**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

- Mayo Clinic
- Bjoraker, AJRCCM, 1998:157/199
Survival in UIP, NSIP and RBILD

Survival in UIP and NSIP

Nicholson, AJRCM 2000; 162: 2213

"Wait a minute! Isn’t anyone here a real sheep?"
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)
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)

- Primarily affects elderly
- Not seen in children
Prevalence IPF according to age

Coultas, AJRCCM 1994:150;967

New Mexico

Prevalence per 100,000

Age (years)

35-44 75+

3 177

18-34 75+

4 227

USA (1999-2000)

Prevalence per 100,000

Age (years)

Raghu, AJRCCM 2006:174;810

USA (2004-2010) age 18-64 (> 40 million adults)

Prevalence per 100,000

Age (years)

Raghu, Eur Respir J 2010:46;179
Deaths due to IPF according to age

IPF: incidence and Prevalence > 65 years

Risk Factors for IPF

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

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

Prognosis of IPF/UIP and Other ILDs

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
Honeycombing
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

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
Idiopathic Pulmonary Fibrosis (IPF)

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

- 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

<table>
<thead>
<tr>
<th>Feature</th>
<th>IPF</th>
<th>NSIP</th>
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<tr>
<td>Honeycombing</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Ground glass</td>
<td>+/-</td>
<td>+++</td>
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</tbody>
</table>

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 O2 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)
<table>
<thead>
<tr>
<th>Serial PFTs Predict Prognosis</th>
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<tbody>
<tr>
<td><strong>IPF (n=81) (Denver)</strong></td>
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<tr>
<td>&gt; 10% decline FVC at 6 or 12 mo assoc with higher mortality</td>
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<td>Collard, <em>AJRCCM</em> 2003:168;538</td>
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<th>Serial PFTs Predict Prognosis</th>
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<td><strong>IPF (n=131); NSIP (n=48) (Korea)</strong></td>
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<tr>
<td>&gt; 10% decline FVC at 6 mo best predictor of mortality</td>
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<tr>
<td>Jegal, <em>AJRCCM</em> 2005:171;169</td>
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- 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**

- AE-IPF, Korea (n=163)
- 1-year: 56.2%
- 5-year: 18.5%

*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

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


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**PANTHER STUDY: IPF**

- Bars showing mortality, hospitalizations, and AE for AZ + pred + NAC (n=77) vs. placebo (n=78)


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"Oh, for heaven’s sake, Miss Carlisle! ... They’re only cartoon animals!"
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 ($\Delta $FVC 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

- No difference survival, DL$_{CO}$, 6MWT, $\Delta $O2 sat
- Less decline FVC at 72 weeks
  [Capacity II (004); not Capacity I (006)]
CAPACITY (004 + 006): ΔFVC 72 wks

Pirfenidone for IPF

ASCEND Trial (52 wks):
- Primary end-point:
  - disease progression
  - (Δ FVC > 10% or death)

Pirfenidone for IPF

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

% decline FVC > 10% or death by 52 weeks

- Pirfenidone (n=278)
- Placebo (n=277)

King, N Engl J Med 2014:370;2083

$p < 0.001$

Pirfenidone Trials (IPF)

% of patients with ≥10% decline in FVC

- Pirfen 004 (72 wk)
- Pirfen 006 (72 wk)
- NEJM 2014 (1 yr)

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)

Nintedanib for IPF

Primary endpoint:

- Δ FVC at 52 weeks


Nintedanib: ΔFVC 52 wks


Nintedanib: ΔFVC 52 wks

Nintedanib: Mortality 52 wks

Richeldi, N Engl J Med 2014;370;2072

p=0.14

Impulse-1 + 2

5.5

Richeldi, N Engl J Med 2014;370;2072

"Whoa! Watch where that thing lands—we'll probably need it."
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?**

![Bar chart showing survival rates for single (SLT) and bilateral (BLT) lung transplants.](Schaffer_JAMA_2015;313:936)

**Lung Transplant for Elderly**

**ISHLT Guidelines (2006)**

- Age > 65 “relative contraindication” to LT

![Image showing survival by LT recipient age (Adults).](Orens_JHLT_2006:25:745)

**Survival by LT Recipient Age (Adults)**

*Median survival (years): 18-34=6.5; 35-49=6.7; 50-59=5.3; 60-65=4.3; >65=3.6*

*All pair-wise comparisons were significant at p < 0.05 except 18-34 vs. 35-49*
Lung Transplant for Elderly

UNOS, 1999-2006

8,363 adult LT recipients

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


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Lung Transplantation

Age as predictor of mortality

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