crohn's disease
• Ulcerative colitis
• Idiopathic inflammatory myopathy
• Familial IPF
• Granulomatosis Pudital syndrome
• Gaucher's disease
• Goodpasture's Syndrome
• Nitrofurantoin
• Methotrexate
• Amiodarone
• Taic granulomatosis
• Siderosis
• Tannosis
• Coal worker's pneumoconiosis
• Sulfasalazine
• Minocycline

Interstitial Lung Disease

• Diffuse Parenchymal Lung Diseases
  • DPLD of known cause
  • Drugs induced
  • Radiation therapy
  • Collagen vascular diseases
  • Systemic diseases
  • Occupational exposures
  • Granulomatous diseases
  • Hypersensitivity pneumonitis
  • Sarcoidosis
• Other DPLD: cystic, congenital lung diseases
• Idiopathic Interstitial Pneumonias
Interstitial Lung Disease

Idiopathic Interstitial Pneumonias

- Idiopathic pulmonary fibrosis
- Idiopathic nonspecific interstitial pneumonia
- Respiratory bronchiolitis–ILD
- Desquamative interstitial pneumonia
- Cryptogenic organizing pneumonia
- Acute interstitial pneumonia
- Rare idiopathic interstitial pneumonia
- Idiopathic lymphoid interstitial pneumonia
- Idiopathic pleuroparenchymal fibroelastosis
- Unclassifiable idiopathic interstitial pneumonias

Diagnostic Approach to ILD

- Clinical
  - Smoking history
  - Medications, other drug history and treatments
  - Hobbies, travel
  - Exposures
    - Occupational
    - Industrial, agricultural
    - Environmental
  - Pets, bird feathers/down bedding, hot tubs, contaminated water sources
  - Family history
  - Comorbid diseases

Diagnostic Approach to ILD

- Physical Examination
  - Crackles, dry or velcro
  - Clubbing
  - Signs of right heart strain/failure
  - Signs of systemic disease (vasculitis, connective tissue diseases)
    » Potential biopsy sites (rashes)

Diagnostic Approach to ILD

- Pulmonary Function Testing
  - Interstitial inflammation and scarring results in restrictive defect
  - Impaired gas exchange with a reduced diffusing capacity
  - Measures of O2 saturation with exercise
    » 6 Minute walk
  - Not diagnostic but characterizes severity
  - Obstructive physiology not typical features of ILD
    » May be present with coexisting COPD
**Diagnostic Approach to ILD**

- **Laboratory Testing**
  - No specific laboratory tests or biomarkers
  - Routine laboratory testing with chemistries, CBC with differential
  - Evaluation for autoimmune diseases
    - ANA/ENA
    - Rheumatoid factor/CCP
    - CK, aldolase
    - If signs /symptoms of vasculitis, consider ANCA

- **Chest imaging**
  - CXR findings nonspecific
  - High resolution chest CT is central in the diagnosis and evaluation of ILDs
    - Patterns suggestive of certain disorders
    - Replaced biopsy in some cases

- **Lung biopsy**

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**Case**

- Diagnosed with interstitial lung disease and hypoxemia
- Referred to pulmonary
- Chest CT showed interstitial lung disease
- Lung biopsy with diagnosis of Usual Interstitial Pneumonitis (UIP)
- Idiopathic Pulmonary Fibrosis

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**Idiopathic Pulmonary Fibrosis**

- Most common ILD of unknown etiology
- Mainly affects over age of 50, most over 60
- Incidence is estimated at 7.4-17 cases per 100,000 per year
- Prevalence of IPF is estimated at 13-60/100,000
- More men than women (1.5:1 ratio)
- 5-15% have a familial form
  - Present at a younger age
- Possible risk factors for developing IPF include cigarette smoking, occupational/environmental exposures (dusts)
### What causes IPF?

**#1 Genetic Predisposition**
- Surfactant proteins C
- Surfactant protein A2
- Telomerase genes
  - TERT, TERC
  - 18% familial cases
- Mucin (MUC) 5B
  - 1/3rd sporadic cases

**#2 Epithelial Injury**
- Inhaled exposures
- Dusty environment (organic and inorganic materials)
- Tobacco smoke
- Viruses
- Acid reflux/aspiration

### Familial Pulmonary Fibrosis

- Patients look just like IPF
- Typically ages 50-70
- Definition: first degree relative with IPF
- Probably autosomal dominant with variable penetrance
- Accounts for 5-15% of patients with IPF
- Genetic cause found in about 10% of familial pulmonary fibrosis
- Treatment is the same as IPF

### Idiopathic Pulmonary Fibrosis

- **History/Exam**
  - Gradual onset and progressive dyspnea
  - Nonproductive cough
  - Bibasilar inspiratory crackles (Velcro crackles)
  - Clubbing also common
  - Later in the clinical course, signs of right heart failure, peripheral edema, cyanosis

- **PFTs** show restriction, low diffusing capacity and desaturation with exertion
- +ANA, +RF unclear clinical significance
- Diagnosis confirmed by imaging, lung biopsy
**Chest CT in IPF**

- Subpleural basal predominance
- Reticular abnormality
- Honeycombing
- Traction bronchiectasis
- Absence of features listed as inconsistent with UIP pattern
  - Upper lung or mid lung predominance
  - Ground-glass abnormality, nodules, discrete cysts, mosaic attenuation/air trapping, consolidation

**Normal Chest CT**

- Presence of these findings on HRCT in a patient without evidence of an alternative diagnosis
- Sufficient for a confident diagnosis of IPF
- Accuracy of 79-90%

**Chest CT: subpleural reticular infiltrates**

**Chest CT: traction bronchiectasis**
Role of Lung Biopsy

- In about 1/3rd of patients, require tissue to confirm diagnosis
  - Atypical findings on CT scan or clinical history
  - Early in disease process

- Bronchoscopy with transbronchial biopsy
- Bronchoscopic biopsy does not confirm diagnosis of IPF
- Useful to evaluate for alternate diagnosis
  - Granulomatous disorders (sarcoidosis, hypersensitivity pneumonitis)
  - Malignancy, lymphangitic carcinomatosis
  - Eosinophilic pneumonia, alveolar proteinosis, Langerhans
  - Bacterial, viral, and fungal infections
- Thoracoscopic lung biopsy (VATS)

IPF Lung Pathology: UIP

- Usual Interstitial Pneumonitis (UIP pattern)
- Evidence of marked fibrosis, architectural distortion
- Honeycombing in a predominantly subpleural/paraseptal distribution
- Presence of patchy involvement of lung parenchyma by fibrosis
- Presence of fibroblast foci
- Absence of features against a diagnosis of UIP suggesting an alternate diagnosis

Chest CT: basilar honeycomb infiltrates

**Chest CT: basilar honeycomb infiltrates**

**Role of Lung Biopsy**

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**IPF Lung Pathology: UIP**
- Fibrosis with collagen deposition
- Temporal heterogeneity

**IPF Lung Pathology: UIP**
- Fibroblastic foci
- Microcystic changes

**Causes Of Usual Interstitial Pneumonitis**
- Idiopathic pulmonary fibrosis (IPF)
- Collagen vascular disease
  - Rheumatoid arthritis
- Drug toxicity, radiation-induced
- Post-inflammatory pulmonary fibrosis
- Chronic hypersensitivity pneumonitis
  - May see granulomas or other clues of HP
- Occupational exposures
  - Asbestosis
- Familial idiopathic pulmonary fibrosis
- Hermansky–Pudlak syndrome

**Clinical Course of IPF**
- Unpredictable course for an individual patient
- Progressive disease
- Median survival of about 3-5 years
- Cause of death in about ½ related to IPF and respiratory failure
- Others: CAD/MI, infection, strokes
- Limited treatment options in the past
- Lung transplant
<table>
<thead>
<tr>
<th>Coexisting conditions with IPF</th>
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<tbody>
<tr>
<td><strong>Pulmonary hypertension</strong></td>
<td><strong>Combined Pulmonary Fibrosis and Emphysema</strong></td>
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<tr>
<td>• In about 1/3 patients and most with advanced disease</td>
<td>• ~8% IPF cases, male, smoking history</td>
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<tr>
<td>• Associated with worse pulmonary function, hypoxemia</td>
<td>• Disproportionately low DLCO and gas exchange</td>
</tr>
<tr>
<td>• Decreased exercise capacity and worse survival</td>
<td>• Chest CT upper lobe emphysema, lower lobe fibrosis</td>
</tr>
<tr>
<td><strong>GERD</strong></td>
<td>• High incidence of pulmonary hypertension, lung cancer and worse prognosis</td>
</tr>
<tr>
<td>• Common in IPF (65-94%)</td>
<td><strong>Lung Cancer</strong></td>
</tr>
<tr>
<td>• Potential causal relationship between GERD and IPF through microaspiration of gastric contents</td>
<td>• Increased risk in IPF patients, independent of other risks (smoking)</td>
</tr>
<tr>
<td>• Acid-suppression therapy was associated with a slower rate of decline in pulmonary function and longer survival</td>
<td><strong>OSA, CAD, depression</strong></td>
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<table>
<thead>
<tr>
<th>Acute Exacerbation of IPF</th>
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<tr>
<td>• Acute deterioration with rapid, irreversible clinical decline</td>
<td>• Clinical evaluation to rule out an identifiable cause</td>
</tr>
<tr>
<td>• 1 and 3-year incidence of AE estimated 14% and 21%</td>
<td>• Infection</td>
</tr>
<tr>
<td>• Mortality rate associated with AE as high as 50% to 80%</td>
<td>» Consider bronchoscopy</td>
</tr>
<tr>
<td>• Survival times 4-15 months in those who “recover”</td>
<td>» Often limited by hypoxemia and risk of respiratory failure</td>
</tr>
<tr>
<td><strong>Etiology of decline unknown</strong></td>
<td>• Progressive heart failure, ischemic disease</td>
</tr>
<tr>
<td><strong>Chest imaging shows diffuse ground glass infiltrates</strong></td>
<td>» ROMI, Echo, BNP</td>
</tr>
<tr>
<td><strong>Lung biopsy shows diffuse alveolar damage (identical to ARDS) superimposed on UIP pattern</strong></td>
<td>• Pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>» CTPE study, LE duplex</td>
</tr>
<tr>
<td></td>
<td>• No well established therapy</td>
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</tbody>
</table>
IPF Diagnosis Requires A Multi-Disciplinary Approach

Know your patient Diseases, exposures, meds, family
** Pulmonary Fibrosis ≠ Idiopathic Pulmonary Fibrosis **

Get to know your radiologist

- Agree on definition of UIP
- Presence or absence of honeycombing
- Presence or absence of ground glass infiltrates
- Geographic location of infiltrates
**Diffuse interstitial infiltrates ≠ IPF**

Get to know your thoracic surgeon

- 2 or 3 lobe biopsies
- Avoid the tip of the lingula, middle lobe or lower lobes
- Target ground glass infiltrates or transition zones

**End stage fibrosis ≠ IPF**

Get to know your pathologist

- Presence or absence of fibroblastic foci
- Temporal heterogeneity?
- Presence or absences of microcystic changes
- Presence or absence of collagen deposition
- Granulomas?

**End stage fibrosis ≠ IPF**
IPF Treatment: What Works?

Jim Allen, MD  
Medical Director, University Hospital East  
Professor of Internal Medicine  
Division of Pulmonary & Critical Care Medicine  
The Ohio State University Wexner Medical Center

IPF Treatment: What Works?

- Oxygen
- Pulmonary rehabilitation
- Lung transplant
- Esophageal reflux treatment
- Pirfenidone
- Nintedanib
- Sildenafil (?)

Home oxygen options

Stationary home units:
- Oxygen concentrators  
  - Standard (1-5 L)  
  - High flow (10 L)  
- Liquid oxygen reservoir

Portable units
- Compressed gas tanks  
  - E cylinders  
  - M-6 cylinders  
- Portable liquid oxygen tanks  
- Portable oxygen concentrators

Pulmonary Rehabilitation

- 8 week programs
- 3 days per week
- 1-2 hours per session

- Focus on:  
  - Education  
  - Aerobic conditioning  
  - Quality of life
Effect of pulmonary rehabilitation on interstitial lung disease

- Significant improvement in 6MWT distance
- Significant improvement in fatigue severity scale

Pulmonary rehabilitation in IPF


Swigris, et al. Respir Care 2011; 56:783-9

Lung transplant contraindications

- Age > 65 (sort of…)
- BMI > 30
- Smoking in the past 6 months
- Uncured malignancy
- HIV, active hepatitis C/B
- Active infection
- Chest wall deformity
- Non-compliance
- Inadequate psychosocial support

Survival after lung transplant for IPF


Esophageal reflux and IPF mortality


- Treatment
- No treatment
**IPF Treatment: What Doesn’t Work?**

- Corticosteroids
- Azathioprine
- Cyclophosphamide
- Everolimus
- Anticoagulation
- N-acetylcysteine

- Bosentan
- Ambrisentan
- Interferon-gamma
- Etanercept
- Imatinib
- Ribavarin

**New drugs for IPF**

- A confident diagnosis of IPF is required!!
- Nintedanib*
- Pirfenidone*

Approved by the FDA
October 15, 2014

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**Pirfenidone (ASCEND trial)**

- Reduced loss of lung function (FVC)
- Reduced loss of exercise tolerance
- Improved progression-free survival

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**Pirfenidone versus Placebo**

![Graph showing change in FVC over weeks for Pirfenidone vs Placebo](image)

- Change in FVC (ml)
- Weeks 0 12 24 36 52
- Pirfenidone
- Placebo
### Pirfenidone

**Dosing:**
- Week 1: One capsule three times daily with food
- Week 2: Two capsules three times daily with food
- After week 3: Three capsules three times daily with food
- Dose can be reduced if side effects occur

**Laboratory monitoring:**
- LFTs monthly x 6 months
- LFTs every 3 months thereafter
- Dose adjustments:
  - LFTs 3-5 times normal: reduce dose to 100 mg every 12 hours
  - LFTs > 5 times normal: stop pirfenidone

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### Nintedanib (IMPULSIS trials)

- Reduced loss of lung function (FVC)
- Reduced time to first exacerbation (IMPULSIS-2 trial)

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### Nintedanib

**Dosing:**
- 150 mg every 12 hours with food
- Dose can be reduced to 100 mg every 12 hours if side effects occur

**Laboratory monitoring:**
- LFTs monthly x 3 months
- LFTs every 3 months thereafter
- Dose adjustments:
  - LFTs 3-5 times normal: reduce dose to 100 mg every 12 hours
  - LFTs > 5 times normal: stop nintedanib
Side Effects:

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone</th>
<th>Nintedanib</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>36%</td>
<td>24%</td>
</tr>
<tr>
<td>Rash*</td>
<td>28%</td>
<td>62%</td>
</tr>
<tr>
<td>Adverse effect requiring discontinuation</td>
<td>14%</td>
<td>21%</td>
</tr>
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</table>

*Photosensitvity

Pirfenidone and Nintedanib: practical considerations

- Both drugs roughly equally effective
- Both drugs very expensive ($90-100,000/year)
- If patients are intolerant of one, consider changing to the other
- Giving both drugs together is NOT advised

Which patients benefit most from treatment?

- We don’t know
- Probably patients with earlier stage disease
  - FVC > 50% and DLCO > 30%
  - Patients with advanced disease are untested
- We do not know about non-IPF conditions:
  - Post-inflammatory pulmonary fibrosis
  - Rheumatoid arthritis-associated ILD
  - Chronic hypersensitivity pneumonitis

These drugs do not cure, they merely slow down the progression of the disease

Cure
Sildenafil Prevents Loss Of 6 MWT Distance In IPF Patients with RVH

Sildenafil in IPF*

- No nitrates or unstable angina
- Initial dose: 20 mg then monitor for 1 hour:
  - Symptoms
  - Blood pressure
  - Oxygen saturation
- Maintenance dose: 20 mg three times daily

Sildenafil is not FDA-approved for treatment of IPF

When patients with IPF are worse:

- Progression of IPF
- Anemia
- Heart failure
- Pulmonary embolism
- Lung cancer
- Infection
- Pneumothorax

Typical Clinical Course

Chest 2013; 143:1699-1708
Acute interstitial pneumonitis

- Diagnosis of exclusion
- Sudden-onset of worsened oxygenation and ground glass infiltrates
- Lung biopsy = diffuse alveolar damage (identical to ARDS)
- Steroids may help

Acute Interstitial Pneumonitis

- Hyaline membranes
- Ground glass infiltrates

April, 2013
August, 2014
Cough and IPF

Are there other causes:
• ACE inhibitors?
• Chronic rhinitis?
• Asthma/COPD?
• Reflux?

Palliating the IPF cough:
• Non-opioid anti-tussives (eg, benzonatate)
• Opioids
• Nebulized lidocaine?
• Thalidomide?
• Low dose corticosteroids?

Thalidomide Reduces Cough In IPF

Thalidomide is not FDA-approved for treatment of IPF

Fatigue and IPF

• Anemia?
• Thyroid disease?
• Sleep apnea?
• Heart failure?
• Exertional hypoxemia?

Sleep apnea is common in IPF:

• Incidence* = 88%!!!
  – 20% mild
  – 68% moderate-severe
• Undiagnosed sleep apnea contributes to fatigue
• Quality of life can improve with CPAP

* Chest 2009; 136:772-778
What else can you do to improve the quality of life?

- Smoking cessation
- Maintenance of a normal BMI
- Vaccinations
- Recognize and treat depression

Vaccinations for patients with IPF:

- Influenza
- Pertussis (Tdap)
- Strep pneumoniae

New CDC Pneumococcal Vaccine Recommendations:

- Adults < 65 and low risk: vaccine not required
- Adults < 65 and moderate risk
  - PPSV-23
- Adults < 65 and high risk
  - PCV-13
  - PPSV-23 6-12 months later
  - Repeat PPSV-23 in 5 years
- Adults > 65
  - PCV-13
  - PPSV-23 6-12 months later
  - Repeat PPSV-23 in 5 years
Idiopathic pulmonary fibrosis is ultimately a terminal disease.

Start end-of-life discussions early

- Resuscitation and intubation
- Hospice
- How patients die

Photo: Anthony Majanlathi
Galata Morente, Capitoline Museum, Rome

Outcome of patients admitted to the ICU with respiratory failure

- Anticipated life expectancy < 6 months
- Levels of care:
  - Routine home care
  - Continuous home care
  - Inpatient care
  - Respite care

Hospice

- Physician services
- Nursing services
- Social services
- Supplies
- Medications
- Bereavement counseling
- Hospice aide
- PT/OT/ST

How do patients with IPF die?

- Subacute Respiratory Failure
- Acute Respiratory Failure
- Non-Respiratory Disease

The improvement in the outcomes of your patients tomorrow will depend on clinical trials in your patients today

IPF Treatment: Summary

- Establish a confident diagnosis!
- New drugs: nintedanib & pirfenidone
- Don’t do things that don’t work
- Consider clinical trials
- Never miss an opportunity for transplant
- The little things make a big difference in quality of life

Case #1