**Idiopathic Pulmonary Fibrosis: an update.**

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Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing interstitial pneumonia of unknown cause (1). Among the idiopathic interstitial pneumonias, IPF is the most common. It typically manifests with a progressive decline in lung function and a poor prognosis with limited therapeutic options.

The American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and the Latin American Thoracic Association (ALAT) recently published updated, evidence-based guidelines for the diagnosis and management of IPF, intended to replace the previous guidelines from 2000 (1, 2). Since this publication, there have been significant advances in the literature carrying substantial implications for the diagnosis and management of IPF. This review will provide updates on the evaluation, diagnosis and management of IPF reflecting recent changes in the literature.

**Epidemiology**

Data on the incidence and prevalence of IPF is limited. Estimates from the United Kingdom and the United States reveal an incidence ranging from 7.42 to 16.3 cases per 100 000 persons, numbers that have been increasing over time (3, 4). The estimated prevalence for IPF varies widely from 2 to 42.7 cases per 100 000 (1, 4,5).

Typically, IPF presents in the sixth and seventh decades of life, and rarely before age 50 (3, 4). Risk factors for the development of IPF include male gender, cigarette smoking and environmental exposures, especially metal dusts and wood dust (6, 7). Other proposed risk factors include gastroesophageal reflux (GER) and microbial organisms such as hepatitis C and Epstein-Barr virus; however, current data does not definitively support these associations (8-10). In familial IPF, an autosomal-dominant transmission with variable penetrance has been suggested, however the clinical utility of genetic testing remains unclear (1).

**Evaluation of the Patient with IPF**

When evaluating a patient with suspected IPF, a clinical assessment should be conducted to exclude other known causes of interstitial lung disease (ILD). This includes a detailed history and physical examination focusing on comorbidities, symptoms of connective tissue disease (CTD), medication use, family history and environmental and occupational exposures (1). Investigations should include a high-resolution computed tomography (HRCT), pulmonary function tests (PFTs), a six minute walk test (6MWT) and an auto-antibody profile.

PFTs assess the severity of disease and may predict mortality. Baseline diffusing capacity (DLCO) of less than 40% predicted or a longitudinal decline in FVC (10%) or DLCO (15%) over 6-12 months have been associated with decreased survival (11, 12). Survival in IPF has also been linked to the extent of fibrosis and honeycombing seen on HRCT (13).
In patients with IPF, the 6MWT is a valid measure of global functional capacity (14). Additionally, desaturation below 88% during the test or a 6-month decline in distance walked of as little as 26-50 metres have been associated with increased mortality in patients with IPF, the latter with a hazard ratio of 3.59 (14, 15).

Routine use of serologic testing to distinguish CTD from IPF is recommended (1). This includes measurement of rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), and anti-nuclear antibody (ANA) titer and pattern. Additional extra-nuclear antigens (ENAs) such as anti-Scl70 (scleroderma), anti-RNP (mixed-connective tissue disease), anti-Jo1 (anti-synthetase syndrome), anti-Ro and anti-La (Sjogren’s syndrome) may be considered in selected cases. A clinical assessment for underlying CTD should accompany laboratory screening, as patients with IPF may have mildly positive serology without other clinical features of CTD.

Diagnosis

Significant changes have been made to the diagnostic criteria for IPF (1, 2). The previous ATS/ERS statement outlined “major” and “minor” criteria in making the diagnosis of IPF which have been eliminated from the current guidelines. Presently, the diagnosis of IPF requires: (1) exclusion of other known causes of ILD such as domestic, occupational and environmental exposures, connective tissue disease (CTD), and drug toxicities, (2) the presence of a UIP pattern on HRCT in patients not subject to surgical lung biopsy, and (3) specific combinations of HRCT and surgical lung biopsy patterns in patients subjected to surgical lung biopsy (1).

These changes reflect evidence supporting the specificity of high-resolution CT (HRCT) scanning in recognizing the histopathologic pattern of usual interstitial pneumonia (UIP) (16). Thus, where the previous guidelines stated that in “the absence of a surgical lung biopsy, the diagnosis of IPF remains uncertain”, the current guidelines stipulate that “a UIP pattern on HRCT is highly accurate for the presence of UIP pattern on surgical lung biopsy... [with a] positive predictive value of 90-100%”. Therefore in the appropriate clinical setting, patients with a definite UIP pattern on HRCT do not require a surgical lung biopsy (see Figure 1).

UIP can be definitively characterized on HRCT by the presence of 4 features: [1]subpleural, basal predominance, [2] reticular abnormality, [3] honeycombing with or without traction bronchiectasis, and [4] absence of features listed as inconsistent with UIP pattern (Table 1, Figure 2). If honeycombing is not present, the term “possible UIP” should be used and surgical biopsy is necessary for a definitive diagnosis.

Similarly, for a histopathological diagnosis, 4 features are required to identify a definite UIP pattern: [1] evidence of marked fibrosis/architectural distortion, + honeycombing in a subpleural/paraseptal distribution, [2] presence of patchy involvement of lung parenchyma by fibrosis, [3] presence of fibroblastic foci, and [4] absence of features against a diagnosis of UIP. If only some features are present, the terms “probable UIP” or “possible UIP” should be used.
When a surgical lung biopsy is performed, results should be combined with HRCT findings in order to establish a diagnosis. This should be done with the help of a multidisciplinary discussion (MDD) among ILD experts (1).

**Figure 1.** Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF). In the absence of an identifiable cause for ILD, an HRCT demonstrating UIP pattern is diagnostic of IPF. In the absence of UIP pattern on HRCT, IPF can be diagnosed by the combination of specific HRCT and histopathological patterns. The accuracy of the diagnosis of IPF increases with multidisciplinary discussion (MDD) among ILD experts. *(Adapted from Raghu, G., et al. Am J Respir Crit Care Med, 2011. 183(6): p. 788-824.)*
### Table 1 – HRCT criteria for a UIP pattern

<table>
<thead>
<tr>
<th>UIP Pattern (All 4 features)</th>
<th>Possible UIP Pattern (All 3 features)</th>
<th>Inconsistent with UIP Pattern (Any of the 7 features)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subpleural, basal predominance</td>
<td>Subpleural, basal predominance</td>
<td>Upper or mid-lung predominance</td>
</tr>
<tr>
<td>Reticular abnormality</td>
<td>Reticular abnormality</td>
<td>Peribronchovascular predominance</td>
</tr>
<tr>
<td>Honeycombing with or without traction bronchiectasis</td>
<td>Absence of features listed as inconsistent with UIP pattern (see 3rd column of this table)</td>
<td>Extensive ground glass abnormality (i.e. greater than extent of reticulation)</td>
</tr>
<tr>
<td>Absence of features listed as inconsistent with UIP pattern (see 3rd column of this table)</td>
<td>Profuse micronodules (bilateral or predominantly upper lobes)</td>
<td>Discrete cysts (multiple, bilateral, away from areas of honeycombing)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discrete mosaic attenuation/air-trapping (bilateral or in 3 or more lobes)</td>
</tr>
</tbody>
</table>


**Figure 2.** High-resolution computed tomography (HRCT) images (axial [left] and coronal [right]) demonstrating usual interstitial pneumonia (UIP) pattern with reticular markings in a basal and subpleural distribution with honeycombing and an absence of features inconsistent with the UIP pattern.

### State of the Art Management of IPF

**Table 3** summarizes the evidence-based recommendations for non-pharmacologic and pharmacologic therapies in IPF. Based on limited evidence, the ATS/ERS/JRS/ALAT statement provides a strong recommendation for the use of long-term Oxygen therapy in patients with resting hypoxemia (1).
weak recommendation was given for the use of pulmonary rehabilitation in patients with IPF, with recent studies demonstrating improvements in quality of life and walk distance (17, 18). A weak recommendation was also provided for treatment of asymptomatic GER. Although GER as a cause for IPF remains debated, it is highly prevalent in patients with IPF (10). Moreover, a recent study suggests that IPF patients receiving medications for GER have longer survival compared to those not on treatment (10). Further studies in this area are needed. All patients should receive pneumococcal and influenza vaccinations and counselling regarding smoking cessation. Finally, unless contraindicated, lung transplantation is recommended for patients with advanced disease at diagnosis or objective evidence of physiologic deterioration.

Similar to non-pharmacologic interventions, pharmacologic therapies have not been shown to improve survival or modify the disease course in IPF. Despite this, the ATS/ERS/JRS/ALAT statement from 2011 states that for the fully-informed patient who strongly desires pharmacologic treatment, an agent receiving a weak recommendation against its use may be considered (1). These include: combined prednisone, azathioprine (AZA), and N-acetylcysteine (NAC); NAC alone; anticoagulation; and pirfenidone. The evidence for each of these therapies will be reviewed briefly, specifically highlighting recent advancements in the literature.

**Prednisone/AZA/NAC regimen**

The combined use of prednisone, AZA and NAC has been considered a reasonable treatment option since the IFIGENIA trial – a multicentre randomized controlled trial that assessed the addition of NAC to prednisone and AZA, compared to prednisone and AZA alone (19, 20). This study randomized 182 patients and found that those in the NAC group had a significantly slower decline in VC and diffusing capacity over 12 months. Unfortunately, this study did not include a placebo group. Therefore, the benefit of triple therapy over no treatment remained unknown.

The PANTHER study (Prednisolone, azathioprine and NAC: a study that evaluates response in IPF) was designed to address this question. This double-blind, placebo-controlled trial randomized patients to one of three groups: (1) prednisone/AZA/NAC, (2) NAC alone, and (3) placebo (21). A planned interim analysis was conducted when 238 of an expected 390 patients had been enrolled with approximately 50% of the final data collected. Findings of the interim analysis revealed an increased rate of death (10% vs. 1%, p=0.01) and hospitalization (30% vs. 9%, p<0.001) in the combination therapy group compared with placebo. More serious adverse events were noted in the combination therapy group (31% vs. 10%, p=0.001) with no improvements in lung function. Because of these findings, the combination regimen arm was stopped in October of 2011. The NAC-only and placebo arms continue recruitment and will follow patients for the pre-specified duration of 60 weeks. These interim findings provide evidence against the use of the three-drug regimen in patients with definite IPF and will certainly change recommendations set forth in future guidelines. Given that combination therapies continue to be useful in the treatment of other ILDs, distinguishing IPF from these conditions now becomes essential.

**NAC monotherapy**
The role of NAC monotherapy in IPF is unknown. Results from the IFGENIA trail suggested a reduced decline in lung function over time as well as fewer myelotoxic side effects (19). The ongoing arms of the PANTHER trial comparing NAC to placebo will provide further insight on the use of NAC monotherapy in IPF and are expected to be published in 2013.

**Anticoagulation**

Studies have proposed that patients with IPF have an activated coagulation system and are therefore at increased risk of developing venous thromboembolic disease (22). This association was evaluated in a Japanese study that allocated patients with IPF to prednisolone plus warfarin (23 patients), or prednisolone alone (33 patients) (22). Significant differences were seen in the survival curves of the two groups (p=0.049) with 3-year survival rates of 63% and 35% in the anticoagulated and placebo groups, respectively. This study’s small sample size, high rate of exacerbations, and potential randomization bias, limit the clinical application of these findings.

A phase 3 study (ACE-IPF) that planned to randomize 256 patients with IPF to either warfarin or placebo for a total of 48 weeks was recently suspended and final results should be published soon (23). Excess mortality was seen in the warfarin group with a very low likelihood that significant benefit would result from ongoing anticoagulation. Although the 2011 ATS/ERS/JRA/ALAT statement has a weak recommendation against the use of anticoagulation, this recent data strongly argues against routine anticoagulation in patients with IPF without other indications (1).

**Pirfenidone**

Pirfenidone is an anti-fibrotic agent with anti-inflammatory and antioxidant properties through TNF-alpha and TNF-beta pathways. Four phase III trials have assessed pirfenidone in patients with IPF (24-26).

Two encouraging early Japanese phase 3 trials of pirfenidone were plagued by methodological flaws which limited their clinical applicability (24, 25). To further confirm the beneficial effect of pirfenidone in IPF, the Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes (CAPACITY) programme designed two concurrent phase 3 multinational trials (26). Both studies were double-blind, placebo controlled trials analyzing a total of 779 patients. The first trial randomized patients to pirfenidone 2403 mg/day, 1197 mg/day, or placebo and showed a difference in forced vital capacity (FVC) at week 72. The second randomized patients to either pirfenidone 2403 mg/day or placebo, but showed no significant difference between study groups. A pooled analysis of both studies showed a pirfenidone treatment effect of reduced decline in FVC (-8.5% vs. -11.0%, p=0.005), 26% increase in progression-free survival time (p=0.025) and reduced decline in 6MWT distance (p=0.0009).

In all of the studies, pirfenidone was tolerated well. Commonly reported adverse events included gastrointestinal symptoms, photosensitivity, skin rash, and dizziness.
Pirfenidone is presently approved for use in Japan and Europe, and acceptance of an application for approval is currently pending in Canada. In the United States, the Food and Drug Administration (FDA) has requested an additional phase 3 study (the ASCEND trial (27)) to confirm the findings of previous trials.

Table 3 – Evidence-based recommendations by the ATS/ERS/JRS/ALAT for treatments in IPF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recommendation</th>
<th>Strength</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pharmacologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term Oxygen therapy</td>
<td>For</td>
<td>Strong</td>
<td>Very low</td>
</tr>
<tr>
<td>Lung transplantation</td>
<td>For</td>
<td>Strong</td>
<td>Very low</td>
</tr>
<tr>
<td>Pulmonary rehabilitation</td>
<td>For</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Treatment of asymptomatic GER</td>
<td>For</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Against</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Pharmacologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid monotherapy</td>
<td>Against</td>
<td>Strong</td>
<td>Very low</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Against</td>
<td>Strong</td>
<td>Very low</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>Against</td>
<td>Strong</td>
<td>Very low</td>
</tr>
<tr>
<td>Combined corticosteroid and immune-modulator therapy</td>
<td>Against</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>Interferon gamma 1b</td>
<td>Against</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Against</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Against</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Treatment of IPF-associated PH</td>
<td>Against</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Combined NAC, AZA, prednisone**</td>
<td>Against</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>NAC only</td>
<td>Against</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Anticoagulation**</td>
<td>Against</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>Against</td>
<td>Weak</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Since these recommendations were put forth, newer data has emerged that suggests these treatments are harmful and should not be used in patients with IPF. AZA = azathioprine, NAC = N-acetylcysteine, PH = pulmonary hypertension, GER = gastroesophageal reflux. (Adapted from Raghu, G., et al. Am J Respir Crit Care Med, 2011. 183(6): p. 788-824.)

Monitoring and Prognosis in IPF

Patients with IPF should be monitored at regular intervals (3-6 months) by their respirologist for evaluation of symptoms, physiologic measures and functional limitations. Doing so allows for the assessment of disease progression, appropriate initiation of oxygen therapy, assessment of complications (acute exacerbations, right sided heart failure, pulmonary embolism, etc...), referral for lung transplantation and timely initiation of palliative measures.

As mentioned above, measures such as increased honeycombing on HRCT and longitudinal declines in FVC, DLCO and distance walked, have prognostic value. Thus, the presence of these features serves as a
Future Directions

Due to the lack of effective therapeutic options, enrolment in clinical trials is recommended for all patients with IPF. A number of phase 2 and 3 therapeutic trials in IPF are currently underway. BIBF 1120, a potent intracellular tyrosine kinase inhibitor, has shown some promise in IPF. In a randomized, placebo-controlled, phase 2 trial, BIBF 1120 showed a trend towards a reduced decline in FVC, and showed significant improvements in several secondary endpoints (28). Compared to placebo, BIBF 1120 decreased the number of patients with a >10% decline in FVC, lowered the incidence of acute exacerbations, provided quality of life benefits and reduced absolute declines in oxygen saturation. A phase 3 placebo-controlled trial of BIBF 1120 is currently enrolling patients in Calgary, Hamilton and Halifax. Results of this anticipated study are expected in 2014.

Summary

IPF remains a devastating disease with an increasing incidence. Patients with suspected IPF should receive a detailed assessment focusing on comorbidities, CTD symptoms, medication use, family history and exposure history. Along with HRCT, PFTs and a 6MWT, all patients should receive baseline laboratory investigations, including an auto-antibody panel.

The diagnosis of IPF can be made with either a typical HRCT alone, or in combination with a surgical lung biopsy. Longitudinal follow up by a respirologist, that includes clinical and physiologic assessments, is essential to guide decisions regarding Oxygen supplementation, lung transplantation and palliation.

Presently, there are no available pharmacologic therapies that alter the disease course in IPF. Previously used therapeutic regimens including prednisone, combined prednisone/AZA, and combined prednisone/AZA/NAC are likely harmful in IPF and are not recommended. Exciting new therapies are currently being investigated, but in the interim, enrolment in clinical trials is strongly encouraged for all patients.

References