Idiopathic Pulmonary Fibrosis

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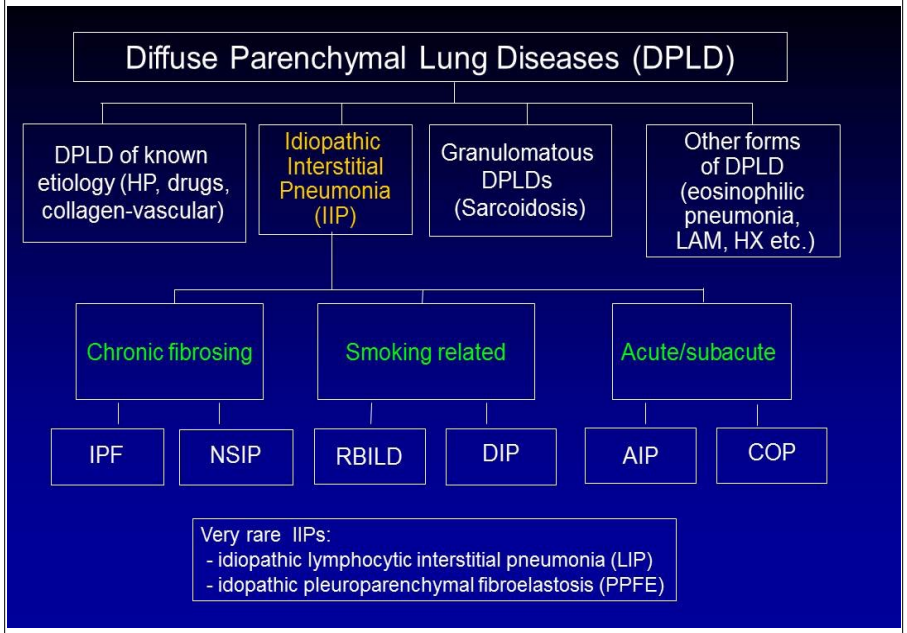
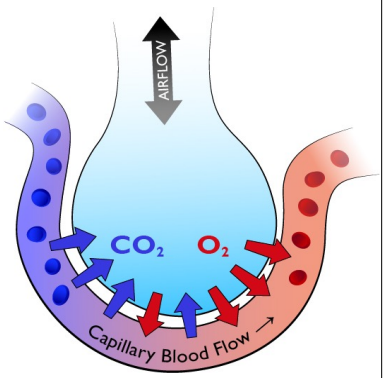


Objectives

- Review basic lung function
- Define the interstitium
- Define interstitial lung disease (ILD)
- Clinical presentation
- Causes
- Diagnosis
- Therapy for IPF

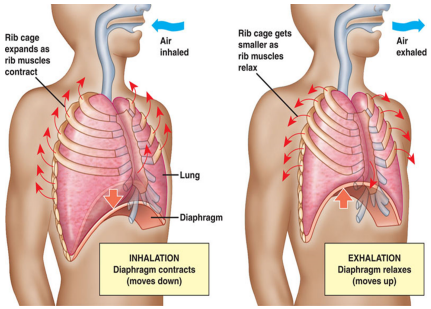
What do the lungs do?

- Primary function is gas exchange
- Let oxygen move in
- Let carbon dioxide move out



How do the lungs do this?

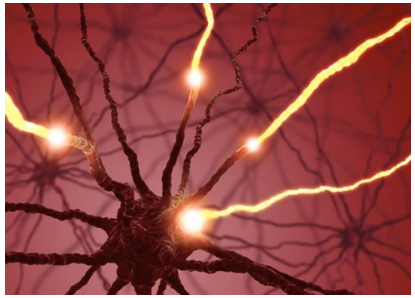
- First, air has to move to the region where gas exchange occurs.
- For this, you need a normal ribcage and respiratory muscles that work properly



Restrictive diseases

Neuromuscular weakness

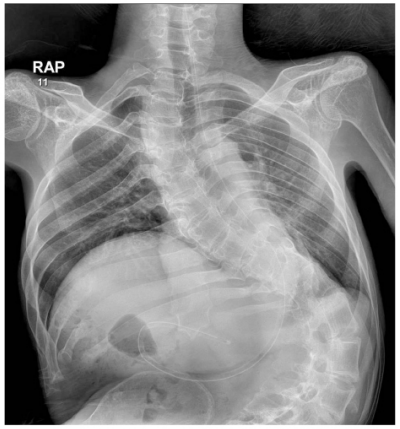
- Spinal cord
  - Trauma, MS, tumor
- Motor nerves
  - ALS, GBS, phrenic nerve
- Neuromuscular junction
  - MG, Lambert Eaton
  - Botulism, organophosphate
- Muscles
  - Muscular/myotonic dystrophy
  - Mitochondrial myopathy



Restrictive diseases

Diseases of the chest wall

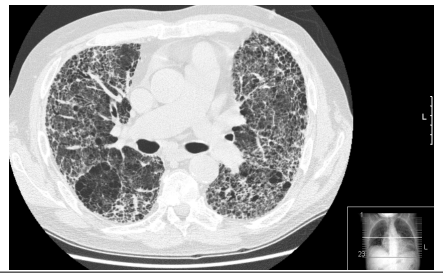
- Ankylosing spondylitis
- Congenital deformities, including pectus excavatum
- Flail chest
- Kyphoscoliosis
- Thoracoplasty
- Fibrothorax
- Abdominal processes, including morbid obesity and ascites
- Chest wall tumors

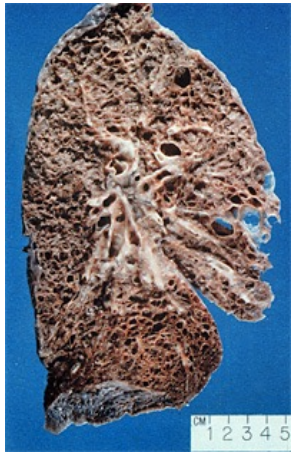


Restrictive diseases

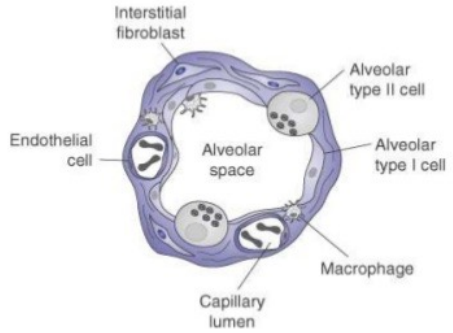
Loss of lung elasticity

- Parenchymal lung disease
- Interstitial lung disease
- Pulmonary fibrosis





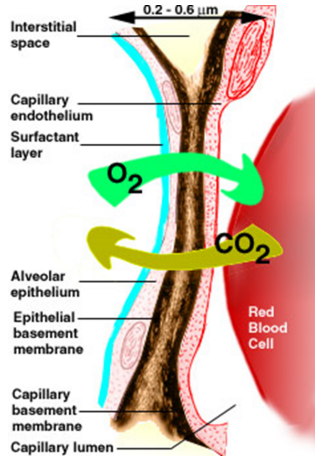
What is the Pulmonary Interstitium?



Interstitial compartment is the area of the lung between the alveolar epithelial and capillary endothelial basement membranes

What happens when there is ILD?

- Interstitial structures become thickened / inflamed. Expansion of the interstitial compartment (portion of lung parenchyma sandwiched b/w the epithelial and endothelial basement membranes)



Nomenclature

- More than 200 diseases can result in interstitial lung disease (ILD)
- The term interstitial is misleading since most of these disorders are also associated with extensive alterations of alveolar and airway architecture

Epidemiology

- ILD is more frequent than previously recognized
- Incidence ranges from 7 to 16 cases per 100,000 in US
- The prevalence of preclinical and undiagnosed ILD is 10 times that of clinically recognized
- Among these, IPF is the most common, representing at least 30% of incident cases

Clinical conundrum

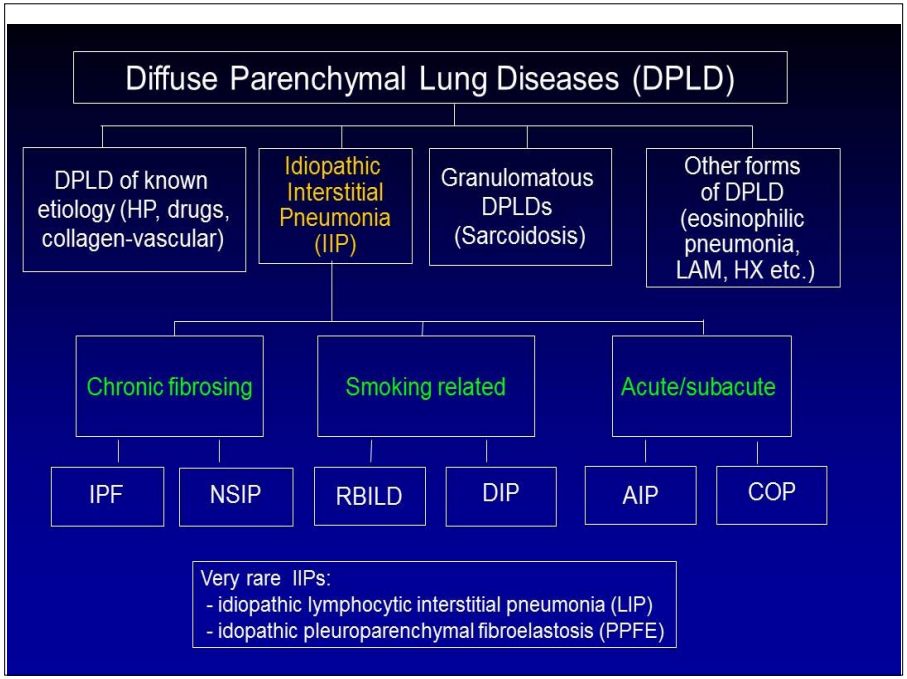
- At least 150 clinical entities associated with ILD
- Difficult to determine the best specific diagnostic approach
- A conclusive cause (even after lung bx) cannot always be ascertained in a significant number of patients
- Even when a specific diagnosis is made, an effective therapeutic regimen is not available for many patients

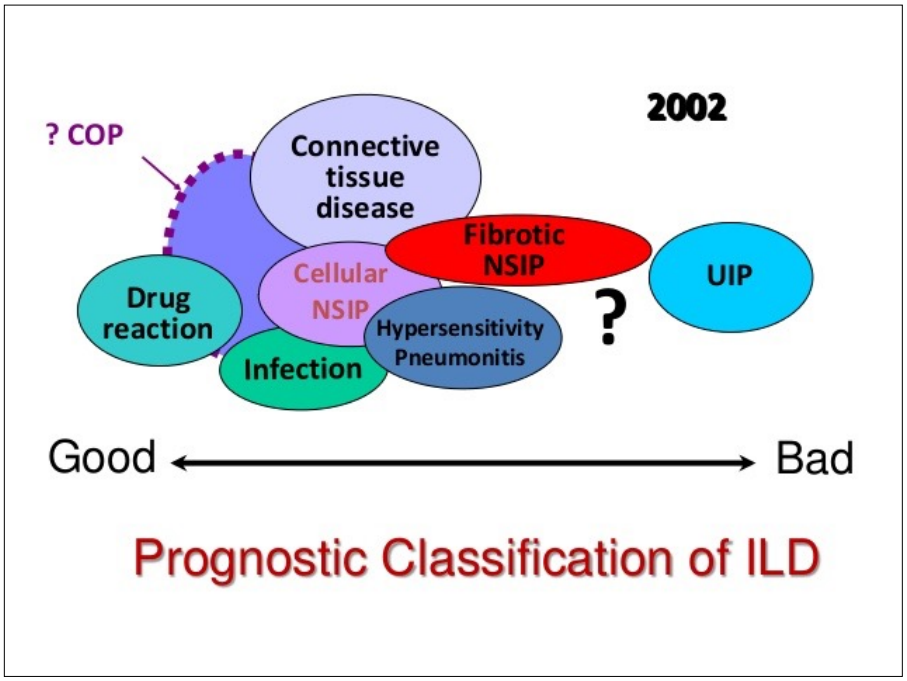
Table 1: Potential Causes /Categories of Interstitial Lung Disease

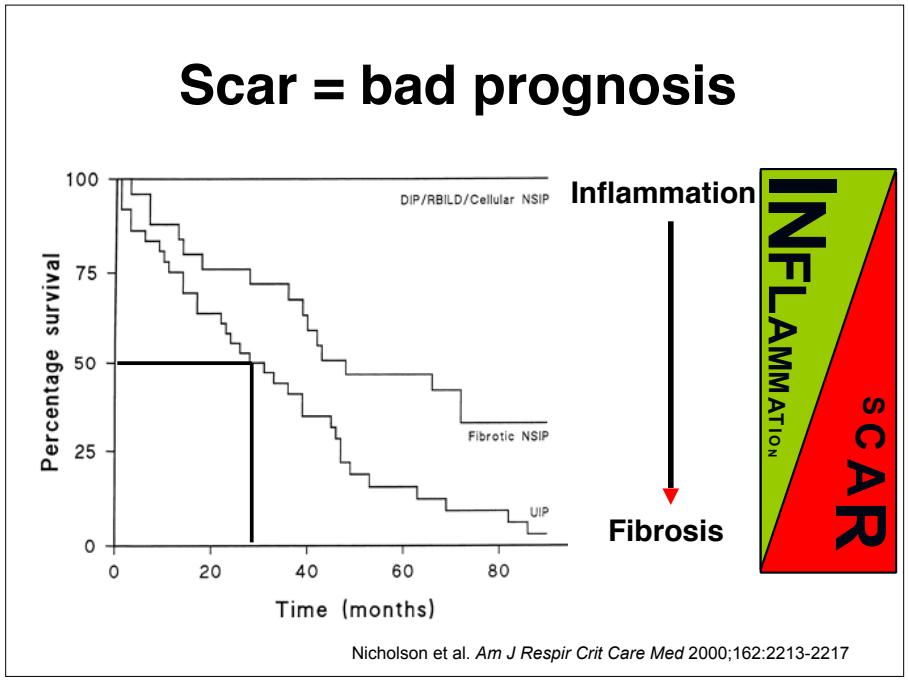
Cause	Categories	
Occupational or other inhaled organic agents (EAA/HP)	Bird fancier's lung Farmer's lung Bagassosis	Byssinosis Malt worker's lung Coffee worker's lung
Occupational or other inhaled inorganic agents	Silicosis Asbestosis Coal worker's pneumoconiosis	Talc pneumoconiosis Berylliosis Hard metal fibrosis
Collagen vascular disease related	SLE Rheumatoid arthritis Scleroderma Mixed CT disease	Ankylosing spondylitis Sjogrens syndrome Bechet`s disease Dermatopolymyositis
Drug related	Chemotherapeutics (Bleomycin, Methotrexate, Busulfan) Drug induced Lupus (Phyenytoin, procainamide) Antiarrhythmics (Amiodarone) Antibiotics (Nitrofurantoin, sulfasalazine) Gold	

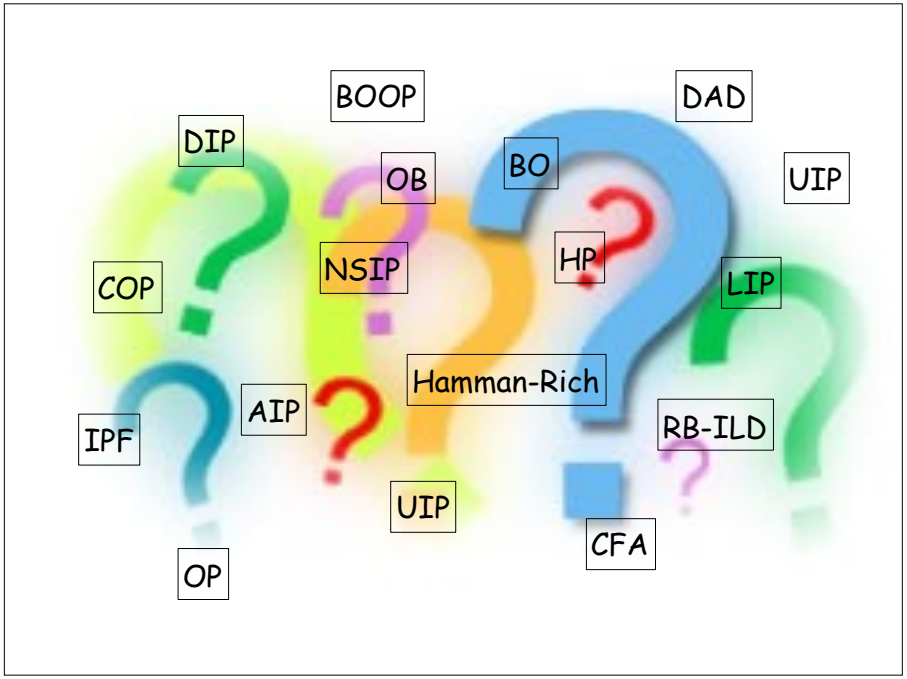
Table 1: Potential Causes /Categories of Interstitial Lung Disease

Cause		
Physical agents & toxins	Radiation / Radiotherapy Oxygen	Paraquat toxicity
Primary disease diagnosis	Sarcoidosis Amyloidosis Lymphangioleiomyomatosis	Tuberous sclerosis Neurofibromatosis Niemann-Pick disease
	Pulmonary Langerhans cell histiocytosis	
Neoplastic diseases	Bronchoalveolar carcinoma Lymphangitis carcinomatosis	
Vasculitides	Churg -Strauss syndrome Wegener`s granulomatosis	
Alveolar filling diseases	Alveolar protienosis Lipoid pneumonia Eosinophilic pneumonia	Pulmonary lymphoma Chronic aspiration
Disorders of circulation	Pulmonary edema Pulmonary veno-occlusive disease	
Infection	Tuberculosis Residue of active infection of any type	









ATS/ERS Classification of Idiopathic Interstitial Pneumonias

Histologic Pattern	Clinical/Radiologic/Pathologic Diagnosis
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis
Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Organizing pneumonia	Cryptogenic organizing pneumonia
Diffuse alveolar damage	Acute interstitial pneumonia
Respiratory bronchiolitis	Respiratory bronchiolitis interstitial lung disease
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Lymphoid interstitial pneumonia	Lymphoid interstitial pneumonia

What type of fibrosis is the PCP most likely to see?

- ++++ Idiopathic pulmonary fibrosis (IPF)
  - Aging population
- ++++ Connective tissue disease-related
  - RA, SLE, Sjogren's syndrome
- + Chronic hypersensitivity pneumonitis
  - Organic exposure

Making the diagnosis

- History
- Exam
- Pulmonary physiology
- Radiography
- +/- lung biopsy

History: chief complaint

- Typically, ILD presents with:
  - Dyspnea—subacute, insidious onset
    - "I thought I was just…"
      - Getting older
      - 5# heavier
      - Out of shape
  - +/- dry cough
  - Fatigue
  - No wheeze, no chest pain

History

- Symptoms/existence of concurrent disease
  - Patients may…
    - 1. Have known CTD
    - 2. Dyspnea from occult CTD-related ILD
- Family history
  - Pulmonary fibrosis
    - Less than 5% of pts with IPF
    - Auto dominant pattern with variable penetrance
    - Mutation of surfactant protiens
  - Rheumatologic disease

History: exposures

- Smoking
  - IPF
  - DIP
  - RB-ILD
  - Langerhans cell histiocytosis
  - Anti-GBM disease (Goodpasture's)

History: exposures

- Current or previous medications
  - www.pneumotox.com
    - Chemotherapy
    - Amiodarone
    - Nitrofurantoin
    - Amino acid supplements
    - Oily nose drops
- External beam radiation
- Current or previous recreational drug use
- Occupational, environmental, avocational

History: exposures

- Birds (proteins)
  - Bloom on feathers
  - Mucin in excrement
  - Feather pillow/down comforter
- Fumes, dusts, gases
- Asbestos
- Beryllium
- Microbial agents
  - Hot tubs (indoor/enclosed)
  - Basement shower
  - Free-standing humidifiers
  - Water damage to home
  - Cooling systems (swamp cooler)

History: connective tissue diseases

- RA
  - Symmetric arthritis/small joints
    - Morning stiffness
  - Subcutaneous nodules
  - Smoker
- SSc
  - Raynauds
    - After 40 y.o. in FEMALE
    - After 30 y.o. in MALE
  - Esophageal dysmotility
  - Skin tightening

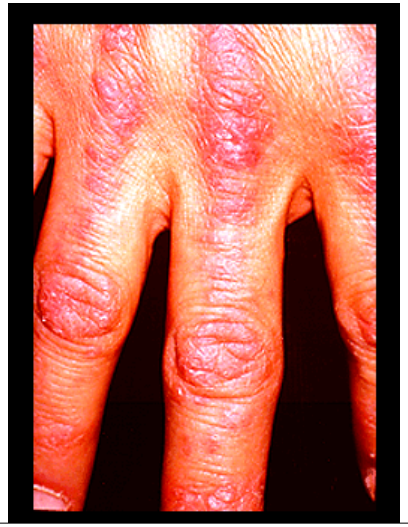
History: connective tissue diseases

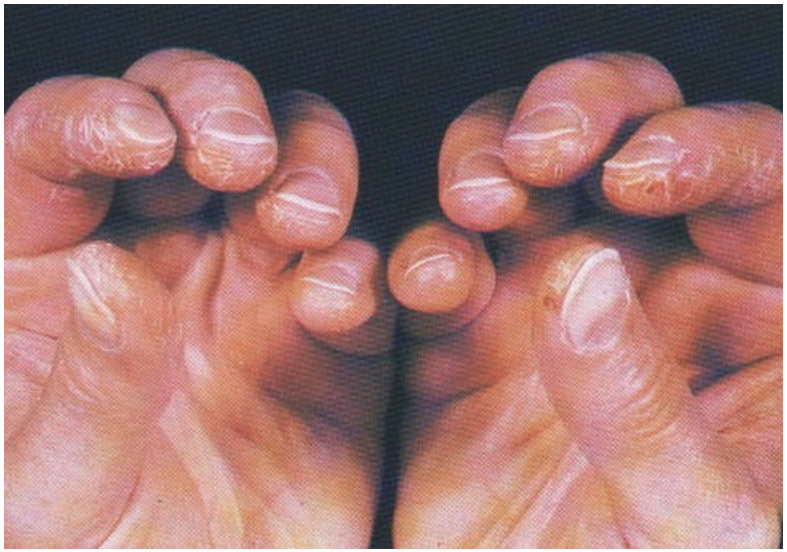
- PM/DM
  - Proximal muscle weakness
  - Rashes
  - Rough skin on the hands
- Sjögren's Syndrome
  - Dry eyes/mouth
  - Dental caries

Physical Exam

Physical examination

- Skin
  - Rash
  - Purupura
  - Telangiectasia
  - Nodules
  - Calcinosis

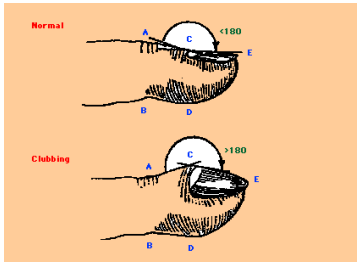




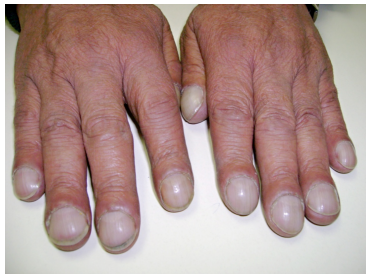
Physical examination

Clubbing
- 25-50% with IPF
- 50% with DIP
- 75% with ILD-RA

Rare in sarcoid, EG



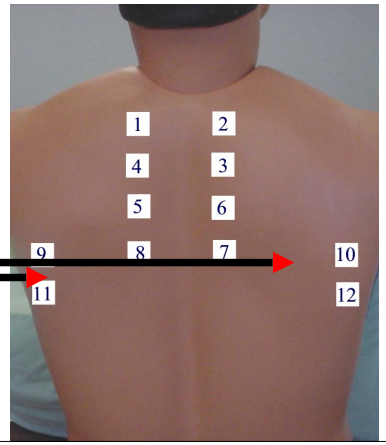
COPD no clubbing !!



Physical examination

- Chest
  - Velcro crackles are NEVER normal

Must listen here



Laboratory

- ANA—the pattern matters
  - Nucleolar ANA any titer – TO RHEUM
- SSA is a myositis associated ab (ANA -)
- ACE level non-specific
  - Don't order it
- HP panels unhelpful
  - Precipitating IgG to organic antigens
  - Don't order them

Laboratory

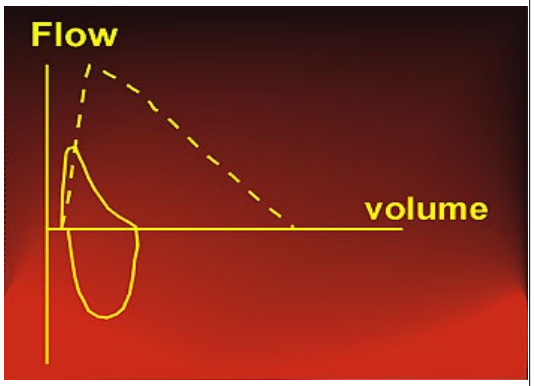
- Isolated high MCV
  - Methotrexate
  - Azathioprine
  - ??? Telomerase abnormality
    - Elevated MCV
    - History of bone marrow irregularities
    - Premature graying
    - Cryptogenic cirrhosis
    - Pulmonary fibrosis

Pulmonary function testing

- Lung volumes
- Spirometry
- DLCO
- ABG

Restrictive Pattern

- Decreased FEV_1
- Decreased FVC
- FEV_1/FVC *normal* or *increased*

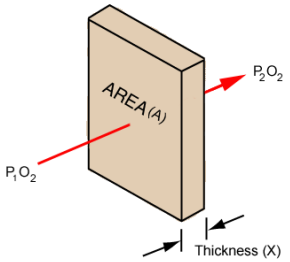


Suspect restriction?

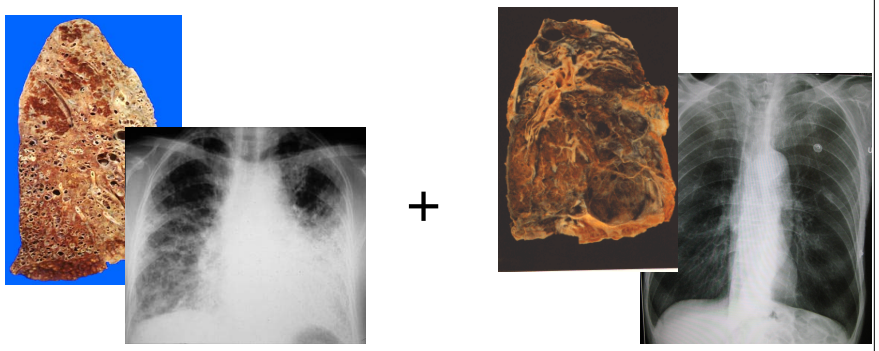
- Obtain lung volumes and diffusing capacity
- TLC less than 80% or below LLN?
  - TLC 80-65% mild
  - TLC 65-50% moderate
  - TLC <50% severe

Check diffusing capacity

- Restriction with normal DLCO
  - Extrapulmonary: obesity, NM weakness, pleural effusion
- Restriction with reduced DLCO
  - Interstitial lung disease



Volumes may be normal if…



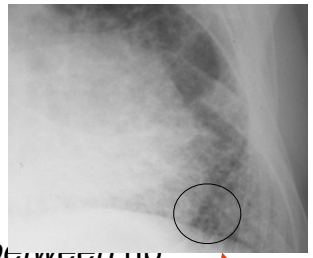
…but the DLCO will be very low

Impaired Gas Exchange

- SpO2 at rest is unhelpful
- Exercise oximetry
  - Never normal to desaturate
- 6-minute walk test

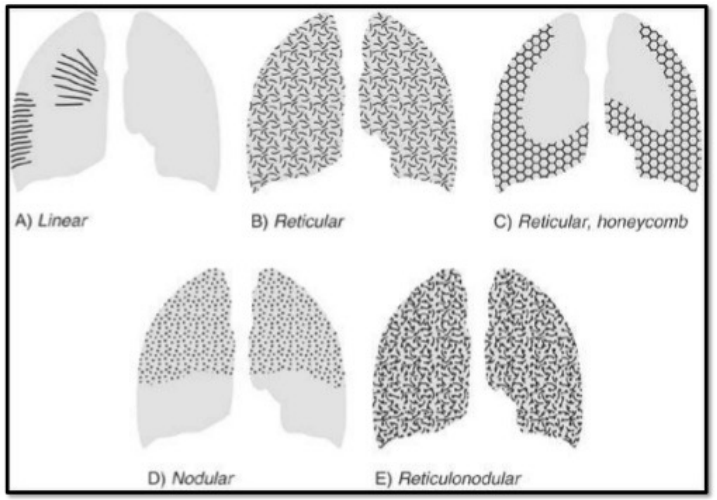
What does ILD look like?

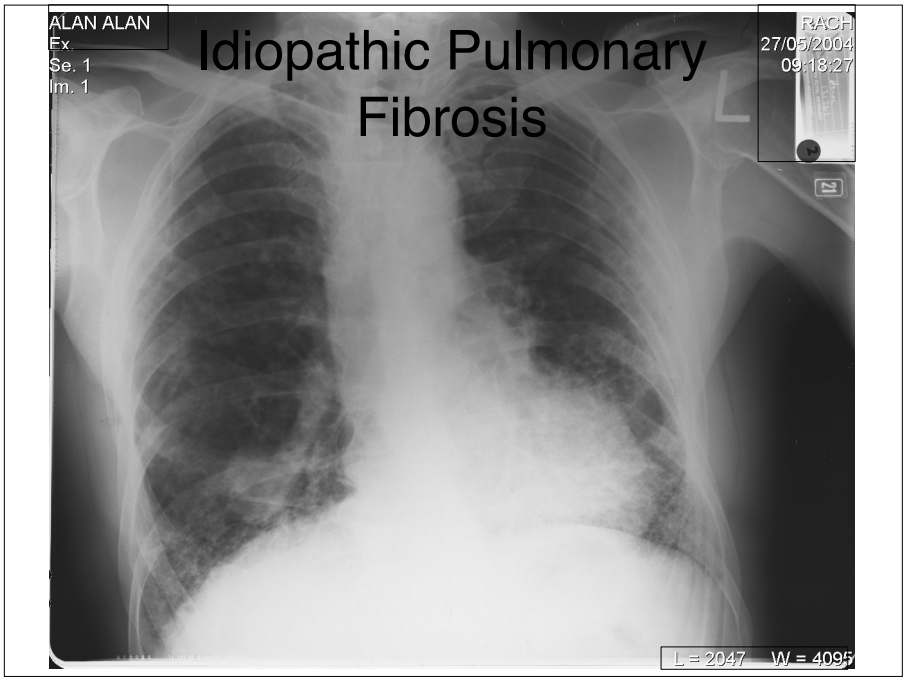
- Abnormal opacities:
  - Linear
  - Reticular
  - Nodular
  - Reticulonodular
  - Honeycombing

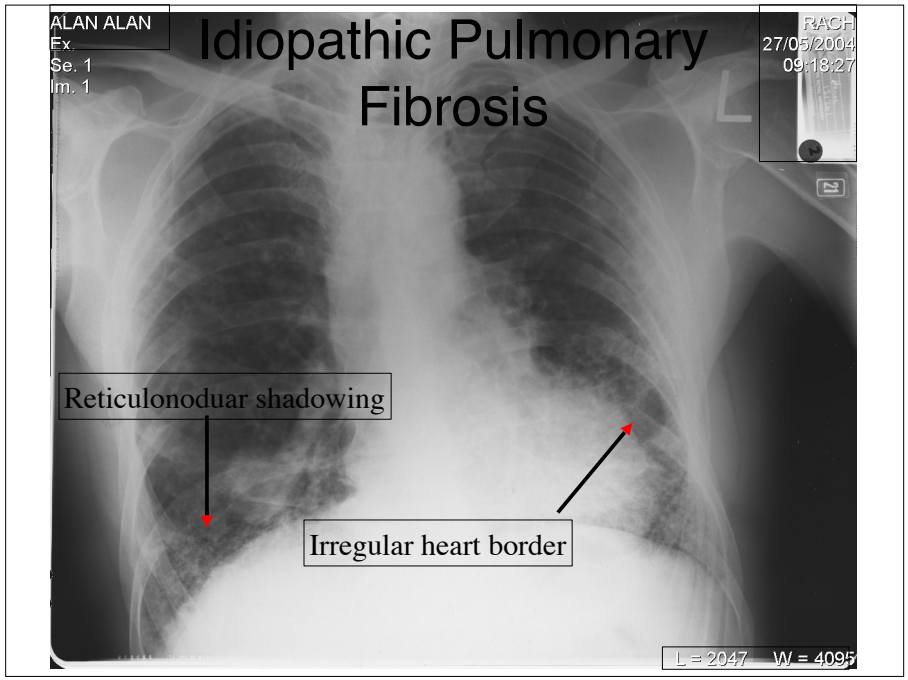


- A good place to look for ILD is *between* rib spaces; close to the chest wall, there should normally be very few lung markings, and certainly no nodules or fine lines

Patterns of Interstitial Lung Disease




ALAN ALAN
Ex.
Se. 1
Im. 1
RACH
27/05/2004
09:18:27
Idiopathic Pulmonary Fibrosis
L = 2047 W = 4095


ALAN ALAN
Ex.
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27/05/2004
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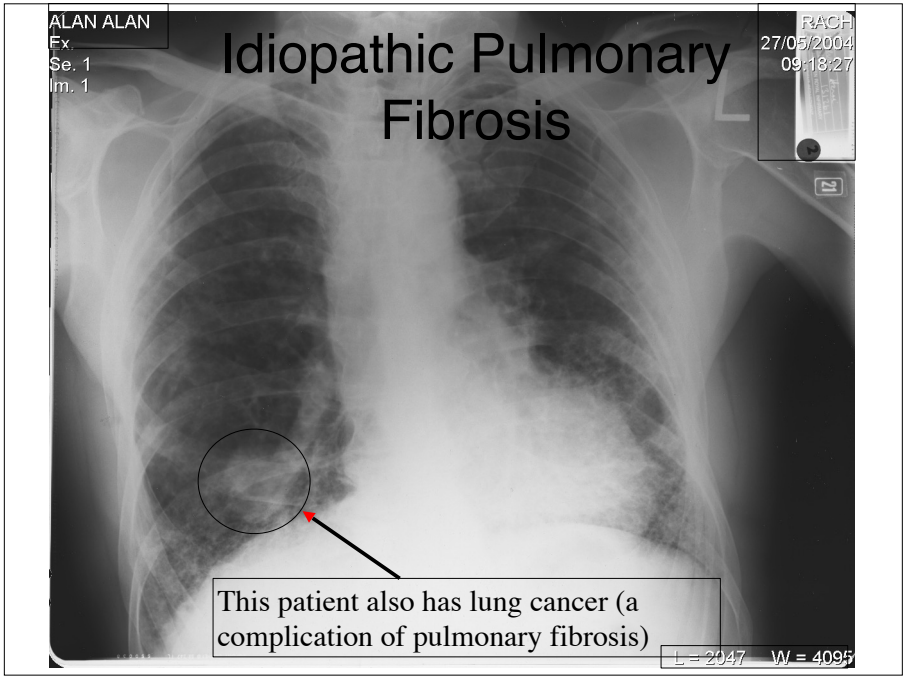
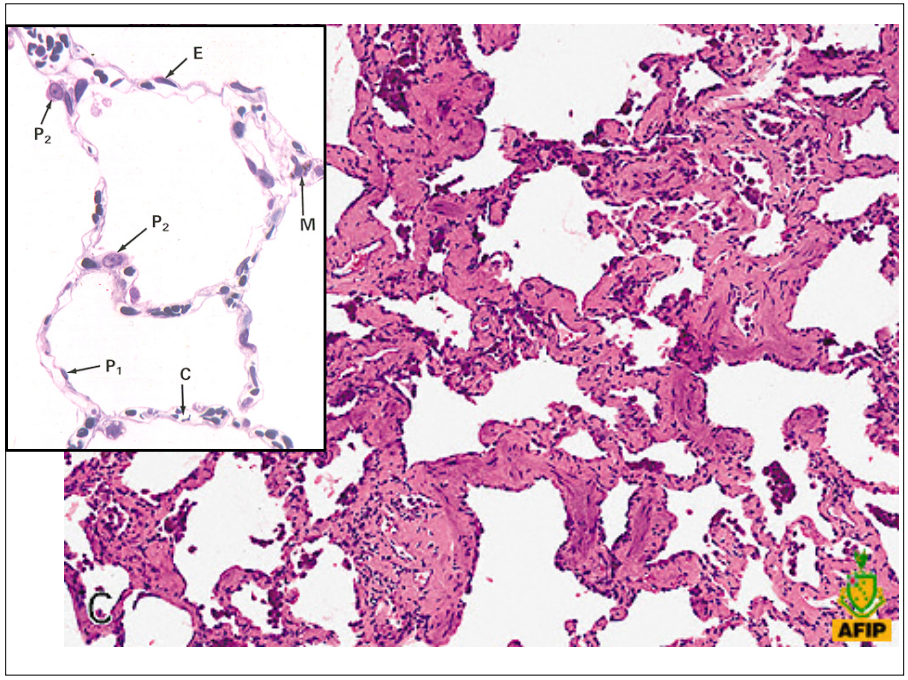
Idiopathic Pulmonary Fibrosis
Reticulonoduar shadowing
Irregular heart border
L = 2047 W = 4095


ALAN ALAN
Ex.
Se. 1
Im. 1
RACH
27/05/2004
09:18:27
Idiopathic Pulmonary Fibrosis
This patient also has lung cancer (a complication of pulmonary fibrosis)
L = 2047 W = 4095


E
P2
P2
M
P1
C
AFIP

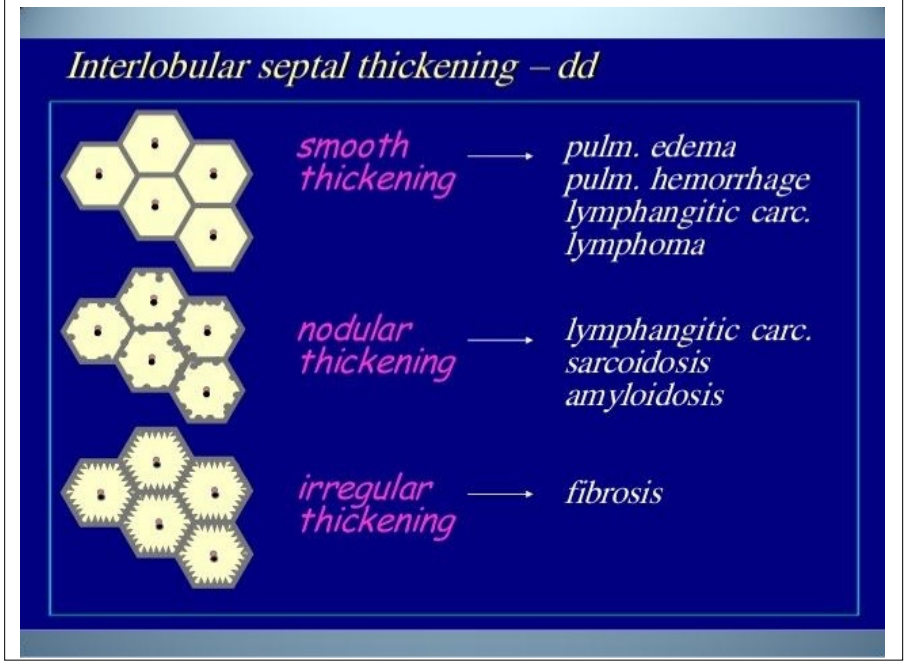
- A normal CXR does not rule out the presence of ILD
- Can be normal in up to 10% of cases
- More so hypersensitivity pneumonitis

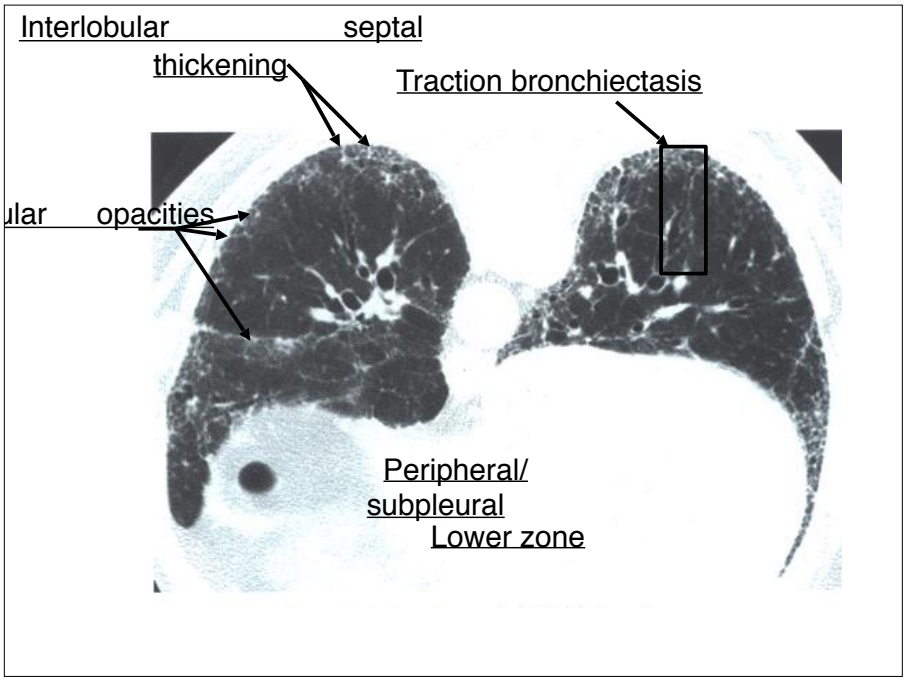
Radiology: diagnosing ILD

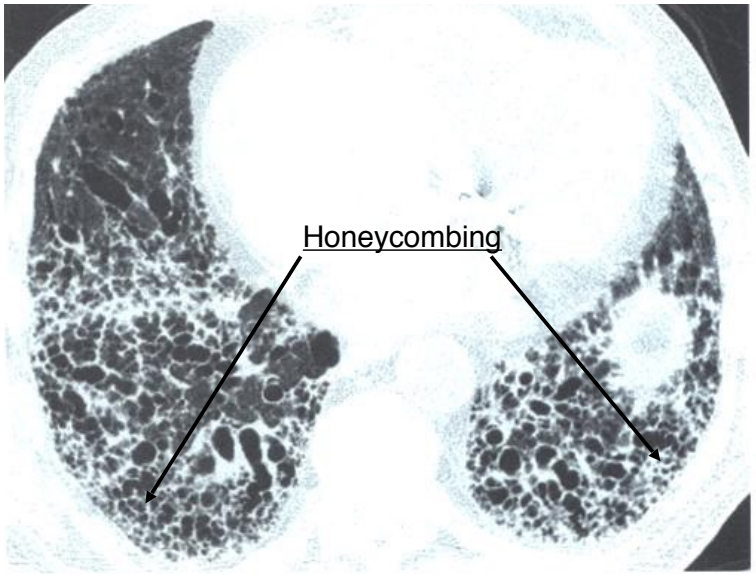
- "ILD protocol" HRCT
  - No IV contrast
  - Supine and prone
  - Inspiratory and expiratory images
  - Reconstruction algorithm — 1-1.5mm thick

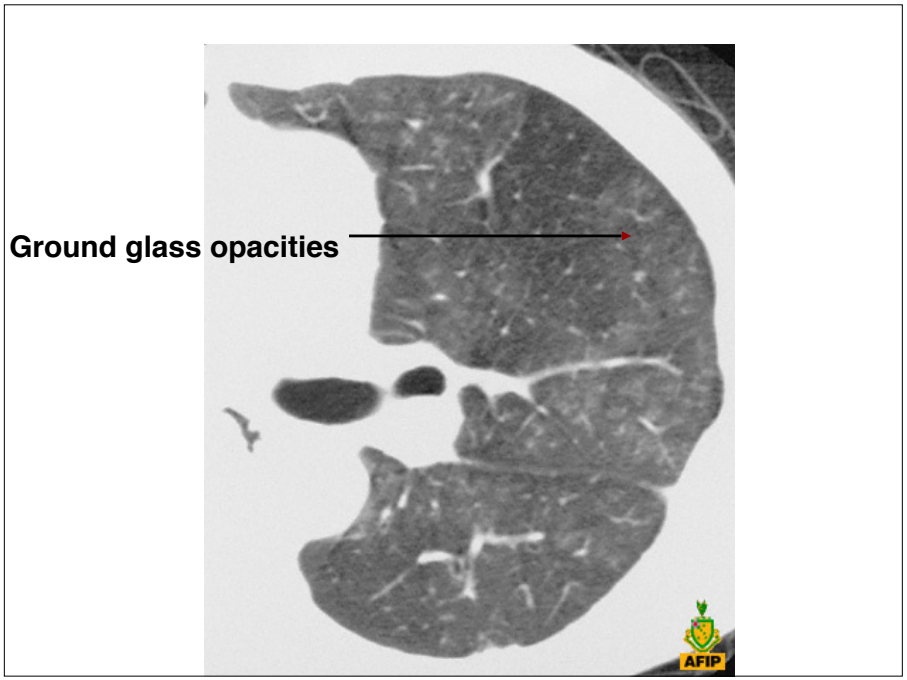
HRCT Terminology

- Opacities
  - Lines (reticular)
  - Dots or Circles (nodules)
  - Patches
- Attenuation (shade of gray)
  - Consolidation – obscures underlying vessels
  - Ground glass – does not obscure underlying vessels









Probability of Histologic Diagnosis of DOLD

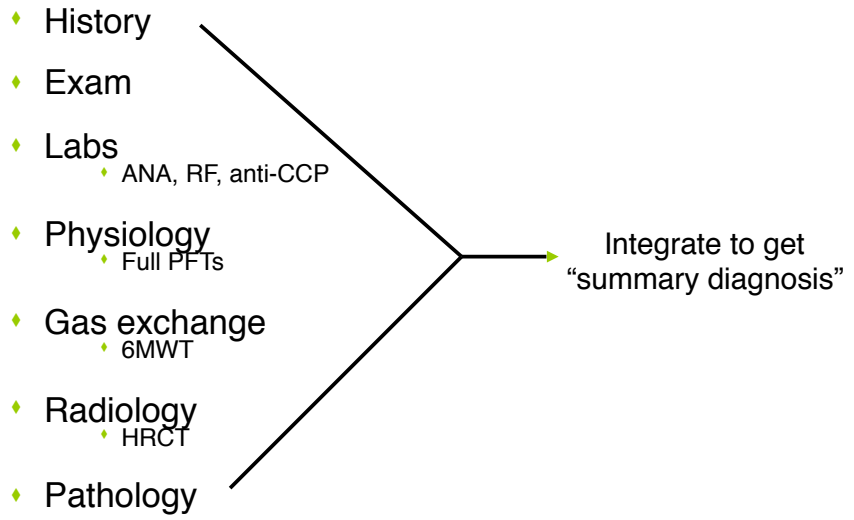
	Transbronchial Biopsy	Surgical Biopsy
1. Granulomatous diseases		
2. Malignant tumors/lymphangitic		
3. DAD (any cause)		
4. Certain infections	Often	
5. Alveolar proteinosis		
6. Eosinophilic pneumonia		
7. Vasculitis		
8. Amyloidosis		
9. EG/HX/PLCH	Sometimes	
10. LAM		
11. RB/RBILD/DIP		
12. UIP/NSIP/LIP COP		
13. Small airways disease	Never	
14. PHT and PVOD		

Courtesy of Kevin O. Leslie, MD.

Criteria for Diagnosis of IPF

- Major criteria
  - Exclude known causes of ILD
  - Abnormal PFT
  - Typical findings on HRCT
  - No findings on transbronchial lung biopsy or BAL supporting other dx
- Minor criteria
  - Age > 50 yr
  - Insidious onset of SOB
  - Durations of symptoms in excess of 3 months
  - "Velcro" rales at lung bases

Putting it all Together



IPF/UIP

- Age: usually greater than 50
- Male to female ratio: between 1:1 and 2:1
- 75% have a smoking history
- Insidious exertional dyspnea which is disabling over time
- Nonproductive cough - refractory to antitussive medication
- Fever, malaise and arthralgia reported in 50%

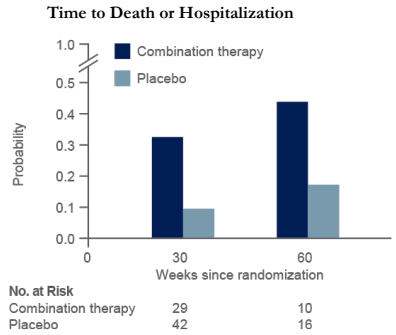
Therapy for ILD

- Not all patients require therapy
  - General: treat clinically significant, progressive dz
- All therapeutic regimens require monitoring
- Glucocorticoids no longer the mainstay
- Steroid-sparing / immune-suppressing / immunomodulatory / cytotoxic agents

Table 6. Selected Clinical Trials for IPF Over the Last Decade			
Drug	**Mechanism of Action**	**Name of Clinical Trial**	**Result**
Bosentan	Endothelin receptor antagonist	BUILD -1 & BUILD -3	Negative
Macitentan	Endothelin receptor antagonist	MUSIC	Negative
Ambrisentan	Endothelin receptor-A antagonist	ARTEMIS- IPF	Negative
Warfarin	Anticoagulant	ACE-IPF	Negative
Sildenafil	Phosphodiesterase-5 inhibitor	STEP –IPF	Negative
Imatinib mesylate	Tyrosine kinase inhibitor	Imatinib-IPF	Negative
Interferon	Immunoregulation	INSPIRE, NCT00047645	Negative
Etanercept	TNF alpha inhibitor	NCT00063869	Negative
Octreotide	Somatostatin analog	FIBROSISAND	Negative
Pirfenidone	Antifibrotic	CAPACITY I &II	Equivocal
Azathioprine+steroids+NAC	Immuneregulator	PANTHER	Negative

2012:
Triple Therapy Harmful for IPF Patients

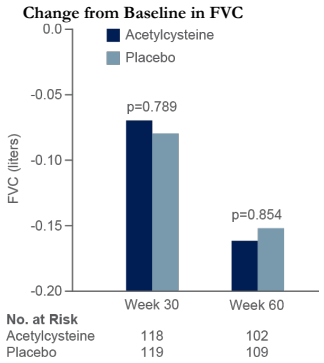
The PANTHER-IPF trial examined the safety and efficacy of a triple therapy with prednisone, azathioprine and N-acetylcysteine.[1]
-Randomized, double-blind, placebo-controlled
-Stopped after 50% of the data had been collected (n=155, 32 weeks) because of increased mortality and hospitalization in the triple therapy group



1.The IPF Clinical Research Network. *NEJM* 2012;366:1968-77.

2014:
NAC Treatment in IPF under Evaluation

The PANTHER-IPF trial was partially continued to examine the safety and efficacy of N-acetylcysteine (NAC) treatment versus placebo.[1]
Randomized, double-blind, placebo-controlled, n=264
Endpoints: FVC, mortality and acute exacerbations
At the end of the trial (60 weeks), no significant benefits in favor of N-acetylcysteine treatment could be shown



1.The IPF Clinical Research Network. *NEJM* 2014:370:2093-101.
2.Oldham J. M, et al. *AJRCCM* 191;2015:A2162.

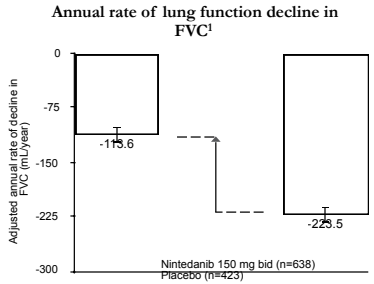
2014/2015:
Two Medications Available for the Treatment of IPF

In the past two years, the first medications for the treatment of IPF have been approved in the United States

- In October 2014, the US Food and Drug Administration (FDA) approved two new drugs, nintedanib and pirfenidone, for the treatment of patients with IPF in the United States
- In January 2015, the European Commission (EC) approved nintedanib for the European Union (pirfenidone has been approved since 2011)

Overview Nintedanib

- FDA and EMA approvals were based on the phase 3 INPULSIS® 1 & 2 trials and data from the Phase 2 TOMORROW trial
- The randomized, double-blind and placebo-controlled INPULSIS® trials enrolled a broad range of patient types with 1066 patients in total



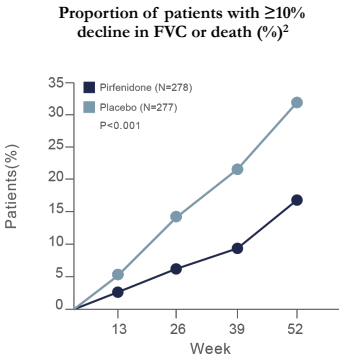
109.9 mL/year; (95% CI: 75.9, 144.0); p<0.0001

Nintedanib is now included in the 2015 update of the ATS/ERS/JRS/ALAT evidence based guidelines for the treatment of IPF.

Richeldi L, et al. *NEJM* 2014;370:2071–2082.

Overview Pirfenidone

- Approved since 2011 by European Commission based on evidence from the CAPACITY trials (Phase 3; n = 779)[1]
- FDA approval in 2014 was based on the phase 3 ASCEND trial (highly selected population with 64% screen failure rate; n = 555)[2]



Pirfenidone is now included in the 2015 update of the ATS/ERS/JRS/ALAT evidence based guidelines for the treatment of IPF.

1. Noble P. W, et al. *Lancet* 2011;377:1760-1769.
2. King T. E, et al. *NEJM* 2014;370:2083-2092.

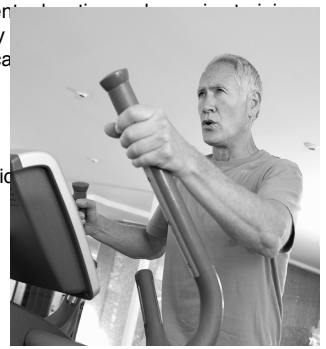
Gauging Response

- Subjective- symptoms
- FVC
- DLCO
- 6MWT
- Not HRCT unless scenario mandates

Pulmonary Rehabilitation and BOC Beneficial for Patients with ILD

Pulmonary rehabilitation improves exercise capacity and dyspnea perception[1]
An individualized PR program for ILD patients including patien
for 12 weeks with 3 sessions per week showed a significantly
dyspnea perception (assessed through 6MWD and Borg's sca

"Bundle of Care" (BOC) in the initial year of management in IPF may improve survival in patients with IPF[2]
BOC included: clinic visits with pulmonary function tests at 6-month intervals; 6-minute walk test, screening trans-thoracic
rehabilitation and anti-reflux therapy at initial visit



1. Rastogi S. A, et al. *AJRCCM* 191;2015:A2020.
2. Kulkarni T, et al. *AJRCCM* 191;2015:A4401.

Lung Transplant

- Second most frequent disease for which transplant is performed
- Five year survival after transplant is 40-50% (compared to 53% of all txp pts)
- Better outcomes with bilateral lung txp
- Living donor lobar lung txp (LDLLT)
  - Options for those likely to die waiting SLT
  - Lower lobe donation by healthy relatives

Agents	2015 Guideline	2011 Guideline
Anticoagulation (warfarin)	⊘	⚠
Prednisone + AZA + NAC	⊘	⚠
Ambrisentan	⊘	N/A
Imatinib	⊘	N/A
Nintedanib	👍	N/A
Pirfenidone	👍	⚠
Dual endothelin R antags (bosentan)	⚠	⊘
PDE-5 inhibitors (sildenafil)	⚠	N/A

http://www.atsjournals.org/doi/suppl/10.1164/rccm.201506-1063ST

Agents	2015 Guideline	2011 Guideline
Antacid therapy	👍	👍
N-Acetylcysteine monotherapy	⚠	⚠
Antipulmonary HTN therapy	N/A	N/A
Lung transplantation	N/A	N/A

STABILITY = SUCCESS

I don't want my ILD patients leaving clinic thinking they don't have a serious condition

I don't want my ILD patients leaving clinic thinking they should go home, sit on their couch and die