Pulmonary Fibrosis Workshop
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A 65-year-old former smoker presents with chronic cough and progressive dyspnoea. Which of the following modalities is the best diagnostic test for IPF?

- Transbronchial biopsy
- Pulmonary function test
- HRCT of the lungs
- Chest radiograph
Question 2

A 70-year-old man with IPF has significant resting hypoxia and is not experiencing an acute exacerbation. Which of the following treatments is recommended by the 2011 treatment guidelines?

- Mechanical ventilation
- Long-term oxygen therapy
- Corticosteroids
- Etanercept
Definition

- **Interstitial lung disease (ILD)**, also known as *diffuse parenchymal lung disease (DPLD)* and refers to a group of lung diseases affecting the interstitium (the tissue and space around the air sacs of the lungs)
- Commonly this however, involves the surrounding alveolus and the respiratory/terminal bronchioles
- As the disease progresses this involves the pulmonary vasculature leading to pulmonary hypertension
- The end result is healing with fibrosis, worsening hypoxia and right heart failure
Alveolus

Connective tissue
- Alveolar sacs
- Alveolar duct
  - Mucous gland
  - Mucosal lining

Capillary beds
- Pulmonary vein
- Pulmonary artery
- Alveoli
- Atrium
Pathophysiology

• In the current hypothesis regarding the pathogenesis of idiopathic pulmonary fibrosis, exposure to an inciting agent (e.g. smoke, environmental pollutants, environmental dust, viral infections, gastroesophageal reflux disease, chronic aspiration) in a susceptible host may lead to the initial alveolar epithelial damage.

• In idiopathic pulmonary fibrosis, it is believed that after injury, aberrant activation of alveolar epithelial cells provokes the migration, proliferation, and activation of mesenchymal cells with the formation of fibroblastic/myofibroblastic foci, leading to the exaggerated accumulation of extracellular matrix with the irreversible destruction of the lung parenchyma.
Incidence/Prevalence

Worldwide, the incidence of idiopathic pulmonary fibrosis is estimated to be 10.7 cases per 100,000 persons per year for males and 7.4 cases per 100,000 persons per year for females.

The prevalence of idiopathic pulmonary fibrosis is estimated to be 20 cases per 100,000 persons for males and 13 cases per 100,000 persons for females.
Symptoms

- Progressive breathlessness on exertion
- Dry cough
- Rarely systemic symptoms of arthralgia
- Fatigue
- Low grade fever
Signs

- Fine end inspiratory crackles
- Clubbing in 25-50% of cases
- Desaturating and cyanosis after exertion
- Para sternal heave
- Loud P2
- Very rarely a Graham-Steele murmur
- Signs of right heart failure
Investigations

- **Blood**
  - FBC, U&E, LFT, CRP, ESR
  - TPMT if Azathioprine considered
  - Auto antibodies if relevant
  - Total IgE, RAST, Precipitins if relevant
  - Arterial Gas analysis

- **Radiology**
  - CXR
  - HRCT / CTPA

- **Physiological**
  - Simple spirometry (FEV₁/FVC)
  - Lung volumes
  - Gas Transfer (TLCO)
  - 6MWT
  - Overnight oximetry / Sleep study

- **Echocardiography**
- **Cardiac catheter (Right heart)**
- **Bronchoscopy**
- **Surgical Lung Biopsy (SLB)**
Spirometry and Full Lung Function
Flow volume loops and patterns

HRCT in UIP
HRCT in NSIP
UIP vs NSIP
ΔΔ on HRCT

A - Fibrotic variant of NSIP
B - Cellular variant of NSIP
C - Classical UIP
Pathology
Histology
3 Histological variants in NSIP

A - Cellular predominant
B - Mixed
C - Fibrosis predominant
Classification

- Known causes (Not IIP)
- Unknown cause (Possible IIP)

IIP- Idiopathic Interstitial Pneumonia
Classification - known causes 1

- **Inhaled substances**
  - Inorganic: Silicosis, Asbestosis, Berylliosis
  - Organic: Hypersensitivity pneumonitis (EAA)

- **Drug induced**
  - Antibiotics
  - Chemotherapeutic drugs
  - Antiarrhythmic agents
  - Statins

- **Connective tissue disease**
  - Systemic sclerosis
  - Polymyositis
  - Dermatomyositis
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
Classification - known causes 2

- Infection
  - Atypical pneumonia
  - Pneumocystis pneumonia (PCP)
  - Tuberculosis
  - Respiratory Syncytial Virus

- Idiopathic
  - Sarcoidosis
  - Lymphangioleiomyomatosis
  - Langhans giant cell histiocytosis

- Toxic agents
  - Paraquat poisoning (proliferative alveolitis)

- Inherited disorders
  - Tuberous Sclerosis
  - Hermansky-Pudlak syndrome

- Malignancy
  - Lymphangitis carcinomatosis
Classification of unknown causes

Based on clinico-radiologic-pathologic criteria seven entities are defined:

- idiopathic pulmonary fibrosis (UIP)
- nonspecific interstitial pneumonia (NSIP)
- cryptogenic organizing pneumonia (COP/BOOP)
- acute interstitial pneumonia (AIP)
- respiratory bronchiolitis interstitial lung disease (RBILD)
- desquamative interstitial pneumonia (DIP)
- lymphoid interstitial pneumonia (LIP)
Diagnosis with biopsy

- Diagnosis requires clinical findings compatible with interstitial lung disease in combination with either characteristic radiologic findings or a pathologic diagnosis of UIP on surgical lung biopsy.

- Generally, lung biopsy is only undertaken when its risks are outweighed by the potential benefits of identifying an alternative, treatable disease process.

- A lung biopsy is particularly useful in a young patient to give a prognosis.

- If clinical features are inconsistent, then biopsy required.
Diagnosis without biopsy

Based on this evidence, the 2002 ATS/ERS Multidisciplinary Consensus Statement on the Idiopathic Interstitial Pneumonias proposed the following criteria for establishing the diagnosis of IPF without a lung biopsy:

Major criteria (all 4 required):
- Exclusion of other known causes of interstitial lung disease (drugs, exposures, connective tissue diseases)
- Abnormal pulmonary function tests with evidence of restriction (reduced vital capacity) and impaired gas exchange (pO$_2$, p(A-a)O$_2$, DLCO)
- Bibasilar reticular abnormalities with minimal ground glass on high-resolution CT scans
- Transbronchial lung biopsy or bronchoalveolar lavage (BAL) showing no features to support an alternative diagnosis

Minor criteria (3 of 4 required):
- Age > 50
- Insidious onset of otherwise unexplained exertional dyspnea
- Duration of illness > 3 months
- Bibasilar inspiratory crackles
Suggested Diagnostic Algorithm

1. History, physical examination, lung function tests, chest radiograph

2. Not IIP
   - e.g. associated collagen vascular disease, environmental, drug-related etc.

3. Possible IIP
   - HRCT

4. Confident HRCT diagnosis of IPF with consistent clinical features and BAL±TBB that excludes other diseases

5. Atypical clinical or HRCT features for IPF
   - TBB or BAL?
     - Surgical lung biopsy

6. Features diagnostic of another DPLD e.g. PLCH
   - If nondiagnostic
     - TBB, BAL or other

7. Suspected other DPLD

8. IPF
9. DIP
10. RB-ILD
11. AIP
12. COP
13. NSIP
14. LIP
15. Non-IIP confirmed
## ΔΔ between HRCT and Pathology

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Histologic Pattern</th>
<th>Usual Radiographic Features</th>
<th>Typical Distribution on CT</th>
<th>Typical CT Findings</th>
<th>CT Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPF/CFA</td>
<td>UIP</td>
<td>Basal-predominant reticular abnormality with volume loss</td>
<td>Peripheral, subpleural, basal</td>
<td>Reticular, honeycombing Traction bronchiectasis/bronchiolectasis; architectural distortion. Focal ground glass</td>
<td>Asbestosis Collagen vascular disease Hypersensitivity pneumonitis Sarcoidosis UIP, DIP, COP Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>NSIP, provisional</td>
<td>NSIP</td>
<td>Ground glass and reticular opacity</td>
<td>Peripheral, subpleural, basal, symmetric</td>
<td>Ground glass attenuation Irregular lines Consolidation</td>
<td>Infection, vasculitis, sarcoidosis, alveolar carcinoma, lymphoma, eosinophilic pneumonia, NSIP</td>
</tr>
<tr>
<td>COP</td>
<td>OP</td>
<td>Patchy bilateral consolidation</td>
<td>Subpleural/peribronchial</td>
<td>Patchy consolidation and/or nodules</td>
<td>Hydrostatic edema Pneumonia Acute eosinophilic pneumonia</td>
</tr>
<tr>
<td>AIP</td>
<td>DAD</td>
<td>Progressive diffuse ground glass density/consolidation</td>
<td>Diffuse</td>
<td>Consolidation and ground glass opacity, often with lobular sparing. Traction bronchiectasis later Ground glass attenuation Reticular lines</td>
<td>RB-ILD Hypersensitivity pneumonitis Sarcoidosis, PCP DIP NSIP Hypersensitivity pneumonitis Sarcoidosis, lymphangitic carcinoma, Langerhans’ cell histiocytosis</td>
</tr>
<tr>
<td>DIP</td>
<td>DIP</td>
<td>Ground glass opacity</td>
<td>Lower zone, peripheral predominance in most</td>
<td>Bronchial wall thickening Centrilobular nodules Patchy ground glass opacity Centrilobular nodules, ground glass attenuation, septal and bronchovascular thickening, thin-walled cysts</td>
<td></td>
</tr>
<tr>
<td>RB-ILD</td>
<td>RB</td>
<td>Bronchial wall thickening; ground glass opacity</td>
<td>Diffuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIP</td>
<td>LIP</td>
<td>Reticular opacities, nodules</td>
<td>Diffuse</td>
<td></td>
<td></td>
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</tbody>
</table>

**Definition of abbreviations:** AIP = acute interstitial pneumonia; CFA = cryptogenic fibrosing alveolitis; COP = cryptogenic OP; DAD = diffuse alveolar damage; DIP = desquamative interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; LIP = lymphoid interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; PCP = *Pneumocystis carinii* pneumonia; RB-ILD = respiratory bronchiolitis-associated interstitial lung disease; UIP = usual interstitial pneumonia.
<table>
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<tr>
<th></th>
<th>Idiopathic pulmonary fibrosis</th>
<th>Nonspecific interstitial pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of illness</strong></td>
<td>Chronic (&gt;12 months)</td>
<td>Subacute to chronic</td>
</tr>
<tr>
<td><strong>Frequency of diagnosis</strong></td>
<td>47–64%</td>
<td>14–36%</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Poor response to any treatment</td>
<td>Corticosteroid responsiveness</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>50–70% mortality within 5 yrs</td>
<td>&lt;15% mortality in 5 yrs</td>
</tr>
<tr>
<td><strong>Chest radiograph</strong></td>
<td>Bilateral reticular opacities in lower zones; volume loss plus honeycombing</td>
<td>Bilateral hazy and reticular opacity</td>
</tr>
<tr>
<td><strong>HRCT</strong></td>
<td>Peripheral, subpleural, basal predominance; reticular opacities; honeycombing; traction bronchiectasis; architectural distortion</td>
<td>Peripheral, basal, symmetrical; ground-glass attenuation; consolidation; traction bronchiectasis; lower lobe volume loss</td>
</tr>
<tr>
<td><strong>Key histological features</strong></td>
<td>UIP pattern</td>
<td>NSIP pattern: cellular, fibrotic</td>
</tr>
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HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia.
Grading of severity

- CT fibrosis scoring
- 6MWD and VC a useful guide
- On serial testing VC is easier and more meaningful as DLCO can be quite variable
- Function more useful but use with caution!
- The following is a guide only
  - Mild  DLCO 60% to LLN and/or VC 60% to LLN
  - Moderate  DLCO 40% to 59% and /or VC 40% to 59%
  - Severe  DLCO < 39% and /or VC < 39%
Prognosis

- For UIP median survival is about 3 years
- A few cases survive about 7 years since diagnosis
- Bear in mind, they may have had the disease for about a year prior to diagnosis
- Generally 50-70% are dead in 5 years
- UIP diagnosed on biopsy with inconsistent clinical and radiological features fare better
- Other forms, particularly if they respond to standard therapy have a favourable prognosis
- Exacerbations of IIP can be deadly, with a 50-60% mortality within 30 days
Complications of IPF

The following are complications that can be seen in patients with idiopathic pulmonary fibrosis:

- Pulmonary hypertension
- Acute exacerbation of pulmonary fibrosis
- Respiratory infection
- Acute coronary syndrome
- Thromboembolic disease
- Adverse medication effects
- Lung cancer
Long Term Management

- Confirm Diagnosis
- Inform probable prognosis and treatment options
- Assess for suitability for a transplant

Monitoring - FVC (10% 6/12) TLCO (35% at ∆/15% 12/12)
  - 6MWT (Desaturating to less than 88%)

- Specific drug therapy
- Smoking cessation and vaccination
- Enrolment to research trials
- Oxygen – What is the upper limit?
- Palliative care and end of life decisions
Drug therapies

No single drug or combinations have shown significant improvement in prognosis

- Steroids - High dose Prednisolone
- NAC - 600mg tds as anti-oxidant activity
- Vitamin C - Theoretical prolongation of NAC
- PPI - ? Micro aspiration / steroid protection
- Azathioprine - 2mg/Kg
- Cyclophosphamide - 2mg/Kg
- MMF - No strong evidence yet
- Pirfenidone - CAPACITY trial data
- Bosentan/Ambrisentan - BUILD 1-3, ARTEMIS
- TNFα
- INFγ
- Tyrosine Kinase inhibitors - Imatinib 600mg od has not shown any benefit
Acute Exacerbations

The following are diagnostic criteria for an AE-IPF

- Previous or concurrent diagnosis of idiopathic pulmonary fibrosis
- Unexplained worsening or development of dyspnoea within 30 days
- High-resolution computed tomography (HRCT) scan with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with a usual interstitial pneumonia pattern
- Worsening hypoxemia from a known baseline arterial blood gas measurement
- No evidence of pulmonary infection by endotracheal aspiration or bronchoalveolar lavage (BAL)
- Exclusion of alternative causes, including left-sided heart failure, pulmonary embolism, and an identifiable cause of acute lung injury
Acute Exacerbation Management

- Often a terminal event
- Most patients die from complications of IPF rather than with IPF
- Urgently try and identify a treatable cause
  - Typical Infection (Broad spectrum antibiotics)
  - Atypical; needs BAL if stable, blood tests (Cotrimoxazole / Clarithromycin)
  - HRCT+ CTPA (? Ground glass ? “pulmonary embolism’’)
  - Echocardiogram (? Pulmonary hypertension ? LVF)
  - ECG/Troponin (? Acute Coronary Syndrome)
- If no treatable cause inform patient/ family
- Consider a therapeutic trial of Methyl Prednisolone
- Often what happens is oxygen, opiates, sedatives
- If patient survives on to chronic pathway again!
Medicolegal

Note the following medicolegal pitfalls

- Making the diagnosis of IPF without excluding other causes of interstitial lung disease
- Failure to discuss the pros, cons, risk, benefits, and alternatives for the treatment of IPF
- Failure to disclose adverse medication effects of therapies that are used to treat IPF
- Cases diagnosed as Asbestosis need a Coroner’s PM and family need to be aware
- Problems occur in cases diagnosed as Asbestosis and PM suggests IPF
- A commoner problem is one of pleural plaques developing fibrosis later on
Questions?