Idiopathic Pulmonary Fibrosis
“Can we treat? Should we treat?”

Dr. Joe Churton
MBBS BSc FRACP
Respiratory and Sleep Physician

North Coast Respiratory & Sleep Clinic
Who am I?

- Dr Joe Churton
- Born and bred on the NSW South Coast – Gerringong.
- A regular Ocean man when younger – Lifeguard, Lifesaver, Surfing
- Married with 3 beautiful kids
- BSc (Chemistry Major) University of Wollongong 2001
- MBBS University of Queensland 2005
- FRACP – Respiratory and Sleep Physician 2014
- 2015 – Consultant Physician Princess Alexandra Hospital
- 2016 – VMO Lismore Base Hospital
  - Consulting rooms at St Vincents Private
  - Respiratory Function Lab
  - Associate with Queensland Sleep Disorders Unit
Mr DP

- 67 y.o. male referred for progressive dyspnoea over 6/12
- Immigrated from Burma with his family in early 2000’s
- Retired farmer (Burma) and restaurant worker (Australia) who made guitars in his home workshop. He had also been learning to play the guitars himself.
- Immediately prior to Christmas 2014, he was asymptomatic.
- June 2015, he is now only able to manage approx. 150-200m on the flat, and a single flight of stairs.
Medical History
- Chronic Hep B infection, found during immigration screening
- Hypertension

Medications
- Irbesartan

Ex-smoker: Ceased 20 years previously, 20 Pack years in total.

Examination findings
- Bilateral basal fine crackles
- SpO2 92% on room air
- Wife “His hands were very rough, but they are now better with moisturiser”
CT: bilateral basal ground glass changes with septal thickening and associated early honeycombing and traction bronchiectasis.

Consistent with Usual Interstitial Pneumonia.
Patterns of Disease

Usual Interstitial Pneumonia

HRCT features from ATS/ERS guidelines:
- HRCT is a very sensitive, but not 100%, technique for the diagnosis of UIP with a low false-positive rate.
- Typical HRCT appearances of UIP by expert radiologists are correct in the majority (>90%) of cases.
- Peripheral and lower lobe predominance
- Honeycombing
- Reticular opacities and traction bronchiectasis
- Lung architectural distortion which reflects fibrosis
- Absence of other features

Pathological changes
- Fibroblastic infiltrates, mature fibrosis and honeycombing.
Patterns of Disease
Patterns of Disease

- **Non-specific Interstitial Pneumonia**
  - **HRCT**
    - Bilateral ground glass opacification
    - Some reticular pattern
    - Honeycombing is rare but can be seen in the fibrosing variant
    - Doesn’t favour the lower lobes.
  - **Pathology**
    - NSIP is characterised by a mild to moderate uniform chronic inflammation with lymphocytes and type II pneumocyte hyperplasia in the setting of preserved lung architecture.
    - Absence of fibroblastic foci, granuloma, and eosinophilic granulocytes.
Disease association for these patterns

- Considerable overlap
- UIP = idiopathic pulmonary fibrosis
- NSIP: Causes
  - Highly associated with connective tissue diseases.
  - Hypersensitivity pneumonitis
  - Lymphocytic Interstitial Pneumonia
  - Don’t forget malignancy.
Lung Function Testing

- **Spirometry**
  - Reduced, particularly the FVC.

- **Gas diffusion**
  - Reduced in keeping with diffuse loss of lung units. Depends on pattern and course of Disease.

- **Lung Volumes**
  - Reduced. All values.

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### Spirometry (Flow Volume Loop)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Lower Limit</th>
<th>Pre</th>
<th>Post</th>
<th>% Pre</th>
<th>% Post</th>
<th>Change%</th>
<th>Z-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (L)</td>
<td>0.69</td>
<td>0.92</td>
<td>0.95</td>
<td>61.1%</td>
<td>82.8%</td>
<td>1.6%</td>
<td>-1.48</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>1.16</td>
<td>1.15</td>
<td>1.15</td>
<td>61.9%</td>
<td>81.8%</td>
<td>-0.1%</td>
<td>-1.66</td>
</tr>
<tr>
<td>FEV1 % FVC%</td>
<td>64.90</td>
<td>80.02</td>
<td>82.31</td>
<td>105.8%</td>
<td>108.9%</td>
<td>3.0%</td>
<td>1.03</td>
</tr>
<tr>
<td>MEF75/25 (L/s)</td>
<td>0.97</td>
<td>0.89</td>
<td>1.14</td>
<td>37.6%</td>
<td>46.3%</td>
<td>10.7%</td>
<td>-1.44</td>
</tr>
<tr>
<td>PEF (L/s)</td>
<td>2.56</td>
<td>2.56</td>
<td>2.44</td>
<td>51.6%</td>
<td>49.2%</td>
<td>-2.4%</td>
<td>-2.60</td>
</tr>
</tbody>
</table>

### Single Breath Diffusion Capacity (DLCO)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Lower Limit</th>
<th>Post-BD</th>
<th>Post %</th>
<th>Z-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLCO Single Breath mmol/(min*Pa)</td>
<td>4.05</td>
<td>2.73</td>
<td>45.7</td>
<td>-2.78</td>
</tr>
<tr>
<td>DLCO_SB/VA mmol/(min<em>Pa</em>L)</td>
<td>0.88</td>
<td>1.35</td>
<td>91.5</td>
<td>0.85</td>
</tr>
<tr>
<td>DLCOc Single Breath mmol/(min<em>Pa</em>L)</td>
<td>4.05</td>
<td>2.73</td>
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<td>0.88</td>
<td>1.35</td>
<td>91.5</td>
<td>0.85</td>
</tr>
<tr>
<td>VA Single Breath L</td>
<td>3.89</td>
<td>2.02</td>
<td>51.9</td>
<td>0.0</td>
</tr>
</tbody>
</table>

### Lung Volumes

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Lower Limit</th>
<th>Post-BD</th>
<th>Post %</th>
<th>Z-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC (L)</td>
<td>3.06</td>
<td>2.51</td>
<td>62.0</td>
<td>-2.56</td>
</tr>
<tr>
<td>VC (L)</td>
<td>1.27</td>
<td>1.13</td>
<td>57.7</td>
<td>-1.97</td>
</tr>
<tr>
<td>FRCpleth (L)</td>
<td>1.59</td>
<td>1.54</td>
<td>64.0</td>
<td>-1.74</td>
</tr>
<tr>
<td>RV (L)</td>
<td>1.28</td>
<td>1.38</td>
<td>75.1</td>
<td>-1.31</td>
</tr>
<tr>
<td>RV % TLC</td>
<td>33.51</td>
<td>54.90</td>
<td>127.4</td>
<td>2.02</td>
</tr>
</tbody>
</table>

### Trends

<table>
<thead>
<tr>
<th>Measurement Parameter</th>
<th>Spiro</th>
<th>FVC (L)</th>
<th>FEV1 (L)</th>
<th>Body TLC (L)</th>
<th>Diff SB (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>04-Apr-16</td>
<td>1.15</td>
<td>0.95</td>
<td>2.51</td>
<td>2.73</td>
</tr>
</tbody>
</table>
Interstitial Lung Diseases

- Diffuse parenchymal lung disease
  - DPLD of known cause (e.g., drugs) or association (e.g., collagen vascular disease)
  - Idiopathic interstitial pneumonias
  - Granulomatous DPLD, e.g., sarcoidosis
  - Other forms of DPLD, e.g., LAM, HX, etc.

  - Idiopathic pulmonary fibrosis
  - IIP other than idiopathic pulmonary fibrosis

    - Desquamative interstitial pneumonia
    - Respiratory bronchiolitis interstitial lung disease
      - Acute interstitial pneumonia
      - Cryptogenic organising pneumonia
    - Non-specific interstitial pneumonia (provisional)
    - Lymphocytic interstitial pneumonia
If UIP is confirmed either via HRCT or Biopsy, then the diagnosis of IPF can be made.

15 to 18 per 100,000 person years.

Median survival of newly diagnosed patients with IPF is 2-3 years.

The median age of presentation is 70 years, with the disease uncommon below the age of 50 years. It is more common in men with a male:female ratio of 1.5-2.0:1.

In the majority, IPF will progress over a period of months and years towards a terminal phase.

A general management approach comparable to that of patients with inoperable lung cancer is appropriate. This includes providing patient information and support, palliative treatment of symptoms and complications of the disease and best supportive care; both for young patients with IPF awaiting lung transplant, patients in clinical trials of novel therapy and patients with advanced disease facing-end-of-life issues.
Staging and Prognosis

• Co-existing disease such as emphysema and pulmonary hypertension are associated with a poorer outcome.

**TABLE 7. SELECTED FEATURES ASSOCIATED WITH INCREASED RISK OF MORTALITY IN IDIOPATHIC PULMONARY FIBROSIS**

<table>
<thead>
<tr>
<th>Baseline factors*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of dyspnea†</td>
</tr>
<tr>
<td>D_{LCO} &lt; 40% predicted</td>
</tr>
<tr>
<td>Desaturation ≤ 88% during 6MWT</td>
</tr>
<tr>
<td>Extent of honeycombing on HRCT†</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Longitudinal factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in level of dyspnea†</td>
</tr>
<tr>
<td>Decrease in Forced Vital Capacity by ≥ 10% absolute value</td>
</tr>
<tr>
<td>Decrease in D_{LCO} by ≥ 15% absolute value</td>
</tr>
<tr>
<td>Worsening of fibrosis on HRCT†</td>
</tr>
</tbody>
</table>

* Definition of abbreviations: 6MWT = 6-minute-walk test; D_{LCO} = diffusion capacity for carbon monoxide; HRCT = high-resolution computed tomography.

† Baseline forced vital capacity is of unclear predictive value.

† Currently, there is no uniformity in approach to quantification.
Figure 4. Natural history of IPF. There appear to be several possible natural histories for patients with IPF. The majority of patients experience a slow but steady worsening of their disease ("Slow progression"). Some patients remain stable ("Stable"), while others have an accelerated decline ("Rapid progression"). A minority of patients may experience unpredictable acute worsening of their disease (lightning bolt), either from a secondary complication such as pneumonia, or for unrecognized reasons. This event may be fatal or may leave patients with substantially worsened disease. The relative frequency of each of these natural histories is unknown.
Risk Factors

- Smoking history of more than 20 pack-years
- Environmental exposures: A significantly increased risk has been observed after exposure to metal dusts (brass, lead, and steel) and wood dust (pine). Farming, raising birds, hair dressing, stone cutting/polishing, and exposure to livestock and to vegetable dust have also been associated with IPF.
- Microbes: EBV, HepC, CMV, HHV-7 and HHV-8 have been implicated but no definitive conclusions can be made.
- Several studies have suggested that abnormal acid GORD, through its presumed association with microaspiration, is a risk factor for IPF.
The diagnosis of IPF requires the following:

- Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).
- The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy.
- Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.
## Diagnosis

### Table 6: Combination of High-Resolution Computed Tomography and Surgical Lung Biopsy for the Diagnosis of IPF (Requires Multidisciplinary Discussion)

<table>
<thead>
<tr>
<th>HRCT Pattern*</th>
<th>Surgical Lung Biopsy Pattern* (When Performed)</th>
<th>Diagnosis of IPF?</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP</td>
<td>UIP</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>Probable UIP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Possible UIP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonclassifiable fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not UIP</td>
<td>No</td>
</tr>
<tr>
<td>Possible UIP</td>
<td>UIP</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>Probable UIP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Possible UIP</td>
<td>Probable¹</td>
</tr>
<tr>
<td></td>
<td>Nonclassifiable fibrosis</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Not UIP</td>
<td>No</td>
</tr>
<tr>
<td>Inconsistent with UIP</td>
<td>UIP</td>
<td>Possible¹</td>
</tr>
<tr>
<td></td>
<td>Probable UIP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Possible UIP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonclassifiable fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not UIP</td>
<td>No</td>
</tr>
</tbody>
</table>
Idiopathic Pulmonary Fibrosis

- **Complications**
  - Much higher rate of Lung Cancer, particularly if they continue to smoke.
  - Pneumothorax due to honeycombing. Very poorly tolerated.

- **Treatment**
  - All patients should be put on a PPI. This has been shown to improve symptom of cough and may reduce progression, but link not certain.
  - Currently in Australia there is no targeted treatment.
    - Perfenidone: is a pyridone which inhibits fibroblast proliferation and collagen synthesis in vitro and ameliorates bleomycin-induced pulmonary fibrosis in animals. Shown to slow progression in trials.
    - Nintedanib: Tyrosine kinase inhibitor that has anti-fibrotic properties.
Other considerations
- Long term O2 therapy in resting hypoxaemia
- Appropriate pts should be considered for lung transplantation
- Asymptomatic GORD should be treated

- Pulm. HTN should not be treated
Management

**Figure 1. Enrollment and Outcomes.**
DLco denotes carbon monoxide diffusing capacity, FVC forced vital capacity, IPF idiopathic pulmonary fibrosis, and NAC N-acetylcysteine.
Management

Table 2. Safety End Points.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Combination Therapy (N=77)</th>
<th>Placebo (N=78)</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — no. (%)</td>
<td>8 (10)</td>
<td>1 (1)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>7 (9)</td>
<td>1 (1)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>From respiratory causes</td>
<td>23 (30)</td>
<td>7 (9)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for any cause — no. (%)</td>
<td>5 (6)</td>
<td>0</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Acute exacerbation — no. (%)</td>
<td>24 (31)</td>
<td>8 (10)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Based on Kaplan–Meier estimate at 60 wk — %</td>
<td>19.8 (9.9–37.2)</td>
<td>2.0 (0.3–13.6)</td>
<td>9.26 (1.16–74.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>43.6 (10.7–59.0)</td>
<td>16.9 (8.7–31.5)</td>
<td>3.74 (1.68–8.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from any cause or hospitalization</td>
<td>36.3 (23.7–53.0)</td>
<td>32.4 (19.7–50.3)</td>
<td>1.46 (0.70–3.05)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

* FVC denotes forced vital capacity.

Figure 2. Kaplan–Meier Curves for the Time until Death, Disease Progression, or Hospitalization.
Shown are the time until death (Panel A), until a composite of death or disease progression (defined as a decrease in the forced vital capacity of ≥10%) (Panel B), or until a composite of death or hospitalization (Panel C). Combination therapy refers to a three-drug regimen consisting of prednisone, azathioprine, and N-acetylcysteine.
Mr DP – What did we do?

- FBC - NAD
- ELFTs - NAD
- CRP 20
- ESR 40
- RF - NAD
- ANA - NAD
- ENA – NAD (Anti-RNP, SS-A, SS-B, Sc170, Sm, Jo-1)
- dsDNA - NAD
- ANCA - NAD
- Urinary sediment bland
Admitted to hospital 3 days before his next review.
Unable to mobilise due to dyspnoea.
SpO2 92% on RA at rest. Plummets with mobilisation.
Unable to perform lung function.
CXR appears worse than one performed many months before.
No infective symptoms
DDx: IPF, ?Connective tissue related.

I asked the immunologists for a hand.
  “Why don’t you do an extended myositis screen?”
“What the hell is that?”

Mr DP is Anti-PL-12 positive. His presentation is almost classical for this with few symptoms of DM and more ILD.

Commenced on Methyl-pred pulsed and cyclophosphamide. Discharged after 5/52 with home O2.

Subsequent visits had stabilised but not getting around as much.

Had Rituximab was modest improvement.

Still alive in December 2016 (12 months down the track)
Future Directions – Lung Sampling

- Open Lung Biopsy is invasive
- Transbronchial biopsy is associated with significant sampling error; yield for ILD in general is poor.
- The problem is that standard biopsy forceps crush the sample resulting in a whinging pathologist.

2 New Methods
  - EBUS- radial
  - Cryobiopsy
Cryobiopsy
Take home message

- Think about the pattern of disease.
- Look at lots of CTs.
- IPF is a palliative disease.
- I would do an extended myositis panel before labelling someone as IPF now.
- Bronchoscopic biopsy will be the preferred diagnostic method.
- IPF treatment is around the corner.
Thankyou