This pocket guide is a condensed version of the 2011 American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) Evidence-Based Guidelines for Diagnosis and Management of Idiopathic Pulmonary Fibrosis (IPF) and is NOT an update of the document published in 2011. It was compiled from excerpts from the published document by Ganesh Raghu, MD, Chair of the committee of IPF experts representing the sponsors of the 2011 published guidelines. Readers are encouraged to also consult the full version as well as the online supplement, both of which are available at http://ajrccm.atsjournals.org/content/183/6/788.long.

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**LIST OF ABBREVIATIONS AND ACRONYMS**

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<thead>
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<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>6MWT</td>
<td>6-minute-walk test</td>
</tr>
<tr>
<td>ALAT</td>
<td>Latin American Thoracic Association</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>BAL</td>
<td>bronchoalveolar lavage</td>
</tr>
<tr>
<td>CCL18</td>
<td>chemokine (C-C motif) ligand 18</td>
</tr>
<tr>
<td>CHP</td>
<td>chronic hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>CPI</td>
<td>composite physiologic index</td>
</tr>
<tr>
<td>DLCO</td>
<td>diffusing capacity for carbon monoxide</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>FEV₁</td>
<td>forced expiratory volume in 1 second</td>
</tr>
<tr>
<td>FVC</td>
<td>forced vital capacity</td>
</tr>
<tr>
<td>GER</td>
<td>gastroesophageal reflux</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>HRCT</td>
<td>high-resolution computed tomography</td>
</tr>
<tr>
<td>hTERT</td>
<td>human telomerase reverse transcriptase</td>
</tr>
<tr>
<td>hTR</td>
<td>human telomerase RNA</td>
</tr>
<tr>
<td>IIP</td>
<td>idiopathic interstitial pneumonia</td>
</tr>
<tr>
<td>ILD</td>
<td>interstitial lung disease</td>
</tr>
<tr>
<td>IPF</td>
<td>idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>JRS</td>
<td>Japanese Respiratory Society</td>
</tr>
<tr>
<td>KL-6</td>
<td>Krebs von den Lungen-6</td>
</tr>
<tr>
<td>MDD</td>
<td>multidisciplinary discussion</td>
</tr>
<tr>
<td>MMP</td>
<td>matrix metalloproteinase</td>
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<tr>
<td>NAC</td>
<td>N-acetyl-cysteine</td>
</tr>
<tr>
<td>NSIP</td>
<td>nonspecific interstitial pneumonia</td>
</tr>
<tr>
<td>OSA</td>
<td>obstructive sleep apnea</td>
</tr>
<tr>
<td>P(A-a)O₂</td>
<td>alveolar-arterial oxygen difference in partial pressures</td>
</tr>
<tr>
<td>PH</td>
<td>pulmonary hypertension</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>TLC</td>
<td>total lung capacity</td>
</tr>
<tr>
<td>UIP</td>
<td>usual interstitial pneumonia</td>
</tr>
<tr>
<td>VATS</td>
<td>video-assisted thoracoscopic surgery</td>
</tr>
</tbody>
</table>
METHODS

Relevant section topics and questions were identified by committee members after which, additional input was sought from general pulmonologists in the community and at academic centers. An evidence profile was created for each question using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The quality of evidence (Table 1 and Table 2) was determined according to the ATS GRADE criteria. The strength of the recommendations is either “strong” or “weak” based on the quality of evidence and the voting of the committee members (Table 3).

<table>
<thead>
<tr>
<th>Table 1 Quality of Evidence Determination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Evidence</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>» High</td>
</tr>
<tr>
<td>» Moderate</td>
</tr>
<tr>
<td>» Low</td>
</tr>
<tr>
<td>» Very low</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial.

<table>
<thead>
<tr>
<th>Table 2 Quality of the Evidence Rating and Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of the Evidence (GRADE)</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>High (⊕⊕⊕⊕)</td>
</tr>
<tr>
<td>Moderate (⊕⊕⊕)</td>
</tr>
<tr>
<td>Low (⊕⊕)</td>
</tr>
<tr>
<td>Very low (⊕)</td>
</tr>
</tbody>
</table>
### DEFINITION AND EPIDEMIOLOGY

#### DEFINITION
- Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP) defined in Table 4.\(^1\)
- The definition of IPF requires the exclusion of other forms of interstitial pneumonia including other idiopathic interstitial pneumonias (IIP) and interstitial lung disease (ILD) associated with environmental exposure, medication, or systemic disease.

#### CLINICAL PRESENTATION
- IPF should be considered in all adult patients with unexplained chronic exertional dyspnea, and commonly presents with cough, bibasilar inspiratory crackles, and finger clubbing.\(^1\)
- The optimal HRCT technique for evaluation of ILD is provided in Table 5.
- The incidence of IPF increases with older age, with presentation typically occurring in the sixth and seventh decades.\(^1\)
- IPF is rare in patients younger than 50 years of age.\(^1\)
- IPF is more common among men than among women.\(^1\)
- The majority of patients with IPF have a history of cigarette smoking.\(^1\)
Guidelines for the Diagnosis and Management of Idiopathic Pulmonary Fibrosis

DEFINITION AND EPIDEMIOLOGY

INCIDENCE/PREVALENCE

- There are no large-scale studies of the incidence or prevalence of IPF on which to base formal estimates.¹
- Prevalence estimates have varied from 2 to 29 cases per 100,000 in the general population.¹
- It is unknown if the incidence and prevalence of IPF are influenced by geographic, ethnic, cultural, or racial factors.¹

POTENTIAL RISK FACTORS

- Cigarette smoking (particularly a smoking history of >20 pack-years)¹
- Environmental exposures¹
  » Exposure to metal dusts (brass, lead, and steel) and wood dust (pine)¹
  » Farming, raising birds, hair dressing, stone cutting/polishing, and exposure to livestock and to vegetable dust/animal dust¹
- Although definitive conclusions about the role of infection in IPF cannot be made, several studies have focused on chronic viral infection, in particular Epstein-Barr virus (EBV) and hepatitis C.¹
- Gastroesophageal reflux (GER) through its presumed association with microaspiration.¹

GENETIC FACTORS

- Familial IPF represents <5% of all cases. It is clinically and histologically indistinguishable from sporadic IPF, although it may develop at an earlier age and seems to have different patterns of gene transcription.¹
- Genetic variants within the human telomerase reverse transcriptase (hTERT) or human telomerase RNA (hTR) components of the telomerase gene are found in ≤15% of familial pulmonary fibrosis kindreds and 3% of sporadic IIP cases. At present, there are no genetic factors that are consistently associated with sporadic IPF. Other genetic factors (e.g., associated with MUC 5B expression) reported subsequent to the published 2011 document are not included in this pocket guideline.¹
- Given the present state of understanding, the committee does not recommend genetic testing in patients with either familial or sporadic IPF as part of a clinical evaluation.¹
DEFINITION OF USUAL INTERSTITIAL PNEUMONIA PATTERN

HIGH-RESOLUTION COMPUTED TOMOGRAPHY (HRCT) FEATURES

**Table 4** HRCT Criteria for UIP Pattern

<table>
<thead>
<tr>
<th>UIP Pattern (All Four Features)</th>
<th>Possible UIP Pattern (All Three Features)</th>
<th>Inconsistent with UIP Pattern (Any of the Seven Features)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Subpleural, basal predominance</td>
<td>1. Subpleural, basal predominance</td>
<td>1. Upper or mid-lung predominance</td>
</tr>
<tr>
<td>2. Reticular abnormality</td>
<td>2. Reticular abnormality</td>
<td>2. Peribronchovascular predominance</td>
</tr>
<tr>
<td>3. Honeycombing with or without traction bronchiectasis</td>
<td>3. Absence of features listed as inconsistent with UIP pattern (see third column)</td>
<td>3. Extensive ground glass abnormality (extent &gt;reticular abnormality)</td>
</tr>
<tr>
<td>4. Absence of features listed as inconsistent with UIP pattern (see third column)</td>
<td></td>
<td>4. Profuse micronodules (bilateral, predominantly upper lobes)</td>
</tr>
</tbody>
</table>

HRCT = high-resolution computed tomography; UIP = usual interstitial pneumonia.
**Table 5 Optimal HRCT Technique for Evaluation of Interstitial Lung Disease**

- The scans should be noncontrast and include at a minimum:
  - Scans obtained on full inspiration without respiratory motion
  - Contiguous or noncontiguous axial scans with thin sections, reconstructed at ≤2 cm intervals
  - Reconstructed slice collimation ≤2 mm
  - High-resolution reconstruction algorithm
  - Field of view to include lungs only
  - Expiratory scans are helpful to exclude lobular air trapping suggestive of hypersensitivity
  - Pneumonitis
  - Prone scans if dependent density obscures detail on supine images
  - Optional coronal and sagittal reconstructions if volumetric images are obtained

HRCT = high-resolution computed tomography.
*These criteria represent the consensus opinion of the committee members. Source: Table E6 online Supplement.

**HISTOPATHOLOGY FEATURES**

The histopathologic hallmark and chief diagnostic criterion is a heterogeneous appearance at low magnification in which areas of fibrosis with scarring and honeycomb change alternate with areas of less affected or normal parenchyma (Figure 2; Table 6).1

![Figure 2 Surgical Lung Biopsy Specimens Demonstrating UIP Pattern](image)

(A) Scanning power microscopy showing a patchy process with honeycomb spaces (thick arrow), some preserved lung tissue regions (thin arrow), and fibrosis extending into the lung from the subpleural regions. (B) Adjacent to the regions of more chronic fibrosis (thick arrow) is a fibroblast focus (asterisk), recognized by its convex shape and composition of edematous fibroblastic tissue, suggestive of recent lung injury.1


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### Table 6: Histopathologic Criteria for UIP Pattern (See NOTE)

<table>
<thead>
<tr>
<th>UIP Pattern (All Four Criteria)</th>
<th>Probable UIP Pattern</th>
<th>Possible UIP Pattern (All Three Criteria)</th>
<th>Not UIP Pattern (Any of the Six Criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence of marked fibrosis/ architectural distortion, ±honeycombing in a predominantly subpleural/ paraseptal distribution</td>
<td>1. Evidence of marked fibrosis/architectural distortion, ±honeycombing</td>
<td>1. Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation</td>
<td>1. Hyaline membranes*</td>
</tr>
<tr>
<td>2. Presence of patchy involvement of lung parenchyma by fibrosis</td>
<td>2. Absence of either patchy involvement or fibroblastic foci, but not both</td>
<td>2. Absence of other criteria for UIP (see first column)</td>
<td>2. Organizing pneumonia*†</td>
</tr>
<tr>
<td>3. Presence of fibroblast foci</td>
<td>3. Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
<td>3. Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
<td>3. Granulomas†</td>
</tr>
<tr>
<td>4. Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
<td>4. Honeycomb changes only‡</td>
<td>4. Honeycomb changes only‡</td>
<td>4. Marked interstitial inflammatory cell infiltrate away from honeycombing</td>
</tr>
</tbody>
</table>

UIP = usual interstitial pneumonia.

* Can be associated with acute exacerbation of idiopathic pulmonary fibrosis.

† An isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern.

‡ This scenario usually represents end-stage fibrotic lung disease where honeycombed segments have been sampled but where a UIP pattern might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided by preoperative targeting of biopsy sites away from these areas using HRCT.

**NOTE:** When considered necessary, lung biopsies should be obtained from multiple lobes. The diagnostic yield from surgical lung biopsies obtained from video-assisted thoracoscopic surgery (VATS) and open thoracotomy are similar; thus, the decision on which procedure to perform should be based on individual patient characteristics and surgical expertise.

### DIAGNOSIS

The diagnosis of IPF requires the following:

1. Exclusion of other known causes of ILD.
2. The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy (Table 4).
3. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy (Tables 6 and 7).

The accuracy of the diagnosis of IPF increases with multidisciplinary discussion (MDD) among pulmonologists, radiologists, and pathologists experienced in the diagnosis of ILD.

#### DIAGNOSTIC CRITERIA

The diagnostic criteria for IPF presented in this document have been significantly modified from those stated in the previous ATS/ERS Statement. The new diagnostic criteria and schema for adult patients with ILD and suspected IPF are presented in Figure 3 and Table 7.
• Careful exclusion of alternative etiologies through MDD is of the utmost importance to an accurate diagnosis. In situations in which MDD is not feasible, patients should be referred to experienced clinical experts in ILD for consultation.

• Given the high-quality evidence regarding HRCT, specificity for the recognition of histopathologic UIP pattern, surgical lung biopsy is not essential.

In the appropriate clinical setting (see Clinical Presentation section)—the presence of a UIP pattern on HRCT is sufficient for the diagnosis of IPF.

The major and minor criteria for the clinical (i.e., nonpathologic) diagnosis of IPF published as a consensus statement of ATS/ERS in year 2000 have been eliminated.

<table>
<thead>
<tr>
<th>Table 7 Combination of HRCT and Surgical Lung Biopsy for the Diagnosis of IPF (Requires MDD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRCT Pattern*</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>UIP</td>
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<tr>
<td>Possible UIP</td>
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<td>Inconsistent with UIP</td>
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</tbody>
</table>

HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.

Bold type indicates combinations of HRCT and surgical lung biopsy patterns that correspond with a diagnosis of IPF (YES in the far right column).

The combination of UIP HRCT and probable UIP or possible UIP or nonclassifiable fibrosis (surgical lung biopsy patterns for example) equals a diagnosis of IPF; the combination of UIP HRCT and Not UIP (surgical lung biopsy pattern) does not make the diagnosis of IPF.

* Patterns as described in Tables 4 and 6.

† The accuracy of the diagnosis of IPF increases with MDD. This is particularly relevant in cases in which the radiologic and histopathologic patterns are discordant (e.g., HRCT is inconsistent with UIP and histopathology is UIP). There are data to suggest that the accuracy of diagnosis is improved with MDD among ILD experts compared to clinician-specialists in the community setting; timely referral to ILD experts is encouraged.

‡ Nonclassifiable fibrosis: Some biopsies may reveal a pattern of fibrosis that does not meet the above criteria for UIP pattern and the other idiopathic interstitial pneumonias (see text). These biopsies may be termed "nonclassifiable fibrosis."

§ MDD should include discussions of the potential for sampling error and a re-evaluation of adequacy of technique of HRCT.

NOTE: In cases with an "Inconsistent with UIP" HRCT pattern and a "UIP" surgical lung biopsy pattern, the possibility of a diagnosis of IPF still exists and clarification by MDD among ILD experts is indicated.
EXCLUSION OF OTHER KNOWN CAUSES

The exclusion of other known causes of ILD is a broad and inherently subjective criterion, but several specific points should be made.

- A careful history and physical examination focusing on comorbidities, medication use, environmental exposures, and family history is essential.
- Physicians should utilize a standardized approach. The American College of Chest Physicians has published an approach that may be of use. It is available at:
  

- Patients should be thoroughly evaluated for possible chronic hypersensitivity pneumonitis (CHP), since such patients may mimic IPF. The inciting antigen may not be identifiable in some patients with CHP; bronchoalveolar lavage (BAL) showing a lymphocytosis ≥40% may suggest occult hypersensitivity pneumonitis. Further investigations for environmental exposures, and possibly a surgical lung biopsy should be considered.
- Patients who meet established criteria for connective tissue disease do not have IPF.
- The index of suspicion for connective tissue disease in younger patients (<50 years) and women should be high especially patients without clinical or serologic features of IPF at presentation as these patients may subsequently manifest clinical features of connective tissue disease.
Bronchoalveolar Lavage Cellular Analysis¹
**Recommendation:** BAL cellular analysis should not be performed in the diagnostic evaluation of IPF in the majority of patients, but may be appropriate in a minority.

**Strength of Recommendation:** Weak

**Quality of Evidence:** ⊕⊕○○

**Remarks:** The most important application of BAL in the evaluation of patients with suspected IPF, is in the exclusion of chronic hypersensitivity pneumonitis; prominent lymphocytosis (>40%) should suggest the diagnosis.

It is unclear whether BAL adds significant diagnostic specificity to a careful exposure history and clinical evaluation.

This recommendation is only for BAL differential cell count ("cellular analysis"). It does not refer to the use of BAL in the evaluation of infection, malignancy, etc.

Transbronchial Lung Biopsy¹
**Recommendation:** Transbronchial biopsy should not be used in the evaluation of IPF in the majority of patients, but may be appropriate in a minority.

**Strength of Recommendation:** Weak

**Quality of Evidence:** ⊕⊕○○

**Remarks:** Although transbronchial biopsy specimens may show all the histologic features of UIP, the sensitivity and specificity of this approach for the diagnosis for UIP pattern is unknown.

It is also unknown how many and from where transbronchial biopsies should be obtained.

Serologic Testing for Connective Tissue Disease¹
**Recommendation:** Serologic testing for connective tissue disease should be performed in the evaluation of IPF in the majority of patients, but may not be appropriate in a minority.

**Strength of Recommendation:** Weak

**Quality of Evidence:** ○○○○

**Remarks:** Serologic evaluation should be performed even in the absence of signs or symptoms of connective tissue disease, and should include rheumatoid factor, anti-cyclic citrullinated peptide, and anti-nuclear antibody titer and pattern.

Routine use of other serological tests such as antisynthetase antibodies (e.g., Jo-1), creatine kinase and aldolase, Sjogren's antibodies (SS-A, SS-B), and scleroderma antibodies (scl-70, PM-1) is of unclear benefit, but may be helpful in selected cases.

Patients with IPF may have a mildly positive antinuclear antibody titer and/or rheumatoid factor level without any other clinical features of connective tissue. Such patients should be carefully screened for signs and symptoms of connective tissues disease (e.g., arthritis, Raynaud’s phenomenon, skin changes, abnormal esophageal motility).

Multidisciplinary Discussion¹
**Recommendation:** MDD should be used in the evaluation of IPF.

**Strength of Recommendation:** Strong

**Quality of Evidence:** ⊕⊕○○
NATURAL HISTORY OF IPF AND COMORBID CONDITIONS

IPF is a fatal lung disease; the natural history is variable and unpredictable:

- The natural history of IPF has been described as a progressive decline in subjective and objective pulmonary function until eventual death from respiratory failure or complicating comorbidity.
- There are several possible natural histories for patients with IPF (Figure 4). The relative frequency of each is unknown.
  - Most patients demonstrate a gradual worsening of lung function over years; a minority remains stable or declines rapidly.
  - A minority of patients may experience unpredictable acute disease worsening either from a secondary complication such as pneumonia, or for unrecognized reasons.
- There are insufficient data to allow a clear assessment of median survival in IPF.
- Some patients may experience episodes of acute respiratory worsening despite previous stability.
- Disease progression is manifested by increasing respiratory symptoms, worsening pulmonary function test results, progressive fibrosis on HRCT, acute respiratory decline, or death.
- Patients with IPF may have subclinical or overt comorbid conditions including pulmonary hypertension (PH), GER, obstructive sleep apnea (OSA), obesity, and emphysema. The impact of these conditions on the outcome of patients with IPF is unclear.

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.

Guidelines for the Diagnosis and Management of Idiopathic Pulmonary Fibrosis

DIAGNOSIS

► Acute Exacerbation of IPF

- Acute respiratory worsening occurs in about 5–10% of patients with IPF.
- Acute exacerbation of IPF may be a manifestation of an unidentified respiratory complication (e.g., pulmonary emboli, infection) or may represent an inherent acceleration in the pathobiological processes involved in IPF.
- Recent data from gene expression profiling of patients with acute exacerbation of IPF do not suggest an infectious etiology.
- Historically, criteria for acute exacerbation of IPF have included the following:
  » Unexplained worsening of dyspnea within 1 month
  » Evidence of hypoxemia (defined by worsened or severely impaired gas exchange)
  » New radiographic alveolar infiltrates
  » Absence of an alternative explanation (e.g., infection, pulmonary embolism, pneumothorax, or heart failure)
- Acute exacerbation can occur at any point in the course of IPF and occasionally can be its presenting manifestation.
- Worsened cough, fever, and/or increased sputum have been observed.
- There are no known risk factors for acute exacerbation of IPF.
  » There have been reports of acute respiratory decompensation after thoracic surgery and BAL.
  » It is unclear whether these events represent true acute exacerbations or complications of the respective procedures.
- Acute exacerbation of IPF histologically manifests as acute or organizing diffuse alveolar damage, or, less commonly, organizing pneumonia in zones of relatively preserved lung tissue away from the most fibrotic regions.
- Anecdotal experience indicates that sampling issues in some patients may result in specimens demonstrating only uncomplicated UIP or the organizing phase of diffuse alveolar damage without histologic evidence of underlying UIP.

► Vital Statistics

- Deaths from pulmonary fibrosis increase with increasing age.
- Evidence suggests that mortality from pulmonary fibrosis has increased over the past 2 decades.
- Using the most rigorous definition of IPF, the mortality rate in the United States in 2003 was 61.2 deaths per 1,000,000 in men and 54.5 per 1,000,000 in women.
- In Japan, the mortality rate for IPF was estimated to be 33 per 1,000,000 in men and 24 per 1,000,000 in women.
- The mortality burden attributable to IPF is higher than that of some cancers.
- Recent evidence suggests that mortality from IPF in the United States is greater in the winter months.
- Progressive lung disease is responsible for 60% of IPF deaths.
- Additional causes of IPF-related morbidity and mortality include coronary artery disease, pulmonary embolism, and lung cancer.
STAGING AND PROGNOSIS

- The proposed stages of IPF (“mild,” “moderate,” “severe,” “early,” and “advanced”) are commonly based on resting pulmonary function test measurements and/or extent of radiologic abnormalities; it is unknown if these staging approaches are relevant to clinical decision making.
- Limited data suggest selected features commonly observed in clinical practice are associated with increased mortality (see following sections and Table 8).
- Because of variability in the natural history of IPF, it is unknown if the presence of one of more of these features identifies a subpopulation of patients with “advanced” or “end-stage” IPF.

**DEMOGRAPHICS**

- Older male patients may have a worse prognosis.
- The effect of smoking on mortality is unclear.
- The prognostic value of geographic, ethnic, cultural, and racial factors is unknown.

**DYSPNEA**

- Baseline dyspnea may correlate with quality of life (QoL) and survival.
- Change in dyspnea over time may be predictive of survival.

**PHYSIOLOGY**

- Baseline pulmonary function test values have mixed associations with survival.
  - Baseline forced vital capacity (FVC) is of unclear predictive value.
  - Baseline diffusing capacity for carbon monoxide (DLCO, single breath, hemoglobin corrected) is more reliably predictive of survival at baseline than FVC; a threshold of ~40% predicted has been associated with an increased risk of mortality.
  - Baseline total lung capacity (TLC) and alveolar-arterial oxygen difference in partial pressures (P[A-a O2]) may be predictive of survival, but no clear threshold exists.
  - Baseline cardiopulmonary exercise testing (maximal oxygen uptake) has been suggested to predict survival.
- Longitudinal change in physiology is an important predictor of mortality in IPF.
  - A decline in FVC over 6 or 12 months is associated with decreased survival.
  - Declines in FVC of 5–10% may be predictive of mortality.
  - A decline in DLCO is associated with decreased survival, although less consistently than FVC.
  - A >15 mm Hg change in P(A-a)O2 after 12 months is predictive of survival.
  - Six-month change in TLC and P(A-a)O2 may be predictive of survival.

**HIGH-RESOLUTION COMPUTED TOMOGRAPHY FEATURES**

- Fibrosis and honeycombing on HRCT are strongly correlated with FVC and DLCO measurements.
- The extent of fibrosis and honeycombing are predictive of survival.

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1 It is unclear which metric (the Medical Research Council Scale, Baseline Dyspnea Index, Quality of Life measurement tools with respiratory questionnaires, the Borg scale, the University of California, San Diego, Shortness of Breath Questionnaire, and/or the clinical-radiological-physiological dyspnea score) is most predictive of outcome in patients with IPF.
STAGING AND PROGNOSIS

COMPOSITE SCORING SYSTEMS
- A composite physiologic index (CPI) using forced expiratory volume in 1 second (FEV₁), FVC, and DLCO to predict the extent of disease more strongly predicts mortality than individual measures of lung function or either of the clinical-radiographic-physiological scoring systems.
- The clinical utility of this CPI is unknown.

SIX-MINUTE-WALK TESTING
The prognostic value of the 6-minute-walk test (6MWT) is limited due to lack of standardization.
- A decline in oxygen saturation to <88% during 6MWT may be a marker for increased mortality risk.
- Shorter walk distance and delayed heart-rate recovery after walk testing have been associated with an increased risk of mortality.

HISTOPATHOLOGY
- Multiple biopsies may show varied histopathologic patterns within individual patients.
- 12–26% of patients display a pattern of UIP and nonspecific interstitial pneumonia (NSIP) with multiple lobe biopsies.
- The prognosis for patients with both UIP and NSIP appears to be similar to that of patients with UIP in all lobes biopsied.
- An increased number of fibroblast foci may be associated with an increased risk of mortality.
- A higher profusion of fibroblast foci is associated with a decline in FVC and DLCO over 6 and 12 months.
- The utility of detailed histopathologic scoring systems in the day-to-day clinical management of patients with IPF has not been evaluated.

PULMONARY HYPERTENSION
- PH has been associated with increased risk of mortality.
- A mean pulmonary artery pressure of 17 mm Hg may be the best discriminator of mortality.
- Echocardiographic estimation of pulmonary artery systolic pressures does not correlate well with right heart catheterization.
- Increased pulmonary vascular resistance has been linked to worse survival.
- It is unclear if IPF with PH represents a distinct clinical phenotype.

EMPHYSEMA
- Patients with IPF and emphysema may have a worse outcome than those without emphysema.
- Patients with IPF and emphysema are likely to require long-term oxygen therapy and may have significant PH.
• The presence of emphysema is not significantly predictive of survival.
• It is unclear whether IPF with emphysema represents a distinct clinical phenotype.

**SERUM AND BRONCHOALVEOLAR LAVAGE BIOMARKERS**

There are limited data on the predictive value of serum and BAL biomarkers:

<table>
<thead>
<tr>
<th>Table 8 Selected Features Associated with Increased Risk of Mortality in IPF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline factors</strong>*</td>
</tr>
<tr>
<td>Level of dyspnea†</td>
</tr>
<tr>
<td>DL\text{CO}, 40% predicted</td>
</tr>
<tr>
<td>Desaturation &lt;88% during 6MWT</td>
</tr>
<tr>
<td>Extent of honeycombing on HRCT†</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td><strong>Longitudinal factors</strong></td>
</tr>
<tr>
<td>Increase in level of dyspnea†</td>
</tr>
<tr>
<td>Decrease in FVC by &gt;10% absolute value</td>
</tr>
<tr>
<td>Decrease in DL\text{CO} by &gt;15% absolute value</td>
</tr>
<tr>
<td>Worsening of fibrosis on HRCT†</td>
</tr>
</tbody>
</table>

6MWT = 6-minute-walk test; DL\text{CO} = diffusing capacity for carbon monoxide; FVC = forced vital capacity; HRCT = high-resolution computed tomography.

* Baseline FVC is of unclear predictive value.
† Currently, there is no uniformity in approach to quantification.

**TREATMENT**

The preponderance of evidence to-date suggests that pharmacologic therapy for IPF is without definitive, proven benefit;† however, potential benefits have been suggested in a few studies. The recommendations for treatment with such agents are listed in Table 9 as a “Weak No.”
### Table 9 Evidence-Based Treatment Recommendations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recommended</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacologic Therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid monotherapy</td>
<td>No</td>
<td>Strong</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Colchicine</td>
<td>No</td>
<td>Strong</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>No</td>
<td>Strong</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Corticosteroid + immunomodulatory*</td>
<td>No</td>
<td>Strong</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Corticosteroid + azathioprine + acetylcysteine†</td>
<td>Majority – No</td>
<td>Weak</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Interferon-γ 1b</td>
<td>No</td>
<td>Strong</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Bosentan</td>
<td>No</td>
<td>Strong</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Etanercept</td>
<td>No</td>
<td>Strong</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Acetylcysteine monotherapy</td>
<td>Majority – No</td>
<td>Weak</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Anticoagulants§</td>
<td>Majority – No</td>
<td>Weak</td>
<td>⊕⊕⊕⊕ to ⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>Majority – No</td>
<td>Weak</td>
<td>⊕⊕⊕⊕ to ⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Sildenafil§</td>
<td>No recommendation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib§</td>
<td>No recommendation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nonpharmacologic Therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term oxygen therapy</td>
<td>Yes for patients with IPF and clinically significant resting hypoxemia</td>
<td>Strong</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Lung transplantation</td>
<td>If appropriate</td>
<td>Strong</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Majority of patients with respiratory failure due to IPF – No</td>
<td>Weak</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Pulmonary rehabilitation</td>
<td>Majority – Yes</td>
<td>Weak</td>
<td>⊕⊕⊕⊕</td>
</tr>
</tbody>
</table>

* e.g., azathioprine, cyclophosphamide

† This recommendation is being revised in an updated version of the guidelines in light of a demonstration of harmful effects and increased mortality associated with this triple therapy. Raghu G et al. N Engl J Med 2012;366:1968.3

§ This recommendation is being revised in an updated version of the guidelines based on the demonstration of harmful effects associated with warfarin therapy for IPF. Noth I et al. Am J Respir Crit Care Med 2012;186:88.4

¶ Data were published subsequent to the final formal face-to-face voting and therefore not considered for evidence-based recommendations. Treatment recommendations are anticipated in an updated version of the guidelines.
TREATMENT OF SELECTED COMPLICATIONS AND COMORBID CONDITIONS

Complications and comorbid conditions frequently associated with IPF include acute exacerbation of IPF, PH, GER, obesity, emphysema, and OSA.

It is unknown if treating these comorbidities influences clinical outcomes.

There are no data on which to make recommendations for treatment of obesity, emphysema, and OSA in the setting of IPF.

Acute Exacerbation of IPF

**Recommendation:** The majority of patients with acute exacerbation of IPF should be treated with corticosteroids, but corticosteroids may not be reasonable in a minority.

**Strength of Recommendation:** Weak

**Quality of Evidence:** ★★★★

Pulmonary Hypertension

**Recommendation:** PH should not be treated in the majority of patients with IPF, but treatment may be a reasonable choice in a minority.

**Strength of Recommendation:** Weak

**Quality of Evidence:** ★★★★

Gastroesophageal Reflux Disease

**Recommendation:** Asymptomatic GER disease should be medically treated in the majority of patients with IPF, but treatment may not be reasonable in a minority.

**Strength of Recommendation:** Weak

**Quality of Evidence:** ★★★★

PALLIATIVE CARE

- Palliative care should be considered an adjunct to disease-focused care.
- Corticosteroids and thalidomide may be beneficial for chronic cough.
- Chronic opioids may be used for severe dyspnea and cough with careful monitoring for side effects.
- Advanced directives and end-of-life care issues should be addressed in the ambulatory setting in all patients with IPF, particularly those with severe physiologic impairment and comorbid conditions.
- Hospice care should be considered for patients who are bedbound due to IPF.
MONITORING THE CLINICAL COURSE OF DISEASE

MONITORING FOR PROGRESSIVE DISEASE

- Increasing respiratory symptoms, worsening pulmonary function test results, progressive fibrosis on HRCT, or acute respiratory decline, may be manifestations of disease progression.
- In the absence of another identifiable cause, the presence of any of the following changes is consistent with progressive disease:
  - Progressive dyspnea (objectively assessed)
  - Progressive, sustained decrease from baseline in absolute FVC
  - Progressive, sustained decrease from baseline in absolute DL_{co} (corrected for hemoglobin)
  - Progression of fibrosis from baseline on HRCT
  - Acute exacerbation
  - Death from respiratory failure
- Disease progression is generally monitored over periods of 3 to 6 months, but sustained changes in symptoms, physiology, and radiology over shorter periods may also identify disease progression.
- Pulmonary function testing provides the most standardized approach to objective monitoring and quantification of disease progression.
- Monitoring for desaturation during 6MWT is useful to assess the need for supplemental oxygen in patients with significant exercise intolerance.
- The presence of significant emphysema impacts FVC measurement; thus changes in FVC alone may not be as reliable an indicator of disease progression in these circumstances.
- FVC and DL_{co} measurements should be performed during routine monitoring in accordance with ATS/ERS standards.
- The optimal time interval for repetition of FVC and DL_{co} has not been formally investigated.
- In the presence of progressive dyspnea or other features of a more rapidly progressive course, a flexible approach to monitoring for disease progression with a lower threshold for earlier repetition of FVC and DL_{co} is required.

MONITORING FOR WORSENING SYMPTOMS

- Patients experiencing worsening respiratory symptoms require evaluation for progressive disease, assessment of oxygenation at rest and with exertion, and prompt detection of secondary complications (e.g., development of deep venous thrombosis and pulmonary embolus).
- Some patients may also benefit from symptom-based therapies.
- It is unclear if any of the research tools available for the quantification of dyspnea have clinical utility.
MONITORING FOR WORSENING OXYGENATION

- Oxygen saturation by pulse oximetry should be measured at rest and with exertion in all patients regardless of symptoms to assure adequacy of oxygenation and identify the need for supplemental oxygen at baseline and during follow-up evaluation.
- Careful attention to the pulse oximetry tracing and signal is required to overcome potential problems related to poor circulation and inadequate signal quality.
  - Generally, desaturation below 88% during a formal 6MWT or equivalent has been used to prescribe supplemental oxygen.
- Such measurements should be performed at baseline and during follow up at 3- to 6-month intervals.
- Formal cardiopulmonary exercise testing does not have a defined role and is not recommended for routine monitoring.

MONITORING FOR COMPLICATIONS AND COMORBIDITIES

Comorbidities including PH, pulmonary embolism, lung cancer, and coronary artery disease are known to occur in IPF. While the development of these comorbidities may influence survival, the role of routine screening to identify such complications (e.g., annual HRCT for lung cancer surveillance) is unknown. Thus, a recommendation for routine screening cannot be made.
- In patients demonstrating progressive disease, the identification of PH may impact consideration for lung transplantation in eligible patients, and evaluation is indicated.
  - Echocardiography is not accurate in estimating pulmonary hemodynamics in patients with fibrotic lung disease and should not be relied upon to assess the presence and severity of PH.
  - Brain natriuretic peptide levels may correlate with the presence of moderate to severe PH, but have not been thoroughly validated as a screening tool.
  - A clinical prediction model has also been proposed but requires independent validation. At the present time, right heart catheterization is required to confirm the presence of PH.
- Some patients with connective tissue disease (e.g., younger women) may present with isolated pulmonary abnormalities characteristic of IPF prior to overt manifestations of systemic disease, appropriate serological monitoring for connective tissue disease should be considered in such patients when symptoms arise.
- For patients manifesting acute respiratory worsening, the possibility of acute exacerbation of IPF should be entertained, and prompt evaluation for alternative etiologies of acute worsening such as pulmonary embolus, pneumothorax, respiratory infection, or aspiration should be undertaken.
- Monitoring for complications associated with pharmacologic therapy will need to be tailored to the known side-effect profiles of the specific treatment regimen.
SUMMARY OF CLINICAL MANAGEMENT OF IPF

Figure 5 Schematic Pathway for Clinical Management of Patients with IPF.

Dx of IPF (Figure 3 and Table 6)

If increased risk of mortality (Table 7), evaluate and list for lung transplantation at the time of diagnosis

TREATMENT CONSIDERATIONS
NONPHARMACOLOGICAL
* Oxygen supplementation (if hypoxemic)
* Pulmonary rehabilitation

PHARMACOLOGICAL
Discuss therapies with Weak No recommendations with patients based on their individual values and preferences

COMORBIDITIES
* Pulmonary hypertension
* Gastroesophageal

SYMPTOM CONTROL

DISEASE PROGRESSION
(see text)

Monitor every 4-6 months or sooner as clinically indicated

ACUTE EXACERBATION
Corticosteroids

RESPIRATORY FAILURE
(due to progression of IPF)

Evaluate and list for lung transplantation

Patients should be made aware of available clinical trials for possible enrollment at all stages.

Dx = diagnosis; IPF = idiopathic pulmonary fibrosis.


References


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IDIOPATHIC PULMONARY FIBROSIS

Guidelines for Diagnosis and Management

An ATS Pocket Publication

To Improve health worldwide by advancing research, clinical care and public health in respiratory disease