Evaluation and Treatment of Idiopathic Pulmonary Fibrosis

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Case

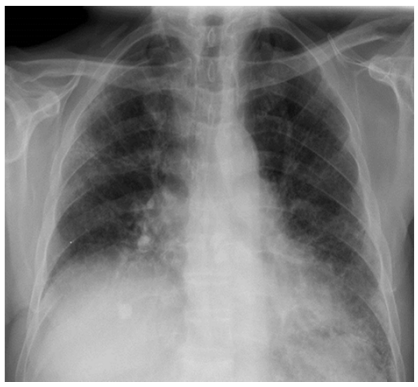
- **57 yo WM**
- **SOB over the past 6 months**
- **Throat clearing, dry cough for 3 years**

- **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**

Case

- 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
- Eosinophilic pneumonia
- Alveolar Proteinosis
- Amyloidosis
- Lymphangitic Carcinomatosis
- Radiation Pneumonitis
- Langerhan's Cell Granulomatosis
- Lymphangioleiomyomatosis
- Tuberous Sclerosis
- Neurofibromatosis
- Hypersensitivity Pneumonitis
- Sarcoidosis
- Berylliosis
- Ankylosing Spondylitis
- Rheumatoid Arthritis
- Silicosis
- Asbestosis
- Lymphoma
- Hemosiderosis
- Wegener's Granulomatosis
- Drug-Induced Fibrosis
- Systemic Sclerosis
- Systemic Lupus Erythematosus
- Sjogren's Syndrome
- Mycobacterial Infection
- Histoplasmosis
- Aspiration
- Lipoid Pneumonia
- Polymyositis
- Mixed Connective Tissue Disease
- Microlithiasis
- Churg-Strauss Syndrome
- Pneumocystis carinii
- Oxygen Toxicity
- Cryptogenic Organizing Pneumonia
- Non-Specific Interstitial Pneumonitis
- Usual Interstitial Pneumonitis
- Bleomycin
- IgG4 disease
- Hard metal disease
- Crohn's disease
- Ulcerative collitis
- Idiopathic inflammatory myopathy
- Familial IPF
- Hermansky-Pudlak syndrome
- Gaucher's disease
- Goodpasture's syndrome
- Nitrofurantoin
- Methotrexate
- Amiodarone
- Talc 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

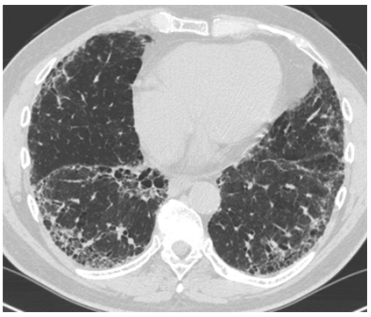
- Laboratory Testing
  - No specific laboratory tests or biomarkers
  - Routine laboratory testing with chemistries, CBC with differential
  - Evaluation for autoimmune diseases
    - » ANA/ENA
    - » Rheumatoid factor/CCP
    - » CK, aldolase
    - » If signs /symptoms of vasculitis, consider ANCA

Diagnostic Approach to ILD

- 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

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



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

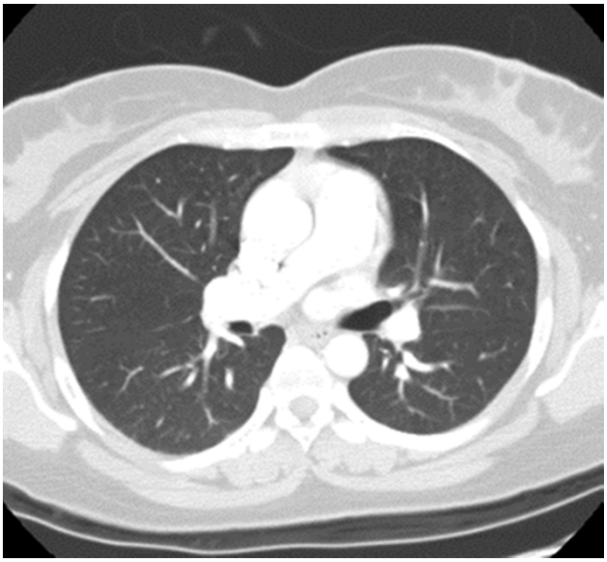
Idiopathic Pulmonary Fibrosis

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

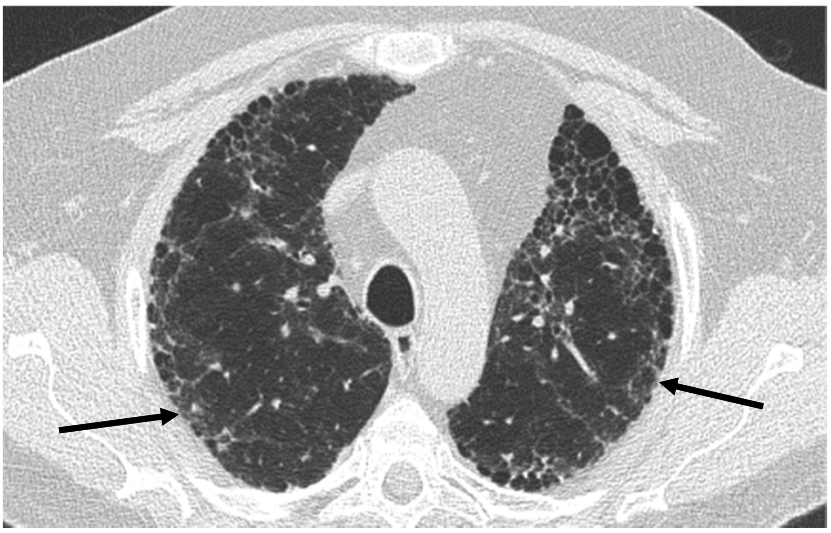
Chest CT in IPF

- 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
- 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%

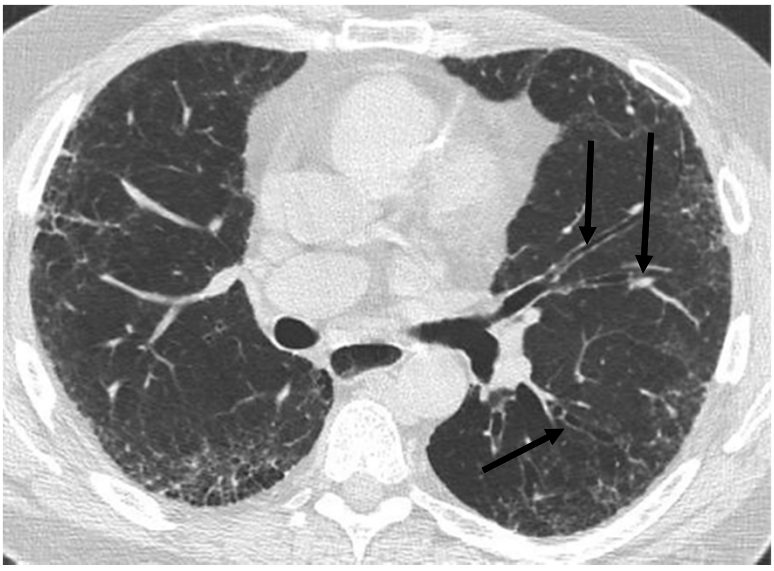
Normal Chest CT



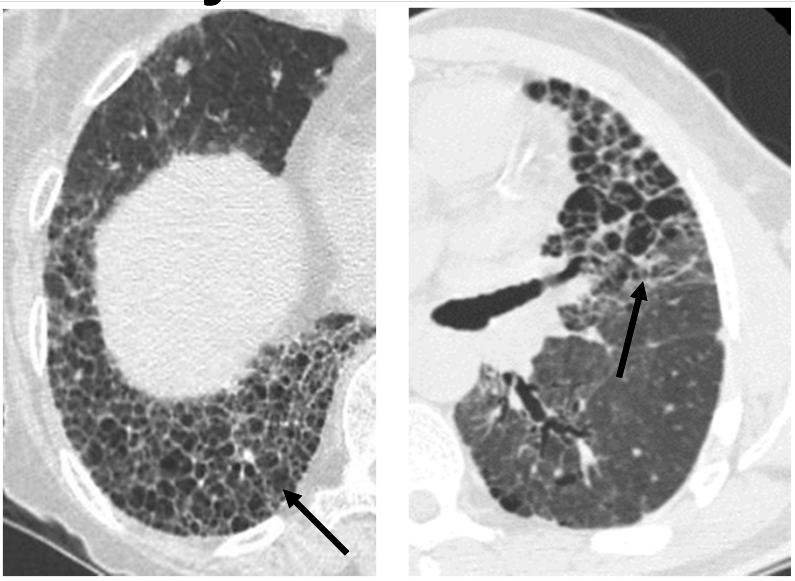
Chest CT: subpleural reticular infiltrates



Chest CT: traction bronchiectasis



Chest CT: basilar honeycomb infiltrates



Role of Lung Biopsy

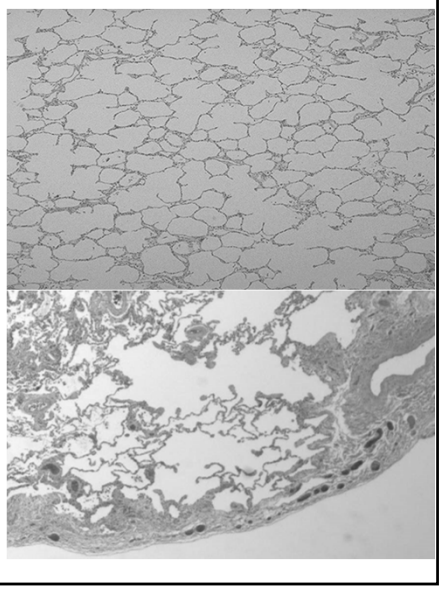
- In about 1/3rd of patients, require tissue to confirm diagnosis
  - Atypical findings on CT scan or clinical history
  - Early in disease process

Role of Lung Biopsy

- 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)

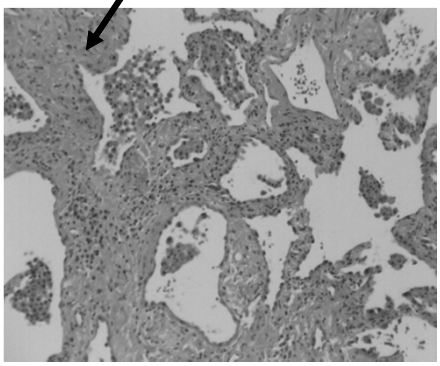
IPF Lung Pathology: UIP

- 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

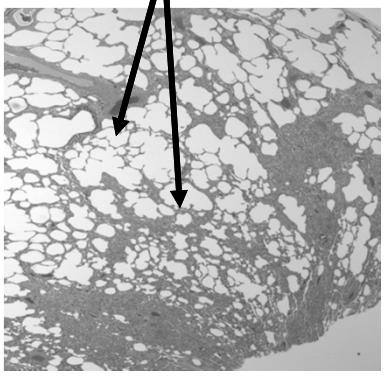


IPF Lung Pathology: UIP

Fibrosis with collagen deposition

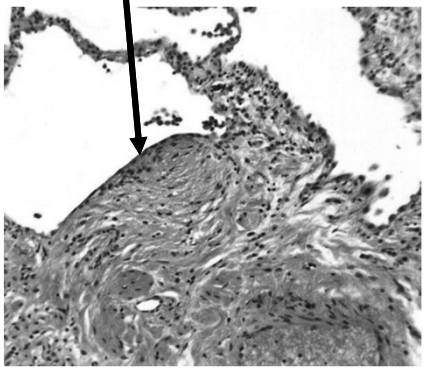


Temporal heterogeneity

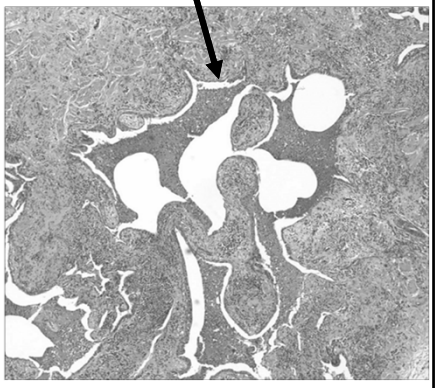


IPF Lung Pathology: UIP

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

Coexisting conditions with IPF

- Pulmonary hypertension
  - In about 1/3 patients and most with advanced disease
  - Associated with worse pulmonary function, hypoxemia
  - Decreased exercise capacity and worse survival
- GERD
  - Common in IPF (65-94%)
  - Potential causal relationship between GERD and IPF through microaspiration of gastric contents
  - Acid-suppression therapy was associated with a slower rate of decline in pulmonary function and longer survival

Coexisting conditions with IPF

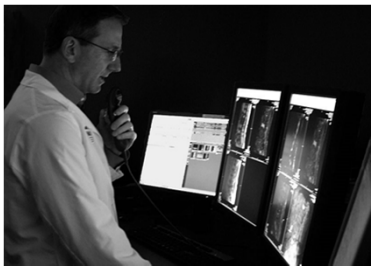
- Combined Pulmonary Fibrosis and Emphysema
  - ~8% IPF cases, male, smoking history
  - Disproportionately low DLCO and gas exchange
  - Chest CT upper lobe emphysema, lower lobe fibrosis
  - High incidence of pulmonary hypertension, lung cancer and worse prognosis
- Lung Cancer
  - Increased risk in IPF patients, independent of other risks (smoking)
- OSA, CAD, depression

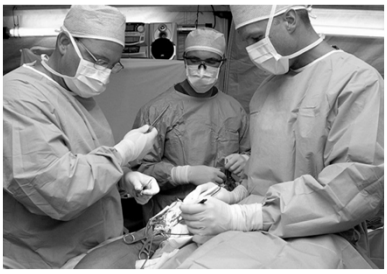
Acute Exacerbation of IPF

- Acute deterioration with rapid, irreversible clinical decline
  - 1 and 3-year incidence of AE estimated 14% and 21%
  - Mortality rate associated with AE as high as 50% to 80%
  - Survival times 4-15 months in those who “recover”
- Etiology of decline unknown
- Chest imaging shows diffuse ground glass infiltrates
- Lung biopsy shows diffuse alveolar damage (identical to ARDS) superimposed on UIP pattern

Acute Exacerbation of IPF

- Clinical evaluation to rule out an identifiable cause
  - Infection
    - »Consider bronchscopy
    - »Often limited by hypoxemia and risk of respiratory failure
  - Progressive heart failure, ischemic disease
    - »ROMI, Echo, BNP
  - Pulmonary embolism
    - »CTPE study, LE duplex
- No well established therapy



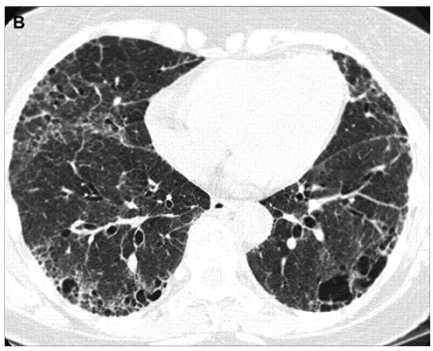


IPF Diagnosis Requires A Multi-Disciplinary Approach

<u>Know your patient</u>
Diseases, exposures, meds, family
**** Pulmonary Fibrosis ≠ Idiopathic Pulmonary Fibrosis ****

Get to know your radiologist

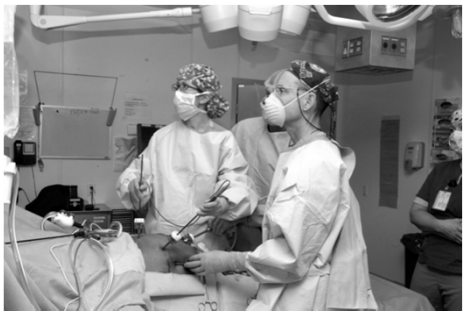
- **Agree on definition of UIP**
- **Presence or absence of honeycombing**
- **Presence or absence of ground glass infiltrates**
- **Geographic location of infiltrates**



****Diffuse interstitial infiltrates ≠ IPF**

Get to know your thoracic surgeon

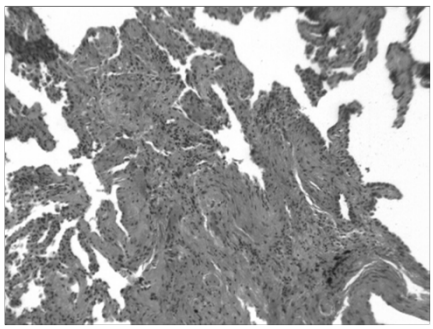
- 2 or 3 lobe biopsies
- Avoid the tip of the lingula, middle lobe or lower lobes
- Target ground glass infiltrates or transition zones



**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?

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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**

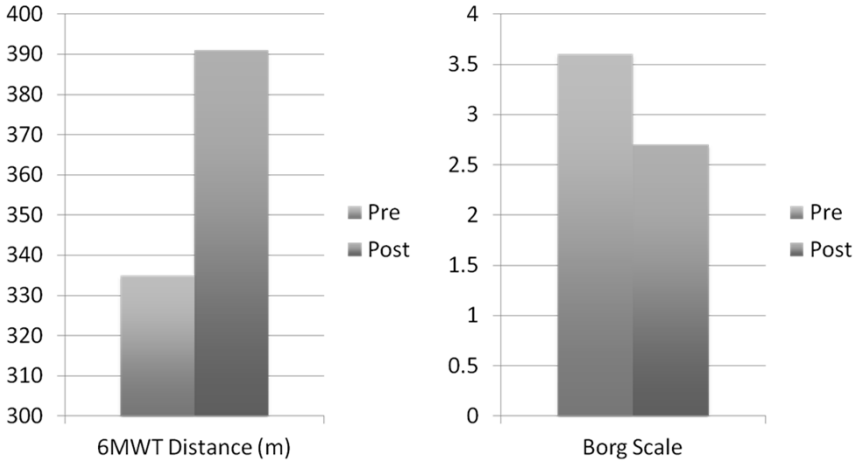
Portable units

- **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**

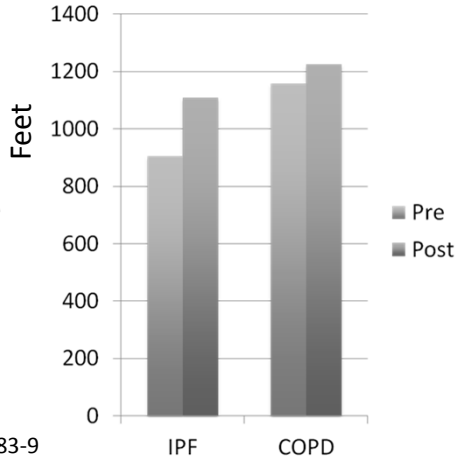
Effect of pulmonary rehabilitation on interstitial lung disease



Collard et al. Chest 2009; 135:442-7

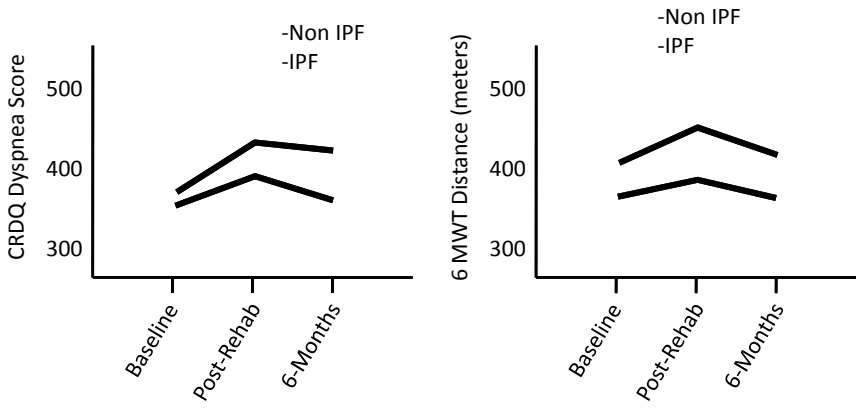
Pulmonary rehabilitation in IPF

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



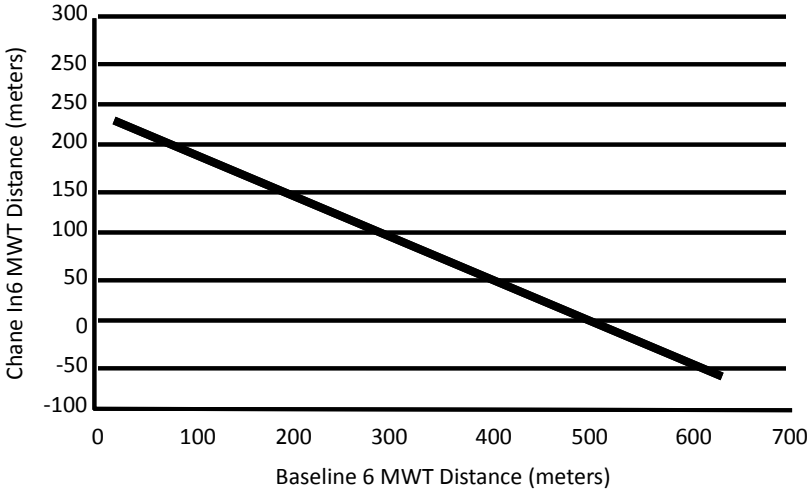
Swigris, et al. Respir Care 2011; 56:783-9

Pulmonary rehabilitation in interstitial lung disease



Holland, et al. Respir Med 2012; 106:429-35

6MWT improvement after pulmonary rehabilitation for interstitial lung disease

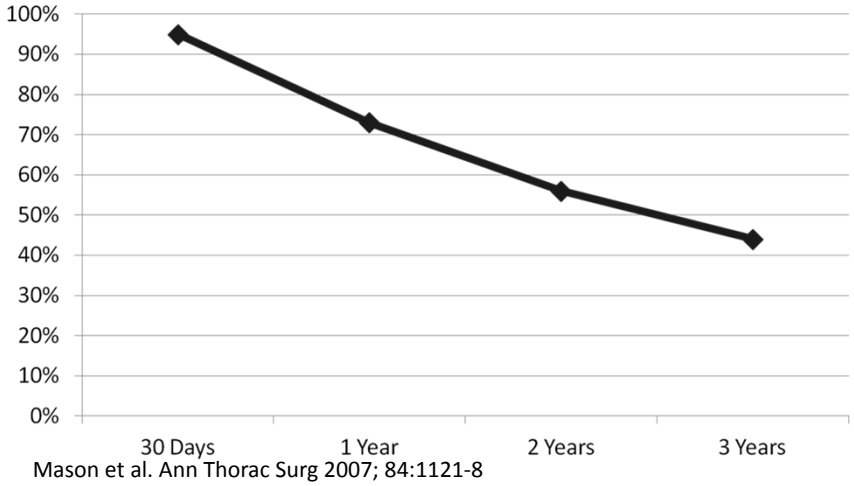


Collard et al. Chest 2009; 135:442-7

Lung transplant contraindications

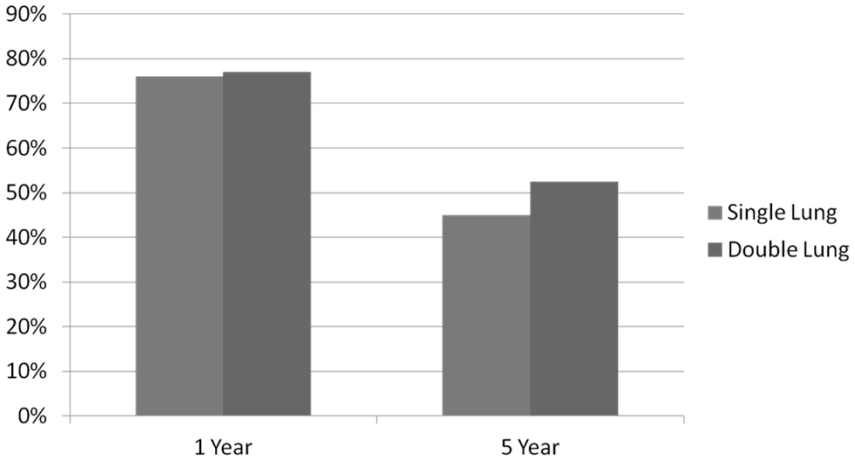
- **Age > 65 (sort of…)**
- **BMI > 30**
- **Smoking in the past 6 months**
- **Uncured malignancy**
- **HIV, active hepatitis C/B**
- **Active infection**
- **Chest wall deformity**
- **Non-compliance**
- **Inadequate psychosocial support**

Survival after lung transplant for IPF



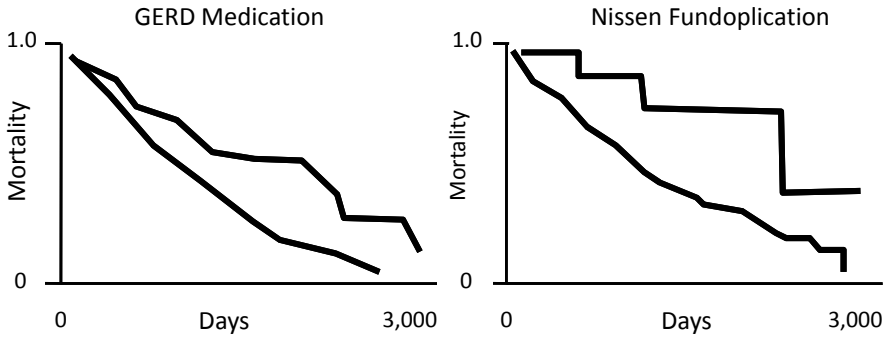
Mason et al. Ann Thorac Surg 2007; 84:1121-8

Survival after lung transplant for IPF



Nathan et al. J Heart Lung Transplant. 2010;29:1165-71.

Esophageal reflux and IPF mortality



Lee, et al. Am J Respir Crit Care Med 2011; 184:1390-4

- 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

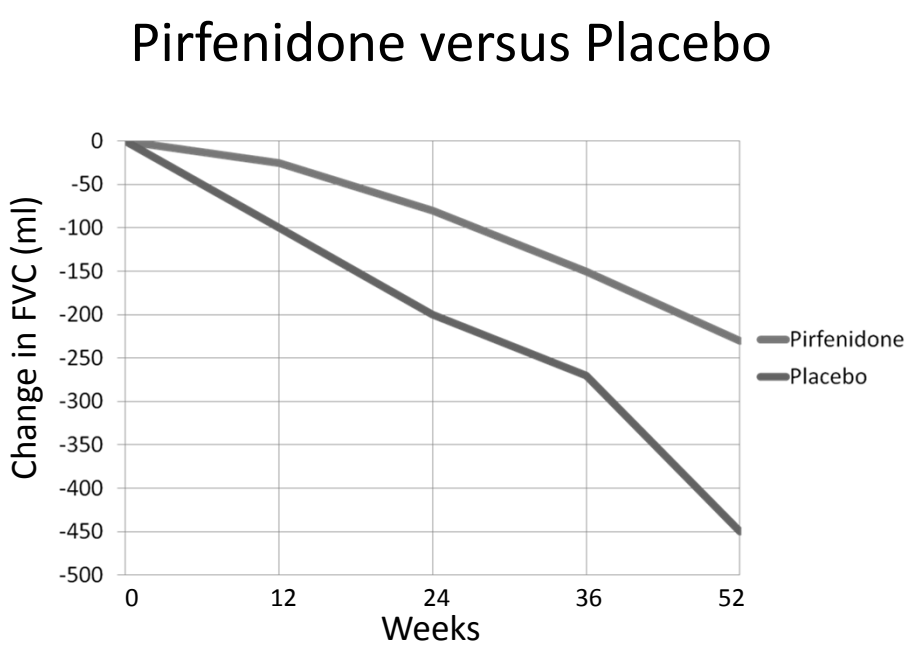
- A confident diagnosis of IPF is required!!!

- Nintedanib*
- Pirfenidone*

Approved by the FDA
October 15, 2014

Pirfenidone (ASCEND trial)

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



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

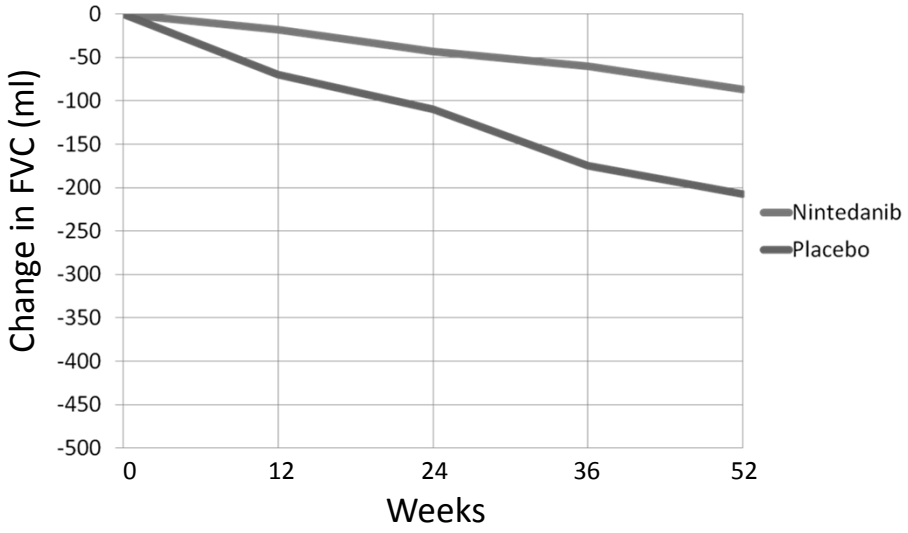
Laboratory monitoring:

- 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

Nintedanib (IMPULSIS trials)

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

Nintedanib versus Placebo



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:

Pirfenidone		Nintedanib	
• Nausea	36%	• Diarrhea	62%
• Rash*	28%	• Nausea	24%
• Adverse effect requiring discontinuation = 14%		• Adverse effect requiring discontinuation = 21%	

*Photosenstivity

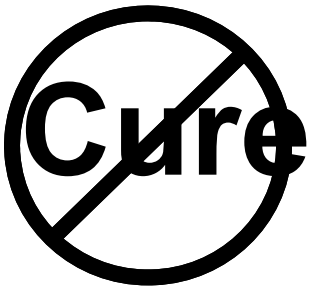
Pirfenidone and Nintedanib: practical considerations

- 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

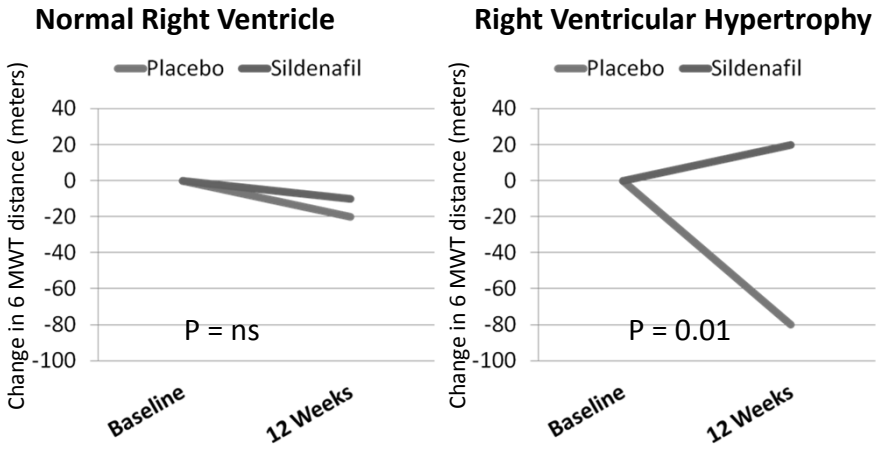
Which patients benefit most from treatment?

- 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



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



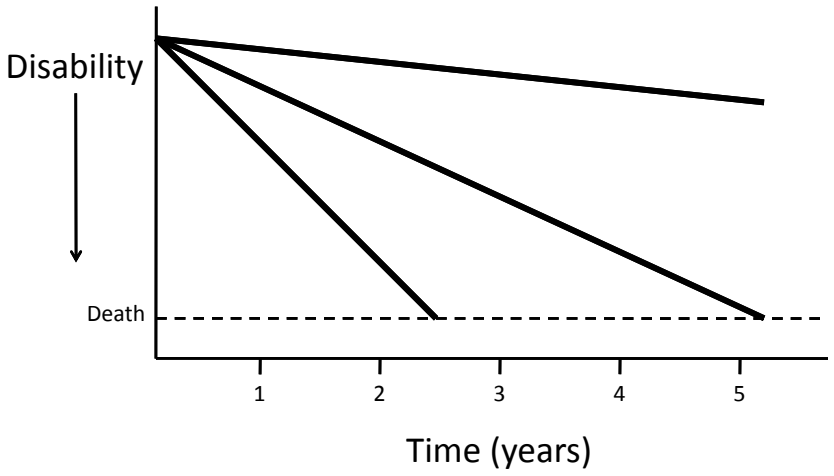
Chest 2013; 143:1699-1708

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

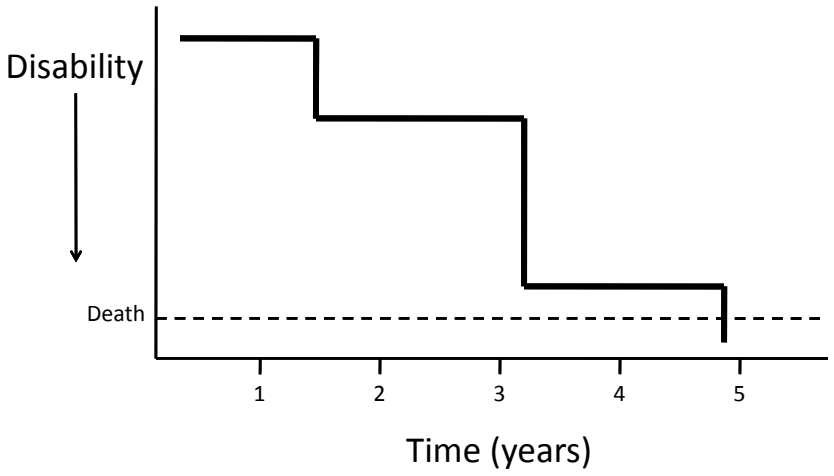
Typical Clinical Course



When patients with IPF are worse:

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

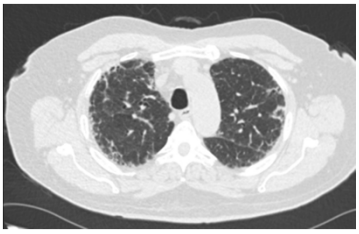
"Stair-Step" Clinical Course



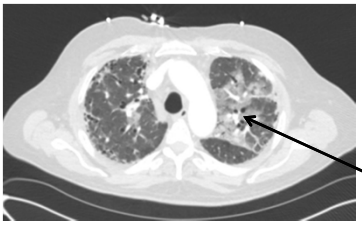
Acute interstitial pneumonitis

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

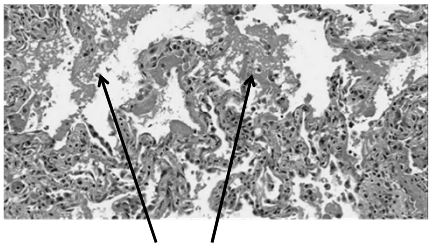
Acute Interstitial Pneumonitis



April, 2013



August, 2014

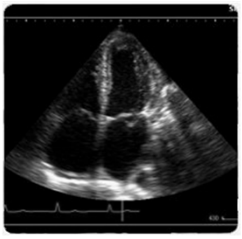


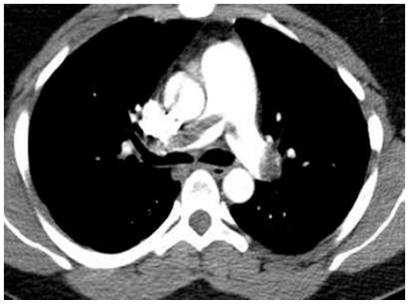
Hyaline membranes

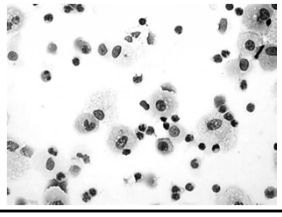
Ground glass infiltrates

Acute interstitial pneumonitis is a diagnosis of exclusion

- Heart failure
  - Consider BNP
  - Consider cardiac echo
- Pulmonary embolism
  - Consider CT-PA
- Infection
  - Consider BAL







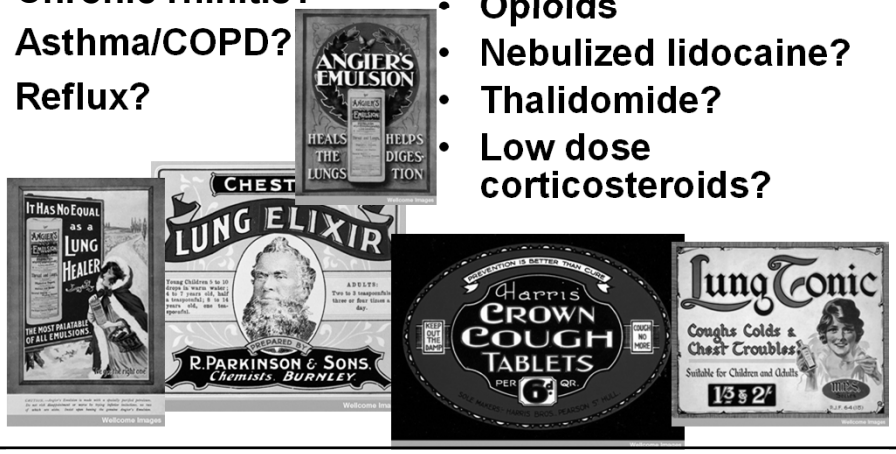
Cough and IPF

Are there other causes:

- ACE inhibitors?
- Chronic rhinitis?
- Asthma/COPD?
- Reflux?

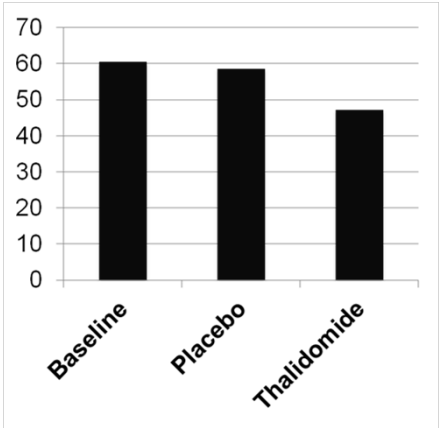
Palliating the IPF cough:

- Non-opioid anti-tussives (eg, benzonatate)
- Opioids
- Nebulized lidocaine?
- Thalidomide?
- Low dose corticosteroids?

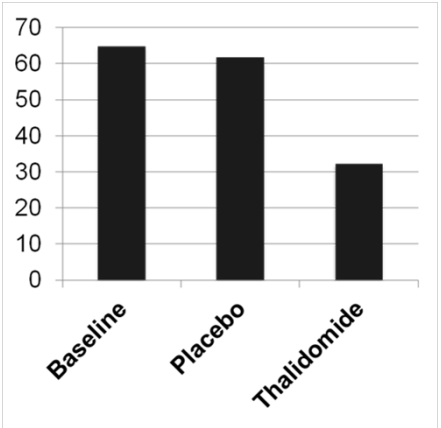


Thalidomide Reduces Cough In IPF

Cough Quality of Life Questionnaire



Cough Visual Analogue Scale



Ann Intern Med 2012; 157:398-406

Thaldidomide 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

Image: JohannesJ

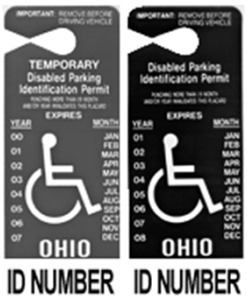


Image: Ohio DMV

Image: Stannah Stairlift

Vaccinations for patients with IPF:

- Influenza
- Pertussis (Tdap)
- Strep pneumoniae

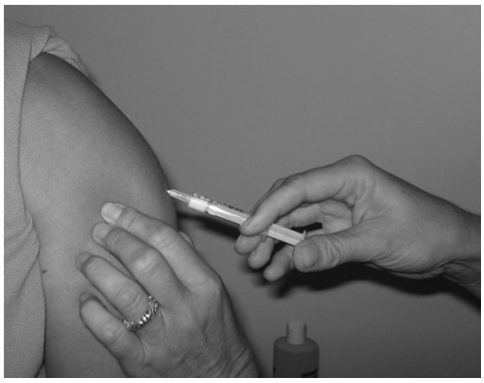


Photo: Grook Da Oger

New CDC Pneumococal 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

CDC: Judy Schmidt

Idiopathic pulmonary fibrosis is ultimately a terminal disease

Start end-of-life discussions early

- Resuscitation and intubation
- Hospice
- How patients die

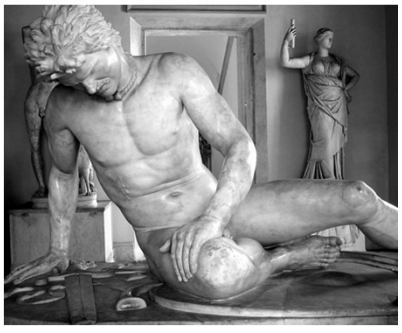
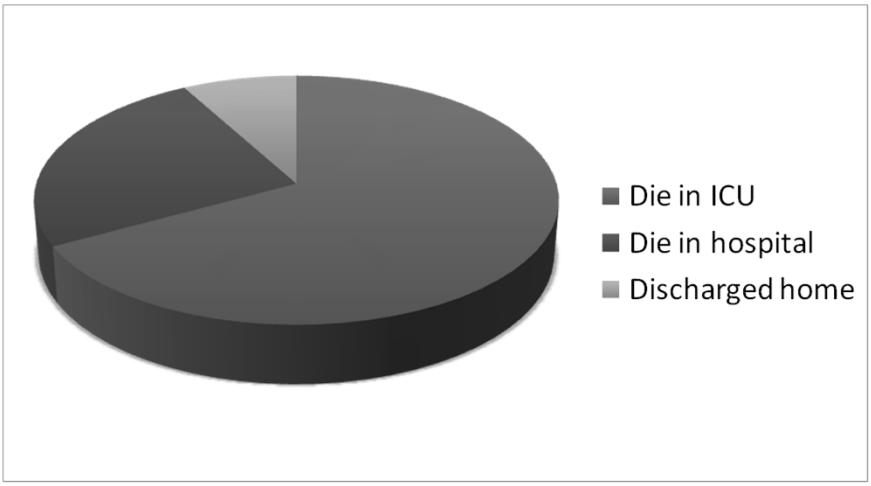


Photo: Anthony Majanlathi

Galata Morente, Capitoline Museum, Rome

Outcome of patients admitted to the ICU with respiratory failure



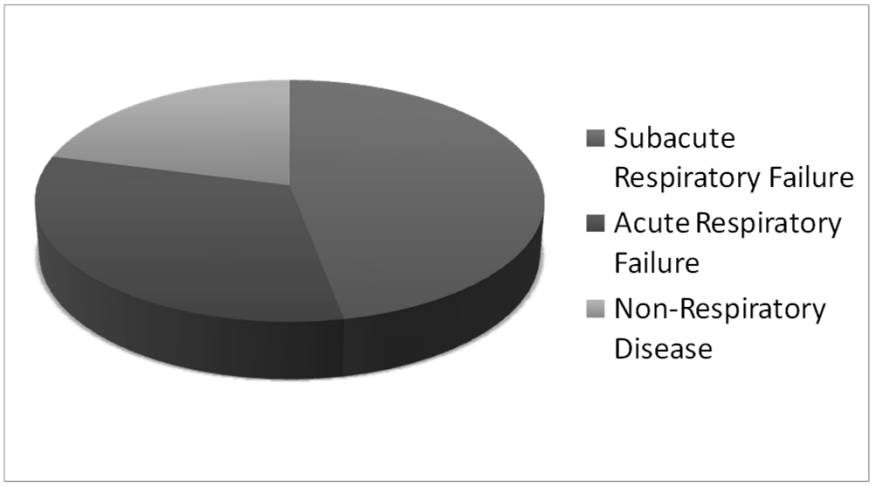
Crit Care Resusc 2009; 11:102-109

Hospice

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

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

How do patients with IPF die?

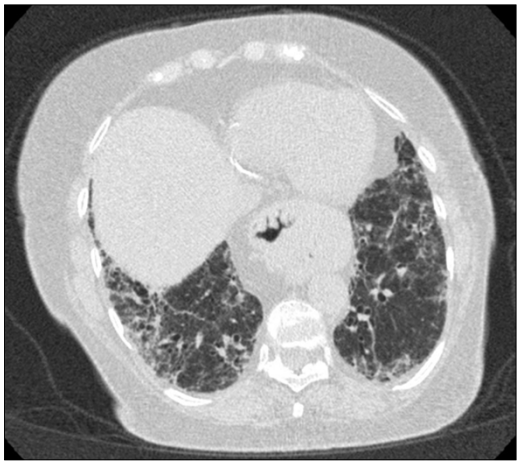


The improvement in the outcomes of your patients tomorrow will depend on clinical trials in your patients today

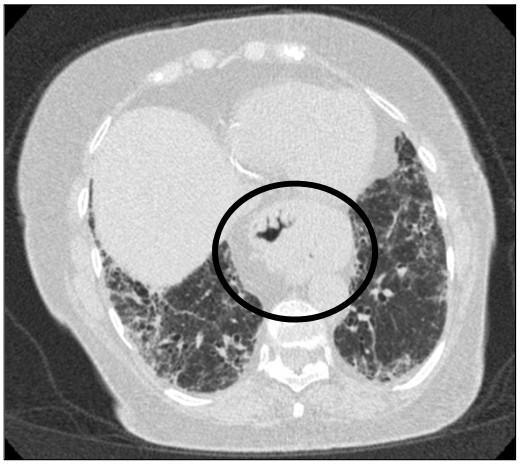
IPF Treatment: Summary

- 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

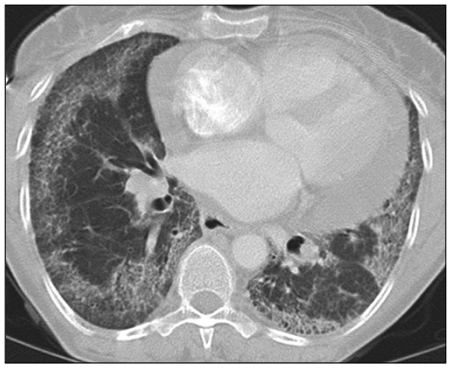
Case #1

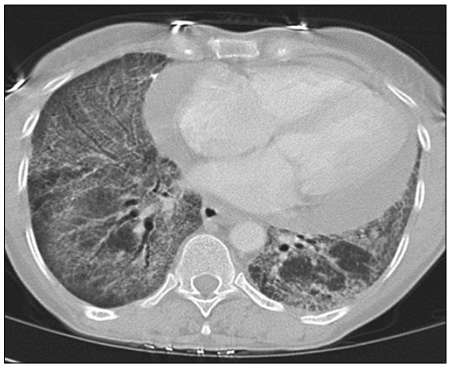


Case #1

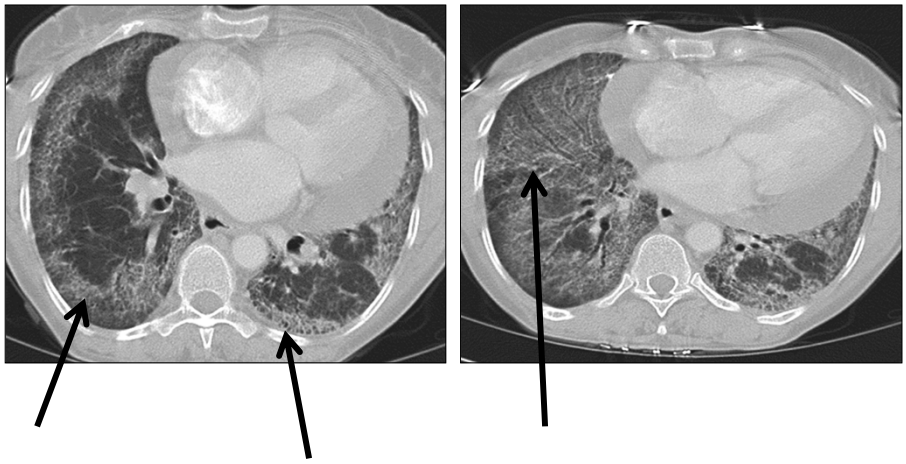


Case #2





Case #2



Case #3