IDIOPATHIC PULMONARY FIBROSIS: A SYSTEMATIC APPROACH TO DIAGNOSIS

MONOGRAPH
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Idiopathic Pulmonary Fibrosis: A Systematic Approach to Diagnosis 4

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NEEDS STATEMENT

Idiopathic pulmonary fibrosis (IPF) is a debilitating disease for which there is no known cause or cure. Progressive scarring or fibrosis of the lungs occurs, gradually interfering with a patient’s ability to breathe and ultimately resulting in death. Recent studies have identified that approximately 80,000 individuals suffer from IPF in the United States and an estimated 30,000 new cases develop each year. IPF is often misdiagnosed or diagnosed at an advanced stage in the disease, since it may mimic other diseases. Education to enhance physician awareness and assist in the early recognition of IPF is essential to improving overall patient care.

LEARNING OBJECTIVES

After completing this monograph, the participant will be able to:
• Differentiate idiopathic pulmonary fibrosis (IPF) from other interstitial lung diseases (ILDs)
• Formulate a higher index of suspicion for the early recognition of IPF
• Summarize the clinical, radiographic, and pathologic tools used to identify IPF
• Diagnose IPF earlier and with greater accuracy, improving patient outcomes

INTENDED AUDIENCE

This educational activity is intended for pulmonologists, pathologists, radiologists, and primary care physicians.

METHOD OF PARTICIPATION

This monograph should take approximately 1 hour to complete. The participant should, in order, read the objectives and monograph.

DISCLAIMER

The content and views presented in this educational activity are those of the author and do not necessarily reflect those of The France Foundation. This material is prepared based upon a review of multiple sources of information, but it is not exhaustive of the subject matter. Therefore, health care professionals and other individuals should review and consider other publications and materials on the subject matter before relying solely upon the information contained within this educational activity.
FACULTY MEMBER

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INTRODUCTION
Idiopathic pulmonary fibrosis (IPF) is a chronic and often fatal lung disease characterized by progressive fibroproliferation, destruction of the alveolar architecture, and a relentless decline in pulmonary function. It affects more than 80,000 men and women in the United States, and approximately 30,000 new cases are diagnosed each year.

The diagnosis of IPF represents a significant challenge for the clinician. The earliest clinical signs of the disease, which include a gradual onset of worsening dyspnea and a chronic nonproductive cough, are rather nonspecific and indistinguishable from those associated with several common diseases, including a number of pulmonary, cardiac, connective tissue, and vascular disorders. Moreover, the absence of reliable biomarkers or specific diagnostic tests further complicates the diagnostic process.

As a result of these challenges, the diagnosis of IPF is often either missed or delayed until it has reached an advanced stage. In a recent prospective study of 238 patients with IPF, King and colleagues reported that the median duration of illness prior to diagnosis was 24 months (range 12–46 months). In light of emerging evidence suggesting that early intervention may improve patient outcomes, there is a critical need to provide physicians with practical, comprehensive continuing education aimed at facilitating the early and accurate diagnosis of IPF.

The following pages outline a detailed approach to the diagnosis of IPF, highlighting the key elements of the clinical, radiographic, and pathologic evaluation of patients with suspected interstitial lung disease. The goal of the monograph is to provide a scientifically based, yet practical approach to the early and accurate diagnosis of IPF.

DEFINITION of IDIOPATHIC PULMONARY FIBROSIS
In 2000, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) published an international consensus statement that defined idiopathic pulmonary fibrosis as a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the histologic appearance of usual interstitial pneumonia (UIP). The hallmark features of the UIP include dense peripheral fibrosis, scattered foci of fibroblast proliferation, microscopic honeycombing, and a temporally heterogeneous pattern (alternating areas of fibrosis adjacent to normal lung tissue).
In 2002, the ATS and ERS published an additional international consensus statement that provided a uniform classification system for the various idiopathic interstitial pneumonias, each of which has a reasonably characteristic clinical/radiologic/histologic pattern (Figure 1).

**FIGURE 1. IDIOPATHIC INTERSTITIAL PNEUMONIAS**

According to the 2000 ATS/ERS statement, idiopathic pulmonary fibrosis is a diagnosis of exclusion. Even when a surgical lung biopsy reveals a histopathologic pattern of UIP, a definitive diagnosis requires the exclusion of other known causes of interstitial lung disease, including collagen vascular disease, drug toxicity, and various environmental exposures (Table 1).

**TABLE 1. DEFINITIVE DIAGNOSIS OF IPF IN THE PRESENCE OF UIP ON LUNG BIOPSY**

1. Exclusion of other known causes of interstitial lung diseases, such as drug toxicities, environmental exposures, and collagen vascular diseases
2. Abnormal pulmonary function studies that include evidence of restrictive disease (decreased VC, increased FEV₁/FVC) and/or impaired gas exchange (increased AaPO₂ difference, decreased DLco)
3. Specific abnormalities on conventional chest radiographs or high-resolution computed tomography (HRCT) scans

In some patients, surgical lung biopsy is unobtainable or simply not necessary to diagnose IPF, and a combination of clinical presentation and noninvasive evaluations can strongly suggest a diagnosis of IPF. The consensus statement further describes 4 major and 4 minor criteria, and suggests that the presence of all 4 major and 3 of the 4 minor criteria significantly increases the likelihood of a correct diagnosis of IPF (see Table 2).
## TABLE 2. CRITERIA FOR DIAGNOSING IPF IN THE ABSENCE OF LUNG BIOPSY

<table>
<thead>
<tr>
<th>Major Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Exclusion of other known causes of interstitial lung disease, such as drug toxicities, environmental exposures, and connective tissue diseases</td>
</tr>
<tr>
<td>• Abnormal pulmonary function studies exhibiting restrictive disease and impaired gas exchange</td>
</tr>
<tr>
<td>• Bibasilar reticular pattern with a minimum of ground glass opacities on HRCT</td>
</tr>
<tr>
<td>• Transbronchial biopsy or bronchoalveolar lavage (BAL) without features that support an alternate diagnosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age &gt; 50 years</td>
</tr>
<tr>
<td>• Insidious onset of otherwise unexplained dyspnea on exertion</td>
</tr>
<tr>
<td>• Duration of illness ≥ 3 months</td>
</tr>
<tr>
<td>• Bibasilar, inspiratory crackles (dry or “Velcro” type)</td>
</tr>
</tbody>
</table>

Many factors must be weighed before making the decision to perform a surgical lung biopsy. Raghu and colleagues demonstrated that a thorough clinical assessment and HRCT are both associated with a very high specificity (97% and 90%, respectively) but a relatively low sensitivity (62% and 78.5%, respectively) for the diagnosis of new-onset IPF. Thus, the investigators concluded that not all patients with suspected IPF require a surgical biopsy for accurate diagnosis, but when the diagnosis is unclear, a biopsy is indicated.

### MEDICAL HISTORY

The evaluation of a patient with suspected IPF begins with a thorough medical history. Patients may note a variety of symptoms. The most prominent is a dry cough and shortness of breath on exertion. Cough is often of insidious onset, occurring in paroxysms that are refractory to treatment with antitussive agents, while dyspnea is the most disabling of symptoms, progressive in nature, and is usually present for greater than 6 months prior to initial presentation. On the other hand, low-grade fevers, weight loss, malaise, fatigue, myalgias, and other constitutional symptoms are infrequent in patients with IPF, and their existence and relative prominence may be suggestive of a systemic disorder, not limited to the lungs.

Of note, patients with IPF are always adults, typically greater than 50 years of age, thus helping to distinguish this condition from diseases such as sarcoidosis and histiocytosis X, which have a predilection for younger patients.
Where IPF is suspected, the goal of a medical history should be to formulate a differential diagnosis. The physician should elicit information indicative of diseases that may mimic IPF. Obtaining historical information about a patient’s occupational background, known environmental exposures, medications, comorbid diseases, family diseases, and social behaviors (use of tobacco, alcohol, and recreational drugs), can direct the physician toward the appropriate work-up and diagnosis. For example, asbestos or silica exposure would prompt evaluation for a pneumoconiosis, while a past malignancy may suggest recurrence, drug toxicity, or radiation induced pulmonary fibrosis, which might present similarly to IPF.2,6

The review of systems is particularly important. Every abnormality should be considered a possible clue to the interstitial lung disease diagnosis. Gastroesophageal reflux, Raynaud phenomenon, or Sjögren symptomatology of dry eyes or dry mouth would suggest a connective tissue disease. Sinus or renal disease should prompt testing for small vessel vasculitis. Each symptom should prompt an inquiry for medications used for symptom relief. Past pneumothoraces should prompt a consideration of those interstitial lung diseases that are associated with air trapping, such as Langerhans cell granulomatosis or lymphangioleiomyomatosis.

**PHYSICAL EXAMINATION**

The single most common finding on physical examination of patients with IPF is crackles on chest auscultation. These crackles are evident in about 80% of patients and are described as dry, end-inspiratory, and “Velcro” in quality, occurring most frequently in a bibasilar pattern.2 Other findings that have been noted include digital clubbing (up to 50% of patients), and in late-stage disease, signs often associated with right ventricular overload: cyanosis, an accentuated pulmonic second heart sound, a right ventricular heave, and peripheral edema. All of these findings are nonspecific but help to confirm an underlying pulmonary process.

The physical examination may provide clues to lung diseases other than IPF. A skin exam should always be performed. The interstitial lung diseases with common skin manifestations include sarcoidosis, systemic lupus erythematosus, systemic sclerosis (scleroderma), and dermatomyositis. Subcutaneous nodules, synovial tenderness or thickening, or joint deformities should prompt an evaluation for rheumatoid arthritis. Occulocutaneous albinism is seen in the Hermansky-Pudlak syndrome.

**PULMONARY PHYSIOLOGIC TESTING**

A restrictive pattern of disease is the most common finding elicited from pulmonary function tests (PFTs) in patients with IPF. Typically, this restrictive impairment manifests itself with reduced measures of lung capacities and volumes, such as total lung capacity (TLC),
It is important to note that these measures may, in fact, be normal in IPF patients suffering from a concomitant obstructive disease, such as chronic bronchitis or emphysema in which the FEV$_1$/FVC may be decreased. Furthermore, it is possible to find patients with IPF that have normal PFTs while at rest although diffusion capacity (DL$_{CO}$) is usually decreased.

**TABLE 3. PHYSIOLOGIC PATTERNS IN IPF**

<table>
<thead>
<tr>
<th>Physiologic Measure</th>
<th>Direction of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>↓ ↔</td>
</tr>
<tr>
<td>FEV$_1$/FVC</td>
<td>↑ ↔</td>
</tr>
<tr>
<td>DL$_{CO}$</td>
<td>↓</td>
</tr>
<tr>
<td>TLC</td>
<td>↓ ↔</td>
</tr>
<tr>
<td>Exercise AaPO$_2$ difference</td>
<td>↑</td>
</tr>
</tbody>
</table>

The fibrotic noncompliant lungs that create the restrictive picture in patients with IPF also have problems with gas exchange. One correlate of the gas exchange abnormality is the degree of decrease in the DL$_{CO}$. The anatomic changes that produce a reduced DL$_{CO}$ include thickening of the alveolar capillary membrane with connective tissue, vascular dropout from fibrosis, and abnormalities with ventilation and perfusion matching from altered airways, blood vessels, and lung parenchyma. This ventilation/perfusion mismatch causes a widened alveolar-arterial oxygen gradient (AaPO$_2$) and ultimately hypoxemia. The degree of gas exchange abnormality is accentuated with exercise.

Exercise testing has, therefore, found a place in the diagnosis and monitoring of patients with IPF. Typically, tests such as the 6-minute walk test (6MWT) have been used to gauge the functional exercise capacity and response to treatment of patients with debilitating heart and lung diseases. After baseline vital signs (blood pressure, pulse, O$_2$ saturation) are measured, patients are instructed to walk as far as they can in a 6-minute period. They can stop as much as necessary and use supplemental oxygen if needed to maintain oxygen saturation. The primary endpoint is walking distance, but other endpoints, such as oxygen saturation and level of dyspnea, are also very useful. Furthermore, repeat measures using the 6MWT can provide information regarding response to therapeutic interventions and change in functional capacity.
In cases where a primary pulmonary process is suspected, exercise desaturation can suggest early stages of interstitial lung disease and pulmonary hypertension, or late stages of obstructive lung diseases, such as COPD and emphysema. In other words, the specificity of the 6MWT is low, but when taken together with other clinical data (history, physical, PFTs), an interstitial lung disease may be suspected and further testing, such as HRCT, may be indicated.

The utility of a 6MWT goes beyond diagnosis and functional capacity. Exercise-induced hypoxia is also an index of the severity of interstitial lung disease and can define prognosis in terms of mortality. Lama and colleagues followed 83 consecutive patients with biopsy-proven UIP with a 6MWT and found that patients with oxygen desaturation (defined as SaO$_2 \leq 88\%$) during the test had significantly reduced survival when compared to those who did not desaturate ($P = .002$). UIP patients with a 6MWT desaturation had 4.2 times the risk of death when compared to the UIP patients who did not experience desaturation. The relative 4-year survival rates for patients with UIP in this study were 69% for those patients who did not experience desaturation during the 6MWT and 35% for those patients who did experience desaturation.

Although right ventricular overload and cor pulmonale are late sequelae of IPF, patients in the early stages of their disease may have evidence of pulmonary hypertension when exercising. Pulmonary hypertension (mean pulmonary artery pressure > 30 mm Hg) at rest is a poor prognostic finding. Patients with IPF also frequently develop sleep disturbances that tend to occur most frequently in patients with daytime SaO$_2 < 90\%$ or a history of snoring. These patients have hypoxemia and reduced rapid eye movement sleep during the night and require overnight supplemental oxygen.

**LABORATORY AND SEROLOGIC TESTS**

Blood tests, like physical examinations, are not used to specifically identify the presence of IPF but rather to help distinguish it from other similar diseases. Among the tests that have been evaluated in association with IPF are ESR, LDH, RF, ANA, and anti–Jo-1 antibody (see Table 4). Of note, when circulating ANA and RF are detected (10%--20% of IPF patients), titers rarely exceed 1:160, in which case a connective tissue disease is more likely. Furthermore, an ECG, which is usually normal in the presence of IPF, may show a pattern consistent with right heart strain or right ventricular hypertrophy in cases where IPF has caused pulmonary hypertension.
### TABLE 4. BLOOD TESTS FOR PATIENTS SUSPECTED OF HAVING IPF*

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete blood cell count</strong></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>4–11 x 10^9/mm³</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Male: 13.5–18 g/dL Female: 11.5–15 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Male: 40%–54% Female: 37%–47%</td>
</tr>
<tr>
<td>Platelets</td>
<td>150–400 x 10^9/mm³</td>
</tr>
<tr>
<td><strong>Liver profile</strong></td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td>0–250 U/L</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>20–115 U/L</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0–1.0 mg/dL</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>0–0.2 mg/dL</td>
</tr>
<tr>
<td>AST</td>
<td>0–35 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>0–35 U/L</td>
</tr>
<tr>
<td><strong>CPK</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>&lt;195 U/L</td>
</tr>
<tr>
<td>Female</td>
<td>&lt;170 U/L</td>
</tr>
<tr>
<td><strong>Aldolase</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>&lt;9 U/L</td>
</tr>
<tr>
<td>Female</td>
<td>&lt;8 U/L</td>
</tr>
<tr>
<td><strong>Antinuclear antibodies (ANA)</strong></td>
<td>Negative (&lt;1:40)</td>
</tr>
<tr>
<td><strong>Rheumatoid factor (RF)</strong></td>
<td>&lt;30 IU/mL</td>
</tr>
<tr>
<td><strong>Erythrocyte sedimentation rate (ESR)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0–20 mm/h</td>
</tr>
<tr>
<td>Female</td>
<td>0–30 mm/h</td>
</tr>
<tr>
<td><strong>Antitopoisomerase I antibody (Scl-70)</strong></td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Anti–Jo-1 antibody</strong></td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Angiotensin-converting enzyme (ACE)</strong></td>
<td>14–70 Units</td>
</tr>
<tr>
<td><strong>Antineutrophil cytoplasmic antibodies (ANCA)</strong></td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Hypersensitivity panel</strong></td>
<td></td>
</tr>
<tr>
<td>Quantitative immunoglobulin analysis</td>
<td>Negative</td>
</tr>
</tbody>
</table>

* These tests are not specific for IPF and are used to identify or eliminate diseases that are among the differential diagnoses associated with IPF.

These tests should be tailored appropriately to the clinical situation. For example, a patient presenting with myalgias with pulmonary symptoms should have CPK, aldolase, and...
anti-Jo-1 antibody testing to assist in identifying the possibility of coexisting dermatomyositis/ polymyositis and interstitial lung disease. In addition, a hypersensitivity panel may be beneficial for patients with pets, especially birds. However, it is crucial to obtain a thorough exposure history from these patients, since the number of potential antigens not represented on any hypersensitivity panel is large.

**CHEST RADIOGRAPH**

Although most patients presenting with the signs and symptoms of IPF have an abnormal chest radiograph at presentation, a normal x-ray cannot exclude the existence of IPF. Typical features seen on a chest radiograph in IPF patients include reticular opacities concentrated primarily at the bases and periphery, as well as “honeycomb” changes reflective of cystic airspace dilation (see Figure 2). Additionally, decreased lung volumes may be evident on the chest radiograph of IPF patients. The identification of other findings on a chest x-ray, such as confluent alveolar opacities, pleural disease, and significant lymphadenopathy, would suggest an alternate diagnosis.

Chest radiography plays a further role in assessing disease progression and in the identification of superimposed processes, such as malignancy or infection. Although optimal timing for a repeat chest x-ray is unknown, most physicians will obtain repeat studies when clinical deterioration is noted.

**FIGURE 2. CHEST RADIOGRAPH IN A PATIENT WITH IPF.**

Pulmonary fibrosis typically shows reticular opacities at the bases and “honeycomb” changes.
HIGH-RESOLUTION COMPUTED TOMOGRAPHY

HRCT has a critical role in the diagnosis of IPF. It has completely altered the practice of assessing patients with IPF, allowing for earlier diagnosis and increased clinical accuracy. The primary role of HRCT in patients with suspected idiopathic interstitial pneumonia (IIP) is to separate patients with IPF from those with other types of IIP. The process of HRCT involves very thinly spaced images (1–2 mm) of the lung tissue, reconstructed to maximize spatial resolution. In an informal meta-analysis of 145 patients with histologically confirmed IPF, a correct HRCT diagnosis of IPF was made in 84% of cases.11

Moreover, in situations where the clinical diagnosis of IPF is uncertain, HRCT helps in limiting the differential diagnosis and can also help in identifying the extent of coexisting conditions, such as emphysema.

The features on HRCT that have been found to correlate with a positive UIP diagnosis include bibasilar reticular abnormalities that are generally patchy, peripheral, and subpleural. The amount of ground glass opacities should be small. The most specific elements consist of a patchy distribution of honeycombing, traction bronchiectasis, and bronchiolectasis (see Figure 3).

Research suggests that certain HRCT findings are highly specific for IPF and can be used to make a diagnosis in the absence of surgical lung biopsy. Hunninghake and colleagues conducted a double-blind, prospective study to assess the accuracy of a correct diagnosis of IPF by HRCT, and found that a confident diagnosis of IPF made by an experienced pulmonologist or radiologist based on clinical and radiologic data alone is sufficient to obviate the need for surgical lung biopsy.13

These investigators analyzed the data from 91 patients suspected of having an IIP. They found that 54 (59%) had IPF, based on a surgical lung biopsy showing UIP, and 37 (41%) had a variety of other diseases (silicosis, respiratory bronchiolitis, hypersensitivity pneumonitis, sarcoidosis, histiocytosis X, cryptogenic organizing pneumonia [COP], nonspecific interstitial pneumonia [NSIP], bronchoalveolar carcinoma, and eosinophilic pneumonia).

A core group of 4 chest radiologists independently evaluated the HRCT scans from 8 referral centers and provided an overall clinical diagnosis with a rating of certainty (certain, uncertain, unlikely). When the core radiologists provided a rating of “certain” to a diagnosis of IPF, they were correct in 26/27 cases for a positive predictive value of 96%. When the core radiologists provided a rating of “certain” to a diagnosis other than IPF, they were correct in 21/25 cases for a positive predictive value of 84%. The study investigators concluded that a
confident clinical and radiological diagnosis of IPF may make a surgical lung biopsy unnecessary, and lung biopsy may be most helpful when clinical and radiologic data result in an uncertain diagnosis or when patients are thought not to have IPF.

A multivariable analysis of the 91 patients found lower-lobe honeycombing (odds ratio 5.36; \(P = .007\)) and upper-lung irregular lines (odds ratio 6.28; \(P = .004\)) were the only predictors of UIP. With these 2 findings alone, the radiologist could correctly identify IPF with a sensitivity of 74%, specificity of 81%, and positive predictive value of 85%. The core pulmonologists in this study evaluated whether symptoms, signs, smoking status, PFT results, or radiologic evaluations reliably predicted UIP on surgical lung biopsy. They found that the only two variables associated with IPF were HRCT consistent with IPF and chest radiograph consistent with IPF. When either HRCT or CXR consistent with IPF was used for diagnosis, the sensitivity was 91%, and the specificity was 72%.

**FIGURE 3. CT IMAGES OF A PATIENT WITH IPF**

The findings of reticular opacity and honeycombing are not pathognomonic of IPF. Instead, there are other disease states that can share the pathology of usual interstitial pneumonia. These include advanced rheumatoid interstitial lung disease, radiation fibrosis, scleroderma interstitial lung disease, polymyositis/dermatomyositis, and asbestosis. In addition, the late stages of chronic hypersensitivity pneumonitis, and COP (previously called bronchiolitis obliterans organizing pneumonia [BOOP]) can show honeycombing and be confused with IPF on HRCT. In the presence of clinical features that are consistent with IPF; however, these findings markedly increase the likelihood of a diagnosis of IPF.
Furthermore, HRCT has been proposed as a technique of delineating disease activity and characterizing its magnitude. Multiple studies have shown that the overall extent of lung involvement correlates with histologic grades of disease activity and physiologic impairment in patients with IPF. The extent of interstitial cellularity and fibrosis has been found to correspond to areas of opacification on CT scan.15-17

Xaubet and colleagues demonstrated an independent association between global disease involvement on HRCT and both the FVC ($P = .003$) and DL$_{CO}$ ($P = .03$) on pulmonary function testing.16 These investigators concluded that the physiologic variables that best reflect the overall extent of disease in IPF are FVC and DL$_{CO}$, and these variables may provide important information about disease progression.

In terms of prognosis, HRCT has been used to help predict mortality in patients with IPF. Flaherty and colleagues hypothesized that the HRCT appearance of IIPs would have an impact on the survival of patients with these diseases.17 Two thoracic radiologists independently reviewed the HRCT scans from 96 patients—73 with a histological diagnosis of UIP and 23 with a histological diagnosis of NSIP—and recorded each case as definite UIP, probable UIP, indeterminate (equal probability of UIP or NSIP), probable NSIP, or definite NSIP. Honeycombing, an abnormality correlating strongly with pathological fibrosis and impaired survival, was the sole finding on HRCT radiologists consistently identified as indicating definite or probable UIP. Of the 96 patients they studied, the radiologists identified 27 as having definite or probable UIP. All 27 patients were confirmed UIP upon pathological examination, and these patients were found to have the worst overall survival. In a median follow-up of 3.1 years, 17 deaths occurred in this group, with a median survival of only 2.08 years.17

In general, patients with a histological diagnosis of UIP have a much worse prognosis than those with a histological diagnosis of NSIP. In Flaherty’s study,17 those diagnosed with UIP had a median survival of 3.98 years, and those with NSIP had a median survival of > 9 years. Moreover, HRCT features add prognostic information to the histological diagnosis of UIP. Patients with both a histological and an HRCT diagnosis of UIP had a significantly decreased rate of survival compared to patients with a histological diagnosis of UIP and an atypical HRCT for UIP (median survival of 2.08 years and 5.67 years, respectively).17 However, some patients with the fibrotic subtype of NSIP present with severely impaired physiology and in this situation have survival similar to UIP. Therefore, the conclusion is that patients with HRCT features typical for UIP are likely to have UIP on histological examination. When UIP is not suggested by HRCT, a surgical lung biopsy is indicated to define the cause of interstitial lung disease and assist with determining the prognosis.
Although HRCT is clearly favorable to conventional chest radiography in detecting even the earliest cases of IPF, it falls short of positively diagnosing all patients. This imperfect sensitivity can cause physicians to erroneously exclude IPF based on a normal HRCT. In a prospective study of patients with IPF, Orens and colleagues found that in 25 patients with biopsy-proven IPF, 3 (12%) had no evidence of interstitial abnormalities on HRCT. It is noteworthy that the investigators in this study identified measures of pulmonary physiology more sensitive than radiologic testing in detecting early cases of IPF.

OTHER IMAGING TECHNIQUES

Other imaging techniques, including magnetic resonance imaging and gallium imaging, remain unproven in their ability to further discriminate between IPF and other pulmonary processes.

BRONCHOSCOPY, BRONCHOALVEOLAR LAVAGE, AND TRANSBRONCHIAL LUNG BIOPSY

BAL and transbronchial lung biopsy (TBB) are of little diagnostic value in specifically identifying IPF, but they play a role in narrowing the differential diagnosis and ruling out diseases that can mimic IPF. IPF has been associated with neutrophilia on BAL fluid examination, but these findings are also evident in many other fibrosing lung conditions, including the fibrosing alveolitis of rheumatologic disease, and asbestosis. On the other hand, BAL fluid lymphocytosis is suggestive of different diseases including drug-induced lung disease, granulomatous diseases, and importantly hypersensitivity pneumonitis. A lymphocytic BAL should prompt a return to the history to review all possible hypersensitivity antigens, since the sensitivity for BAL in making this diagnosis may be greater than the sensitivity of open lung biopsy.

BAL is a useful modality for revealing other conditions, including pulmonary Langerhans cell granulomatosis (histiocytosis X), occupational dust exposures, malignancies, infections, and eosinophilic pneumonia. TBB has many of the same shortcomings as BAL in its ability to specifically diagnose IPF. Importantly, a TBB that shows interstitial fibrosis is not sufficient to establish a diagnosis of IPF.

SURGICAL LUNG BIOPSY

Histopathologic specimens obtained through surgical lung biopsy represent the “gold standard” in diagnosing IPF. The pathologic identification of patients with IPF is based on a pattern of UIP, which distinguishes it from other forms of IIP. Tissue samples for pathologic examination are best obtained surgically with either an open or video-assisted approach. When compared to open-lung biopsy, video-assisted thoracoscopic (VATS) lung biopsy has
earned a reputation as the preferred method of sampling, secondary to studies demonstrating reduced morbidity. When compared to open thoracotomy, patients having a VATS lung biopsy experienced less prolonged chest-tube drainage and reduced hospital stays.21

The histopathologic description of UIP consists of a temporally heterogeneous appearance at low magnification with alternating areas of normal lung, interstitial inflammation, fibrosis, and honeycomb change (see Figure 4). The areas of abnormality are concentrated at the periphery. When viewed at higher power, the areas of interstitial inflammation are seen to be composed of an alveolar septal infiltrate of plasma cells and lymphocytes. These areas are juxtaposed with areas of marked fibrotic scarring and cystic changes, as well as loosely organized groupings of connective tissue and myofibroblasts known as fibroblastic foci. Areas of honeycomb change identified on pathological section are described as cystic fibrotic air spaces lined by bronchiolar epithelial cells and filled with mucin.

**FIGURE 4. PATHOLOGICAL SECTIONS, DEMONSTRATING UIP**

a. Peripheral accentuation of the disease  
b. Transition to uninvolved lung  
c. Pathology of UIP/IPF  
d. Fibroblastic foci in UIP (demonstrated by arrow)

(courtesy of Kevin O. Leslie, MD)
SUMMARY AND CONCLUSIONS

In summary, the diagnostic approach to IPF is multidisciplinary, involving primary care physicians, pulmonologists, radiologists, and pathologists (see Figure 5). It begins with a complete clinical evaluation, including history, physical examination, chest radiograph, laboratory studies, and pulmonary physiologic testing. After this thorough assessment, patients suspected of having an IIP should undergo a HRCT scan of their lungs. In some instances, an experienced chest radiologist can make a confident diagnosis of IPF or other diffuse lung disease without further diagnostic intervention. When the HRCT results are unclear, many patients will proceed directly to surgical lung biopsy, but others may have BAL and/or TBB, which can be used to diagnose diseases that mimic IPF, and thus eliminate it as a primary diagnosis. Ultimately, surgical lung biopsy is the gold standard in diagnosing IPF.

FIGURE 5. DIAGNOSTIC APPROACH TO IPF

![Diagram](image)


Despite the current lack of effective treatments for patients with IPF, data from trials of novel therapies have suggested that patients may, in fact, benefit from appropriate treatment early in the course of their disease. Raghu and colleagues found that among a cohort of 174 IPF patients with less severely impaired lung function (baseline FVC ≥ 62% predicted), those treated with interferon gamma-1b experienced a significantly prolonged survival when compared to those treated with placebo ($P = 0.04$). Although this measure of overall survival was not the primary endpoint, these investigators observed a trend in survival among healthier patients, signifying that IPF patients may be more responsive to therapy when the disease is in its early stages. More research is needed to further elaborate on this trend, but the medical community is now challenged to heighten its awareness of the need for early diagnosis of patients with IPF and to employ the multidisciplinary strategies necessary to realize this goal.
REFERENCES
