Idiopathic Pulmonary Fibrosis (IPF)

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Interstitial Lung Disease

Clinical features:

- Cough
- Dyspnea
- **Restrictive PFTs** (low VC, TLC)

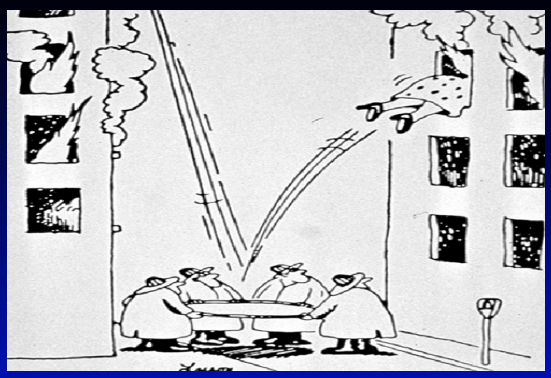
Idiopathic pulmonary fibrosis (IPF)

- Most common interstitial lung disease
- Usual interstitial pneumonia (UIP) pattern on surgical lung biopsy

Nonspecific Interstitial Pneumonia

- Clinical features overlap with IPF
- Much better response to therapy
- Need surgical lung Bx to diagnose

- Distinguishing IPF from NSIP and other ILDs important since prognosis and treatment differ



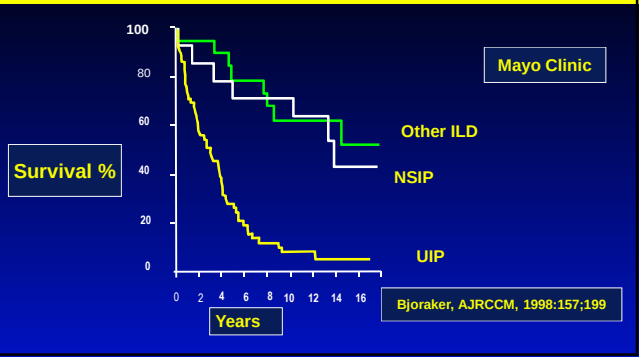
Idiopathic Pulmonary Fibrosis (IPF)

- Affects older adults (> 55 y)

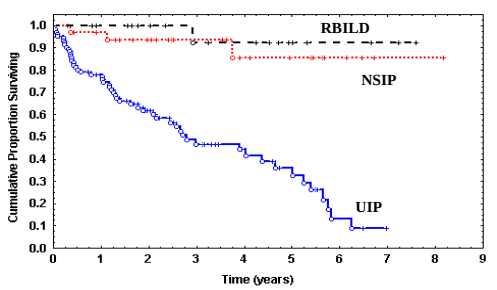
  Progression inevitable

- Mortality > 70% at 5 years

Survival: UIP, NSIP, other ILDs

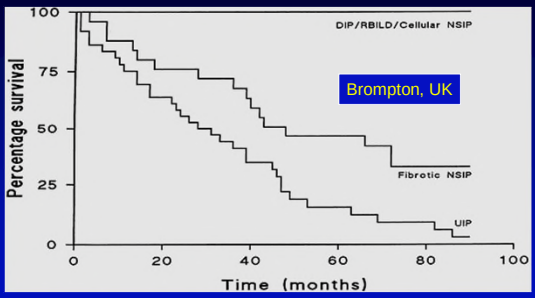


Survival in UIP, NSIP and RBILD

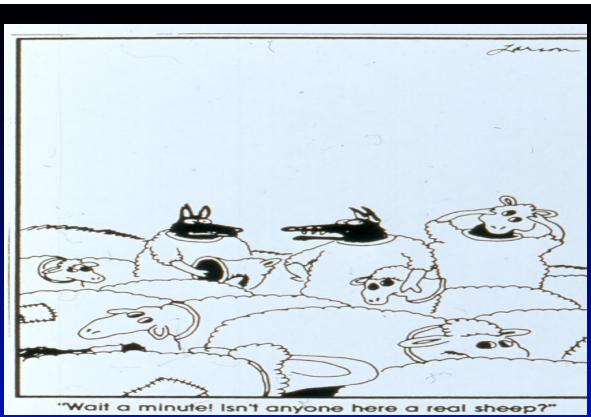


Flaherty, *Eur Respir J* 2002;19;275

Survival in UIP and NSIP



Nicholson, *AJRCCM* 2000; 162: 2213



Interstitial Lung Diseases

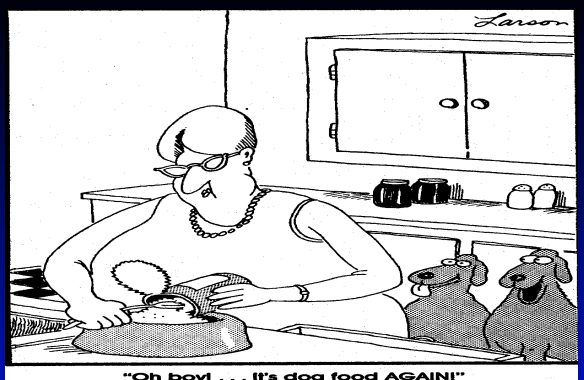
> 150 causes

- Infectious (TB, fungi, PCP)
- Environmental (HP, metals; drugs)
- Connective Tissue Disease (CTD)
- Idiopathic (IPF, LIP, OP, sarcoidosis)

Interstitial Lung Disease

Laboratory evaluation

- Serologies for CTD
- Hypersensitivity pneumonia
- Infection (PPD, histo, cocci IgG, IgM)



"Oh boy! . . . It's dog food AGAIN!"

Environmental History

- **Exposures** (work, home, hobbies)
- **Toxins, irritants** (drugs, chemicals)
- **Cigarette smoking** (LCH; DIP, RB)

Drugs may cause pulmonary toxicity

- Amiodarone
- Methotrexate
- Nitrofurantoin
- Sulfasalazine
- Chemotherapy
  - (Bleomycin; busulfan)

Pneumoconioses

- Beryllium
- Silica
- Hard metals (cobalt, tungsten carbide)
- Asbestos

IPF: Differential Diagnosis

- Connective Tissue Disease
- Pneumoconiosis
- Chronic Hypersensitivity Pneumonia

Pulmonary Complications of CTD

- Interstitial Lung Disease may affect all CTDs
- Histological patterns same as idiopathic IPs
- Multiple patterns may be observed

Distinguishing IPF from other ILDs

- Thin section HRCT scans
- Surgical (VATS) Lung Biopsy

Interstitial Lung Disease (ILD)

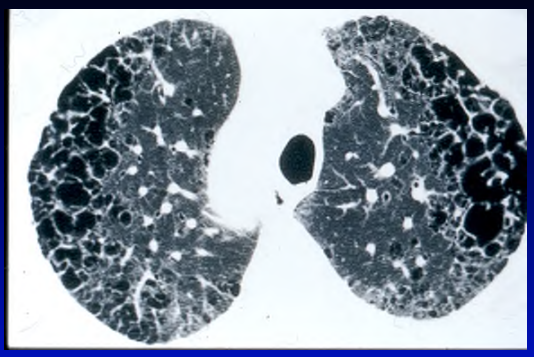
- Surgical lung biopsy ***essential*** to diagnose some ILDs (e.g., NSIP, HP)
- Thin-section HRCT (1-2 mm) can diagnose *some, but not all*, cases IPF

Interstitial Lung Disease (ILD)

- Thin-section (1-2 mm) HRCT in some cases may be pathognomonic

  (e.g., IPF with honeycombing)

Honeycomb cysts (UIP)

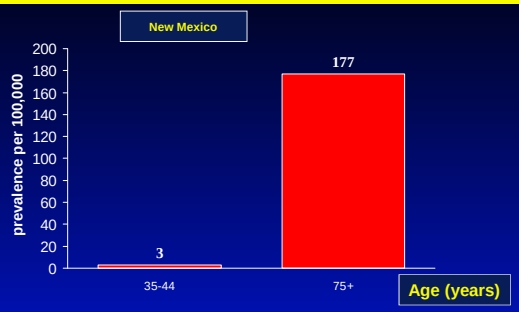


- Epidemiology of Idiopathic Pulmonary Fibrosis (IPF)

Idiopathic Pulmonary Fibrosis

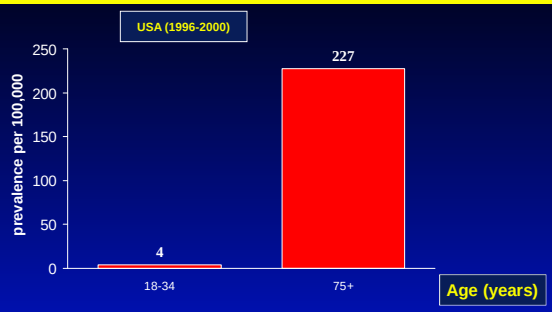
- Primarily affects elderly
- Not seen in children

Prevalence IPF according to age



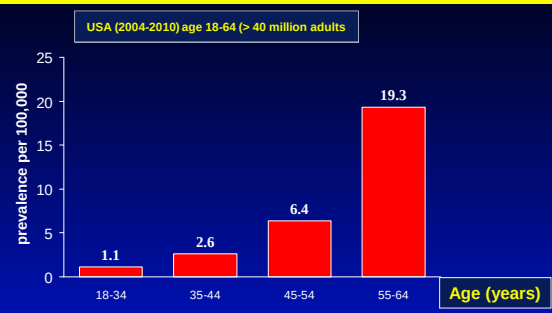
Coultas, *AJRCCM* 1994:150;967

Prevalence IPF according to age



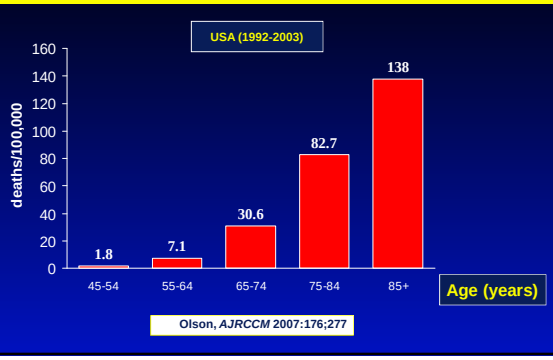
Raghu, *AJRCCM* 2006:174;810

Prevalence IPF according to age



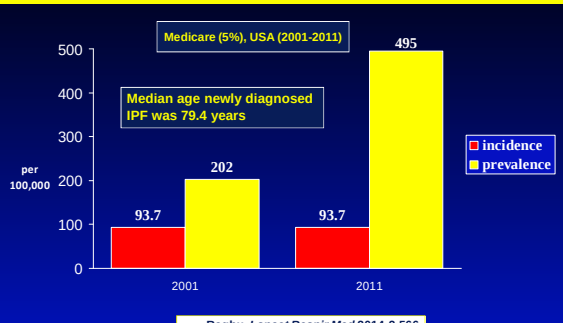
Raghu, *Eur Respir J* 2016:48;179

Deaths due to IPF according to age



Olson, *AJRCCM* 2007:176;277

IPF: incidence and Prevalence > 65 years



Raghu, *Lancet Respir Med* 2014:2;566

Risk Factors for IPF

- Age (predominantly elderly)
- More common in males
- Genetic (familial)

Chu, *Semin Respir Crit Care Med* 2016:37;321

Idiopathic Pulmonary Fibrosis

Familial IPF

- 0.5 to 10% of cases of IPF
- No clear genetic mutation
- Isolated mutations in kindreds

Familial IPF: Mutations

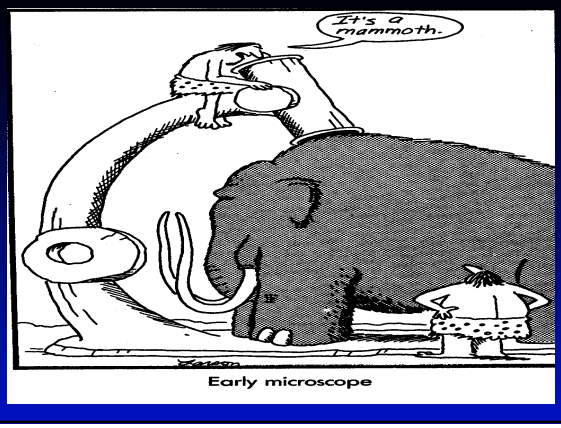
- Surfactant protein C and A
- Mucin genes (MUC5B)
- Telomerase (hTERT and hTR)

Chu, *Semin Respir Crit Care Med* 2016:37;321

Risk Factors for IPF

- Smoking
- Occupational (dusts, metals, sand)
- Gastroesophageal reflux (?)

Chu, *Semin Respir Crit Care Med* 2016:37;321



Early microscope

IPF: Histology

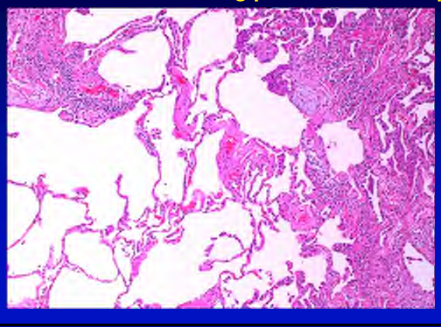
- Usual Interstitial Pneumonia (UIP pattern)

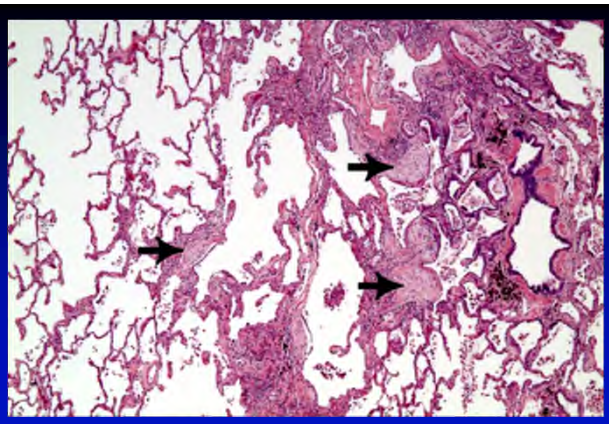
Usual Interstitial Pneumonia (UIP)

- Heterogeneity
- Fibroblastic foci
- Honeycombing

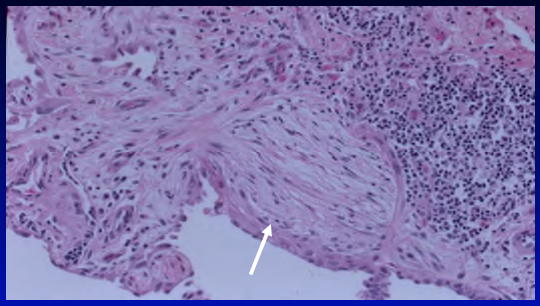
Pathology of UIP/IPF

Transition to uninvolved lung present in the biopsy



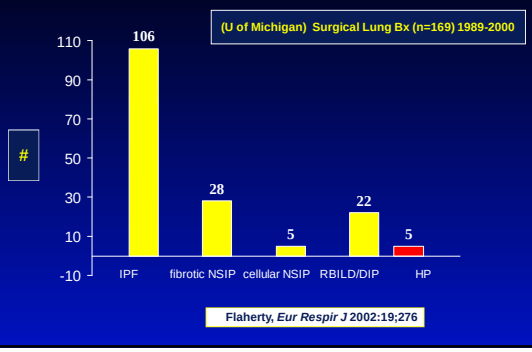


Fibroblastic focus-high power



- Distinguishing IPF from NSIP and other ILDs important since prognosis and treatment differ

Chronic Interstitial Lung Disease



Flaherty, *Eur Respir J* 2002:19;276

Prognosis of IPF/UIP and Other ILDs

Surgical biopsies n=169 (U Mich, 1989-2000)

- Histological UIP most important feature determining mortality
- UIP/IPF RR mortality 28.5 compared to other ILDs ($p < 0.001$)

Flaherty, *Eur Respir J* 2012:19;276

- Surgical (VATS) lung biopsy is *required* to diagnose NSIP

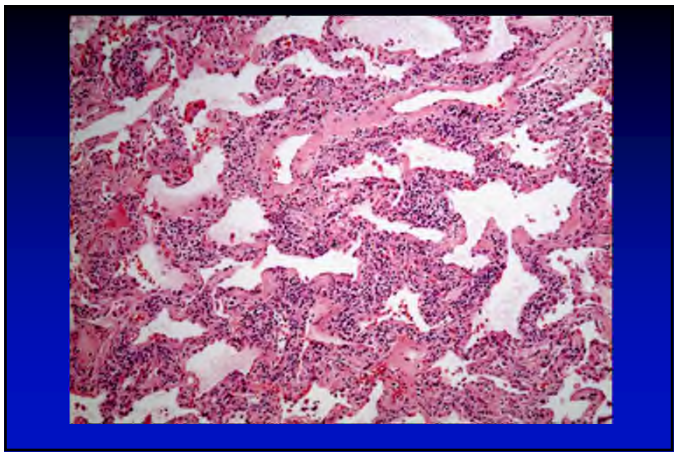
Nonspecific interstitial pneumonia

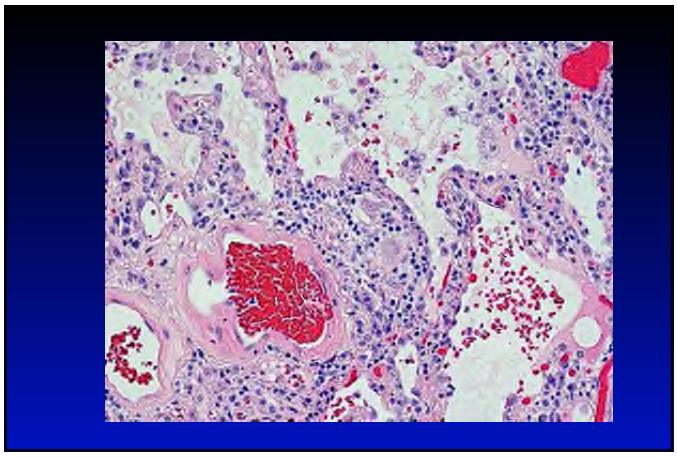
Histological criteria for NSIP:

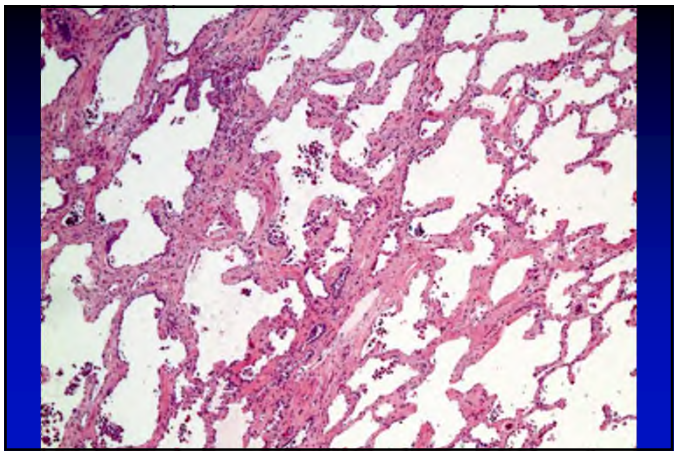
- Temporal homogeneity
  (lesions of same age)
- Lacks features of other IIPs
  (UIP, AIP, DIP/RBILD)

Nonspecific interstitial pneumonia

- Cellular and fibrotic types
- Fibrotic worse prognosis



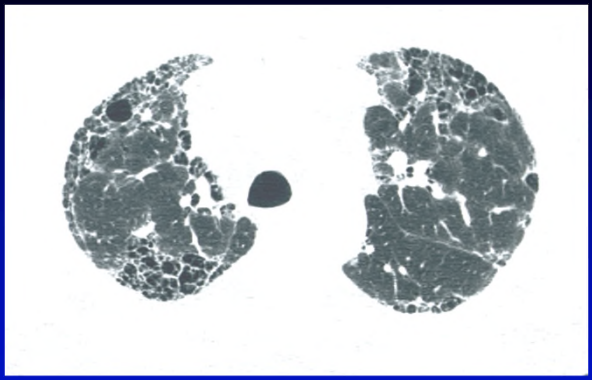




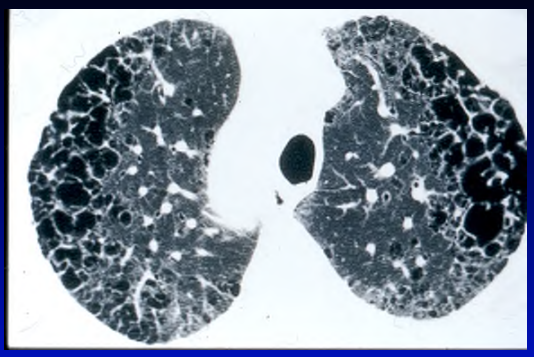
- Can CT distinguish IPF from NSIP?

UIP/IPF: HRCT Features

- Patchy, heterogeneous
- Lower lobes, subpleural
- Reticular (linear) lines
- Honeycomb cysts
- Ground glass minimal or absent



Honeycomb cysts (UIP)



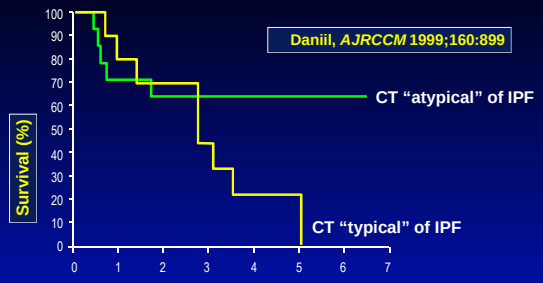
CT criteria (IPF vs NSIP)

Key discriminatory elements:

- **Honeycombing**
- **Ground glass opacities**

- **"Typical" CT (i.e., with honeycombing) is specific for UIP/IPF and *eliminates need for surgical lung biopsy***

HRCT appearance vs survival



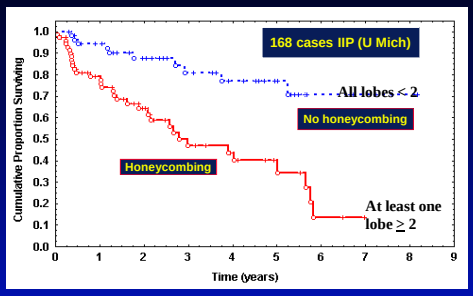
- **Honeycombing reflects:**
  - more advanced disease
  - worse prognosis

168 cases IIP (U Mich)

- Honeycomb change in *any lobe* (CT-fib ≥ 2) associated with higher mortality

Flaherty, *Eur Resp J* 2002:19;276

CT fib ≥ 2 worse survival



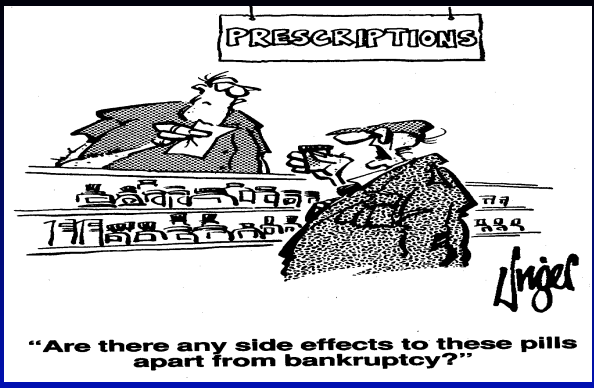
Flaherty *Eur Respir J* 2002:19;275

NSIP and IPF Overlapping Features

- Distinguishing *fibrotic* NSIP from IPF is difficult
- Treatment differs (NSIP vs IPF)

Nonspecific Interstitial Pneumonia (NSIP)

- Immunosuppressive therapy and/or prednisone may be effective, particularly in cellular variants of NSIP



"Are there any side effects to these pills apart from bankruptcy?"

Idiopathic Pulmonary Fibrosis (IPF)

- Immunosuppressive therapy or prednisone **not effective for IPF** and ***may be harmful***

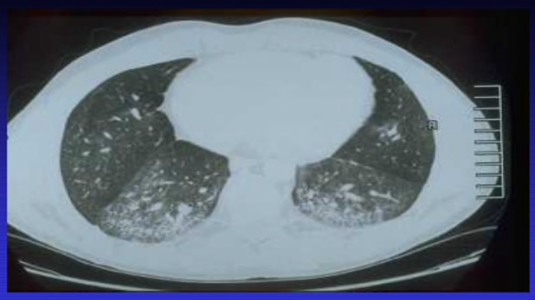
Idiopathic Pulmonary Fibrosis (IPF)

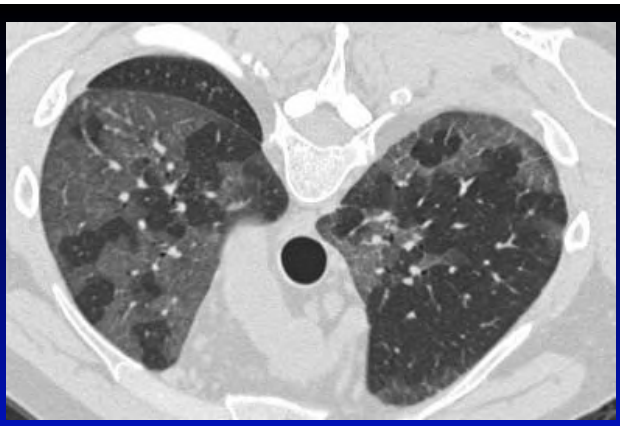
- **Median survival ~ 4 yrs**
- Medical therapy (anti-fibrotic agents) marginally effective
  - **? survival advantage**

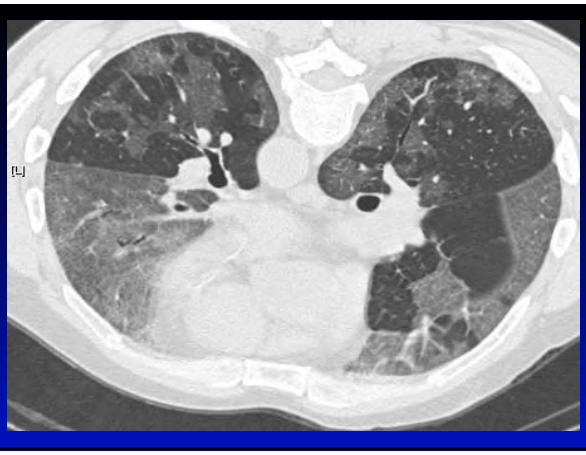
CT criteria (IPF vs NSIP)

- Ground glass opacities strongly favor NSIP

Nonspecific interstitial pneumonia







HRCT scan: NSIP vs IPF

	IPF	NSIP
• Honeycombing	+++	+/-
• Ground glass	+/-	+++

IPF and NSIP

Discriminatory features

- Age
- HRCT (GGO vs HC)

IPF and NSIP

Discriminatory features

- Older age favors IPF
- Honeycombing (IPF)

Discriminating IPF from other ILDs

UIP (n=97); other ILD (n=38) (1995-2006)

- No honeycombing on HRCT
- No connective tissue disease
- All had surgical lung biopsy

Fell, *AJRCCM* 2010:181;832

Discriminating IPF from other ILDs

- Age and extent CT interstitial score most predictive of IPF
- Gender, desaturation, distance walked on 6MWT, PFTs did *not* discriminate IPF from other ILD

Fell, *AJRCCM* 2010:181;832

Age Powerful Predictor of IPF

- Age ≥ 70 yrs, > 95% had IPF
- Age ≥ 75 yrs, 100% had IPF

Fell, *AJRCCM* 2010:181;832

- "Atypical" CT patterns are non-specific; could represent IPF or NSIP or other ILDs
- **Need surgical lung biopsy**

Surgical Lung Biopsy

22,000 SLB in USA for ILD (2000-2011)

Mortality (in-hospital):

- 1.7% (elective)
- 16.0% (non-elective)

Hutchinson, *AJRCCM* 2016 (May 15);1161

Surgical (VATS) Lung Biopsy

- Risk excessive if advanced age or unstable or high 02 requirements

Idiopathic Pulmonary Fibrosis

- Clinical course
- Prognostic factors
- Best parameters to follow

Idiopathic Pulmonary Fibrosis (IPF)

- Median survival ~ 4 yrs
- Medical therapy (anti-fibrotic agents) marginally effective
  - ? survival advantage

Idiopathic Pulmonary Fibrosis (IPF)

- immunosuppressive agents or steroids are *not* beneficial
- **Lung Transplant Best Option**

Therapy for IPF

- **Early referral for lung transplant**
- **May lose "window for transplant"**

- IPF: course highly variable and unpredictable

IPF: Pulmonary Function Tests

Serial PFTs 3-4 months

- Spirometry, DLCO
- 6-minute walk tests

- Course may be fulminant even after initial indolent progression
- PFTs may be stable for prolonged periods
- Acute exacerbations may be fatal

Increased Mortality if:

- Older age
- Severe impairment PFTs
- Hypoxemia
- Honeycombing on CT
- Pulmonary hypertension

PFTs in IPF: Prognostic Significance

- Not surprisingly, severe impairment or decline in FVC, DL_{CO}, oxygenation, or 6MWD predicts worse mortality

Changes in FVC at 6 months

IPF (n=80); NSIP (n=29) (U Mich)

> 10% decline FVC at 6 months independent predictor mortality (HR 2.47)

Flaherty, *AJRCCM* 2003:168;543

Serial PFTs Predict Prognosis

IPF (n=81) (Denver)

> 10% decline FVC at 6 or 12 mo assoc with higher mortality

Collard, *AJRCCM* 2003:168;538

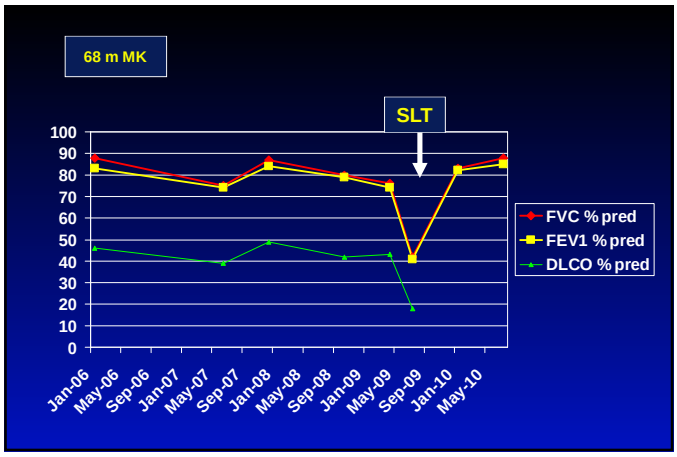
Serial PFTs Predict Prognosis

IPF (n=131); NSIP (n=48) (Korea)

> 10% decline FVC at 6 mo best predictor of mortality

Jegal, *AJRCCM* 2005:171;169

- Declining FVC warrants consideration for lung transplant
- However, fatalities can occur even with prolonged stability

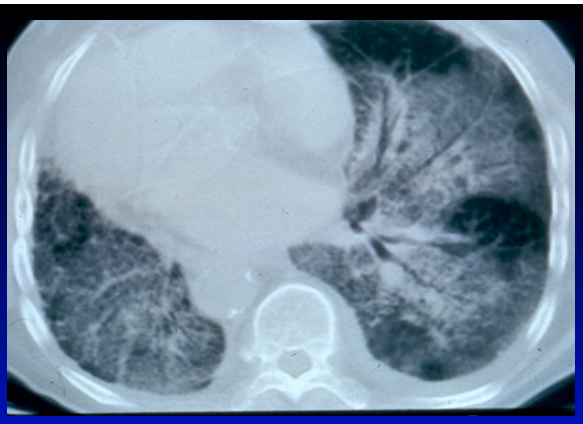


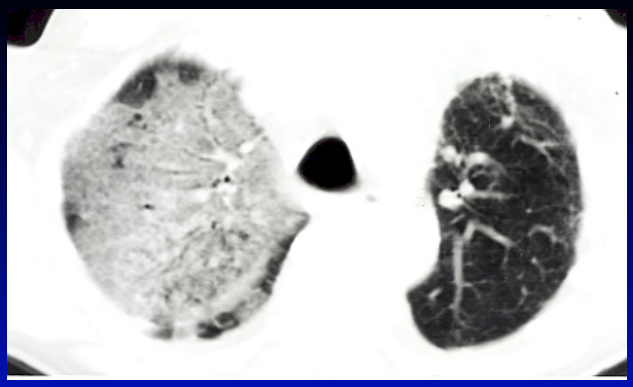
Complications of IPF

- Acute exacerbations of IPF
- Pulmonary Hypertension
- Lung cancer (5-15%)

Acute Exacerbations of IPF

- Incidence 19-35% < 2 years
- Resembles ARDS
- Diffuse lung damage (DAD)
- Ground glass opacities (CT)





Risk Factors for AE-IPF

- More severe disease
- Prednisone or IS therapy
- Winter months
- Pulmonary hypertension
- Thoracic surgery (VATS)

? Cause for AE-IPF

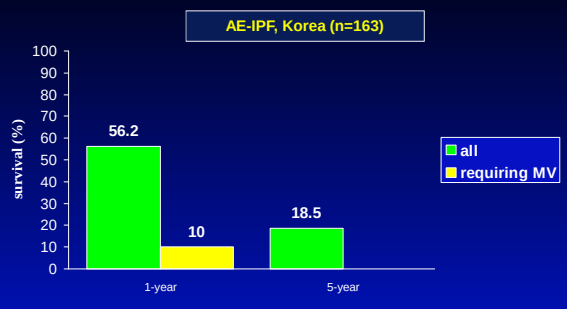
? Infection (viral)

AE- IPF: Treatment

- Optimal treatment not clear
- Randomized trials lacking
- ? value of steroid therapy

Song, *Eur Respir J* 2011:39;357

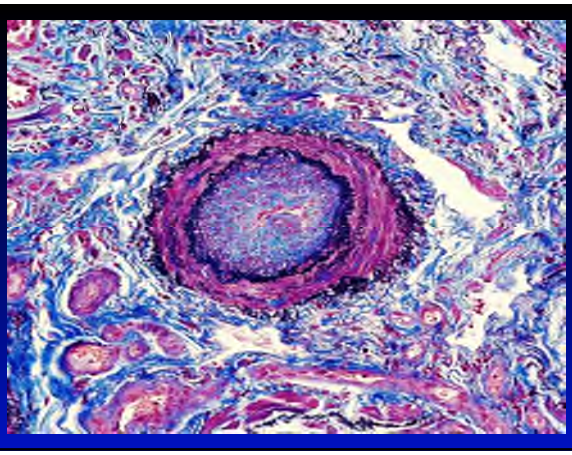
Prognosis of AE-IPF



Song, *ERJ* 2011:39;357

Severe AE-IPF

- Prognosis if require MV poor (> 90% mortality)
- Unless on lung transplant list, consider DNI/DNR



Pulmonary Hypertension

- PAH in 28-84% of patients with advanced IPF
- PAH markedly worsens survival

Pulmonary hypertension in IPF

- 2-D echo to assess sPAP
- ? If treatment of PAH affects outcome
- Anecdotal responses to PAH-specific agents but RCT lacking

PAH due to lung disease

- PAH-specific therapy may have role in patients with *severe* PAH as a bridge to lung transplantation

Shino, *Semin Respir Crit Care Med* (Oct 2013)

Idiopathic Pulmonary Fibrosis

- Medical Treatment
- Lung Transplant

Idiopathic Pulmonary Fibrosis

- Course and "pace" of disease highly variable
- Lung transplant 1st line but only for selected patients
- Who should receive novel agents?

Treatment of IPF

- High dose prednisone was standard of care for > 40 years *despite no evidence for benefit*

Idiopathic Pulmonary Fibrosis

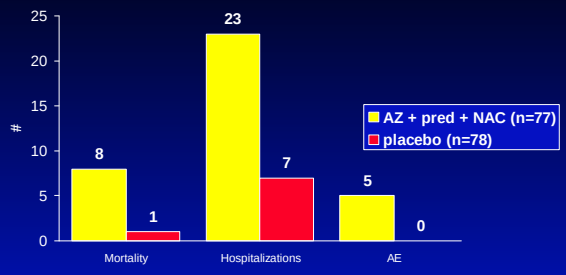
- Despite lack of randomized, placebo-controlled trials, prednisone + azathioprine used for more than 3 decades

Azathioprine for IPF

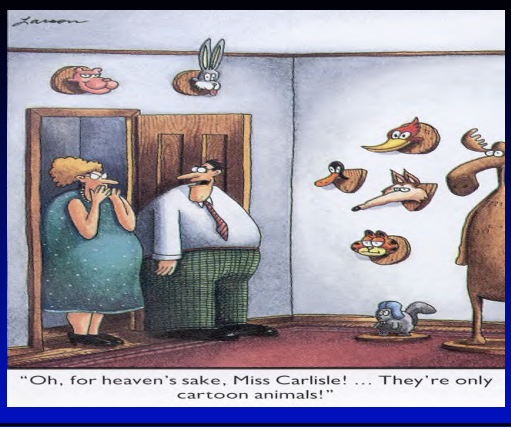
- PANTHER Study (IPFnet) terminated early (Oct 2011) due to higher mortality and morbidity in AZA + prednisone + NAC arm

N Engl J Med (May 24, 2012):366:1968

PANTHER STUDY: IPF



N Engl J Med 2012:366:1968



Therapy of IPF

- Other immunosuppressive agents *unlikely* to be efficacious
  - e.g., mycophenolate mofetil

IPF: which target?

- Multiple "targets" (cells, cytokines, inflammation, fibrosis)
- Mechanisms of injury and fibrosis overlap and redundant

FDA Approved Oct 15, 2014

- Pirfenidone (*Esbriet*)
- Nintedanib *(Ofev)*

Treatment of IPF

- In clinical trials, **pirfenidone and nintedanib** slow *rate of decline* but differences small (ΔFVC 2-4%) at 1 yr

Pirfenidone for IPF

CAPACITY I (006) (n=344)

- pirfenidone (oral) vs placebo

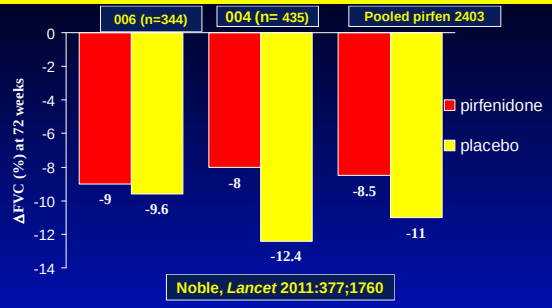
CAPACITY II (004) (n=435)

Noble, *Lancet* 2011:377:1760

Pirfenidone for IPF

- No difference survival, DL_{CO}, 6MWT, Δ02 sat
- **Less decline FVC at 72 weeks**
  [Capacity II (004); not Capacity I (006)]

CAPACITY (004 + 006): ΔFVC 72 wks



Noble, *Lancet* 2011:377;1760

Pirfenidone for IPF

ASCEND Trial (52 wks):

- **Primary end-point:**

  disease progression

  (Δ FVC > 10% or death)

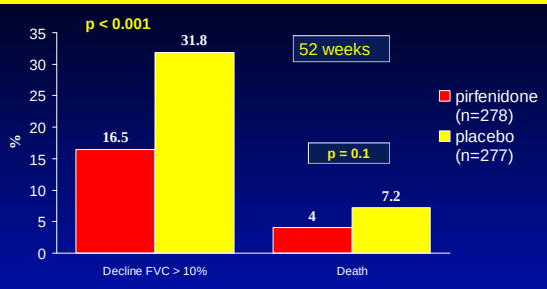
King, *N Engl J Med* May 29, 2014

Pirfenidone for IPF

- Pirfenidone 2403 mg/day (n=278)
- Placebo (n=277)

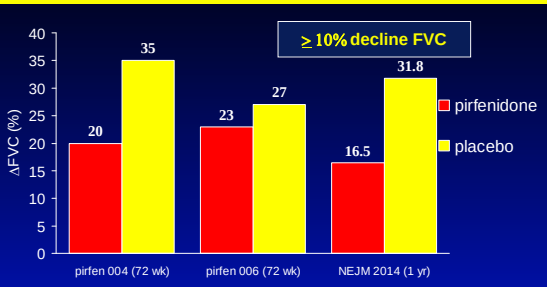
King, *N Engl J Med* 2014:370;2083

Pirfenidone (ASCEND) Study



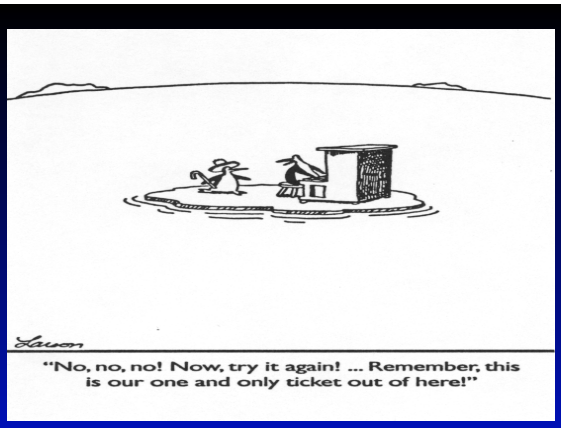
King, *N Engl J Med* 2014:370;2083

Pirfenidone Trials (IPF)



Pirfenidone for IPF

- Slows rate of progression
- Impact on mortality uncertain



- Nintedanib (*Ofev*)
  - Tyrosine kinase inhibitor

Nintedanib for IPF

Nintedanib 150 mg bid or placebo

52 weeks; change FVC

IMPULSIS-1 (n=511)

IMPULSIS-2 (n=544)

Richeldi, *N Engl J Med* 2014:370:2072

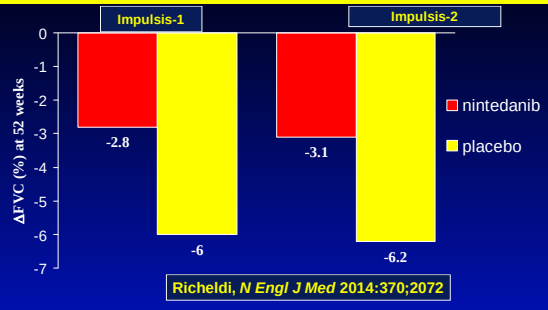
Nintedanib for IPF

Primary endpoint:

- Δ FVC at 52 weeks

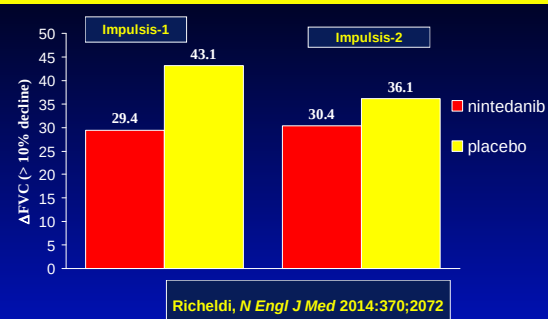
Richeldi, *N Engl J Med*, May 29, 2014

Nintedanib: ΔFVC 52 wks



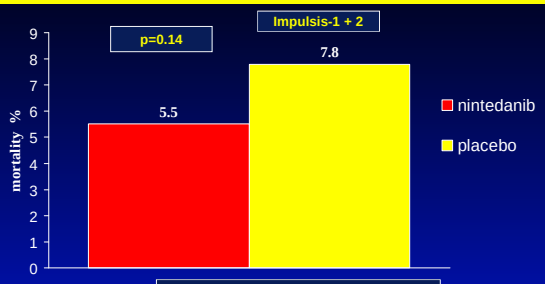
Richeldi, *N Engl J Med* 2014:370;2072

Nintedanib: ΔFVC 52 wks



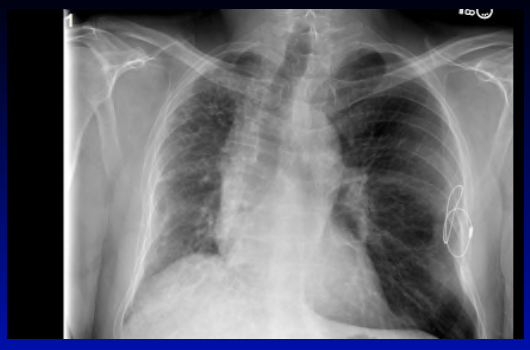
Richeldi, *N Engl J Med* 2014:370;2072

Nintedanib: Mortality 52 wks



Richeldi, *N Engl J Med* 2014:370;2072

RJ

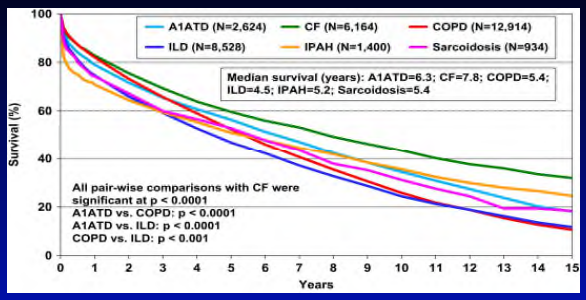


Lung transplant for IPF

- Survival post-LT worse in IPF compared to other diagnoses

(may reflect age, comorbidities)

Survival by Diagnosis (Jan 1990-June 2011)



Yusen, *J Heart Lung Transplant* Oct 2013 :32(10)

Single or Bilateral Transplant?

- Bilateral lung transplant for IPF, *but not COPD*, confers modest improvement in survival

Single or Bilateral Transplant?

USA, LT (adults) May 2005-Dec 31, 2012:

- IPF (n=4,134) (SLT in 49%)
- COPD (n=3,174) (SLT in 41%)

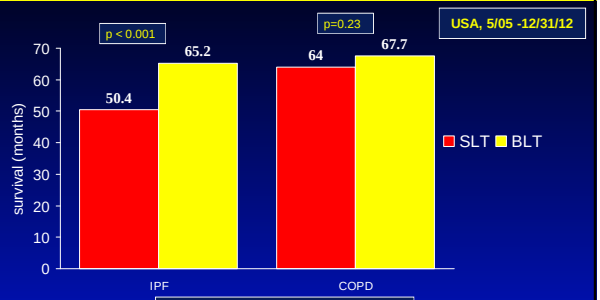
Schaffer, *JAMA* 2015:313;936

Single or Bilateral Transplant?

- After controlling for confounders, **BLT better survival than SLT in IPF** but *not* in COPD

Schaffer, *JAMA* 2015:313;936

Single or Bilateral LT?



Schaffer, *JAMA* 2015;313;936

Lung Transplant for Elderly

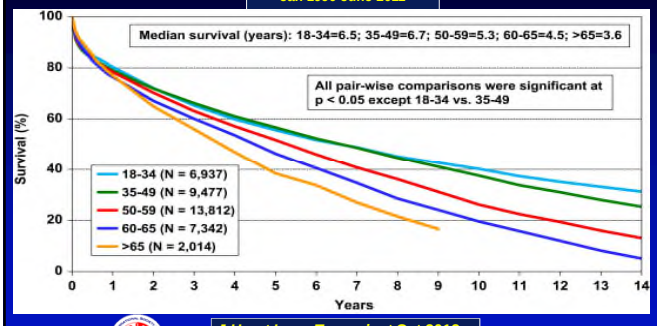
ISHLT Guidelines (2006)

- Age > 65 "relative contraindication" to LT

Orens, *JHLT* 2006:25;745

Survival by LT Recipient Age (Adults)

Jan 1990-June 2011



J Heart Lung Transplant Oct 2013

Lung Transplant for Elderly

UNOS, 1999-2006

8,363 adult LT recipients

Mortality (30 d, 90 d, 1-yr)

Weiss *J Am Coll Surg* 2009:208;400

Lung Transplantation