

# **Medical Education Systems, Inc.**

## **Idiopathic Pulmonary Fibrosis- Diagnosis and Treatment**



Medical Education Systems, Inc.

TOLL FREE: 877-295-4719

LOCAL: 619-295-0284

FAX: 619-295-0252

EMAIL: [info@mededsys.com](mailto:info@mededsys.com)

WEBSITE: [www.mededsys.com](http://www.mededsys.com)

P.O Box 81831 San Diego, CA 92138-3939.



# Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment International Consensus Statement

## INTRODUCTION

Many acute and chronic lung disorders with variable degrees of pulmonary inflammation and fibrosis are collectively referred to as interstitial lung diseases (ILDs) or diffuse parenchymal lung diseases. Idiopathic pulmonary fibrosis (or cryptogenic fibrosing alveolitis) (IPF or CFA) is one of several idiopathic interstitial pneumonias. IPF is now recognized as a distinct clinical disorder. Despite major accomplishments in our understanding of the pathogenesis of lung fibrosis (1), the diagnosis and management of patients with IPF continues to pose significant challenges (2).



## OBJECTIVE

This is an international consensus statement defining the diagnosis, evaluation, and management of patients with IPF that has been produced as a collaborative effort from the American Thoracic Society (ATS), European Respiratory Society (ERS), and the American College of Chest Physicians (ACCP). The purpose of this consensus statement is to provide assistance to clinicians in the diagnosis and management of idiopathic pulmonary fibrosis (IPF). The targeted providers are pulmonary subspecialists.

### Learning Objectives

- Identify the definition of idiopathic pulmonary fibrosis (IPF).
- Identify how idiopathic pulmonary fibrosis is diagnosed/
- Identify current treatment protocols and their likely outcomes.
- List the recommendations regarding idiopathic pulmonary fibrosis made in this course.



## PARTICIPANTS

Panel members are experts in adult pulmonary diseases. Panel members were nominated by the supporting associations. The chair was selected by the American Thoracic Society. Panel members were selected because of an interest and expertise in the interstitial lung disease and to provide a range of opinions, expertise, and geography.

## **EVIDENCE**

The expert panel was provided with background articles that reviewed the existing scientific evidence. Relevant articles from the medical literature were identified by a MedLine search of English language articles or articles with English abstracts, the bibliographies of the articles retrieved, and the authors' files. In addition, articles in other languages were also obtained from the bibliographies of the articles retrieved and were reviewed or translated by pulmonary physicians knowledgeable in this area. All articles in which IPF was identified were included in this review. More than 3,500 published reports were critically reviewed for information on IPF, including its physiologic, radiologic, and pathological findings; its pathogenesis, epidemiology, clinical presentation, and staging; its inheritance or familial occurrence; its treatment (including lung transplant); and its prognosis. The panel was divided into subgroups responsible for the review of the data and writing of a specific section of the statement. The final statement was drafted after a series of meetings of the entire committee.

The level of evidence for the recommendations made in this statement is largely that of expert opinion developed by consensus. There is no supportive evidence from well conducted randomized controlled trials. The best evidence is from well-conducted cohort studies or from case-control studies. Even in these instances the diagnosis of IPF was frequently not well established and the series often included patients with other diseases or potential causes of lung fibrosis.

## **VALIDATION**

The document was subjected to external review by peer reviewers identified by the American Thoracic Society, the American College of Chest Physicians, and the European Respiratory Society. It was submitted for review and approval to the governing bodies of the American Thoracic Society, the European Respiratory Society, and the American College of Chest Physicians.

## **OUTCOMES**

The recommendations are applicable only to immunocompetent adult patients with IPF. The goals of this statement included reevaluating the roles of all investigative methods that apply to

diagnosing IPF. Therefore a revision of the definition of IPF is provided in an effort to make it sufficiently sensitive to include true positive cases while being sufficiently specific to exclude those conditions most likely to be confused with IPF. Key conclusions or recommendations from this consensus panel include the following:

1. The committee concludes that usual interstitial pneumonia (UIP) is the histopathological pattern that identifies patients with IPF. The histopathologic patterns of desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-associated interstitial lung disease (RBILD), nonspecific interstitial pneumonia (NSIP), lymphoid interstitial pneumonia (LIP), acute interstitial pneumonia (AIP), and idiopathic bronchiolitis obliterans organizing pneumonia (idiopathic BOOP) are considered separate entities and are to be excluded from the group of patients with IPF.
2. Clinical criteria are specified for determining the presumptive diagnosis of IPF and distinguishing IPF from other diffuse parenchymal lung diseases.
3. The committee concludes that surgical lung biopsy (open thoracotomy or video-assisted thoracoscopy) is recommended in most patients, especially those with suspected IPF who have clinical, physiological, or radiological features that are not typical for IPF and who are without contraindications to surgery. A major purpose of histological examination is to distinguish UIP from other histological subsets of the idiopathic interstitial pneumonias that have a better response to available treatment.
4. The committee concludes that no data exist that adequately document any of the current treatment approaches improves survival or the quality of life for patients with IPF.
5. The committee suggests that therapy is not indicated for all patients with IPF. If therapy is recommended to a patient, the panel proposes that it should be started at the first identification of clinical or physiological evidence of impairment or documentation of decline in lung function. Recommendations are made regarding therapy for patients with IPF.
6. The committee recommends that a combination of clinical, radiographical, and physiological parameters be used to assess the clinical course and response to treatment of IPF.
7. The committee recommends that lung transplantation be considered for those patients who experience progressive deterioration and who meet the established criteria for lung transplantation.
8. The committee recommends that a multicenter, international consortium be established to determine the natural history and optimal treatment strategy for the management of patients with IPF.



## **DEFINITION**

IPF is defined as a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the histologic appearance of usual interstitial pneumonia (UIP) on surgical

(thoracoscopic or open) lung biopsy. The etiology is unknown. The definite diagnosis of IPF in the presence of a surgical biopsy showing UIP includes the following:

1. Exclusion of other known causes of interstitial lung disease such as drug toxicities, environmental exposures, and collagen vascular diseases
2. Abnormal pulmonary function studies that include evidence of restriction (reduced VC often with an increased FEV<sub>1</sub>/FVC ratio) and/or impaired gas exchange [increased AaPO<sub>2</sub> (alveolar-arterial pressure difference for O<sub>2</sub>) with rest or exercise or decreased DL<sub>CO</sub> (diffusing capacity of the lung for CO)]
3. Abnormalities (described below) on conventional chest radiographs or high-resolution computed tomography (HRCT) scans

In early stages of IPF, pulmonary function or lung imaging studies may be normal or only slightly impaired. Patients with a history of cigarette smoking may have coexisting chronic obstructive lung disease, which will alter the manifestations of the disease as assessed by lung function and chest imaging studies.

In the absence of a surgical lung biopsy, the diagnosis of IPF remains uncertain. However, in the immunocompetent adult, the presence of all of the following major diagnostic criteria as well as at least three of the four minor criteria increases the likelihood of a correct clinical diagnosis of IPF.

### **Major Criteria**

- Exclusion of other known causes of ILD, such as certain drug toxicities, environmental exposures, and connective tissue diseases
- Abnormal pulmonary function studies that include evidence of restriction (reduced VC often with an increased FEV<sub>1</sub>/FVC ratio) and impaired gas exchange [increased AaPO<sub>2</sub> with rest or exercise or decreased DL<sub>CO</sub>]
- Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans
- Transbronchial lung biopsy or bronchoalveolar lavage (BAL) showing no features to support an alternative diagnosis

### **Minor Criteria**

- Age > 50 yr
- Insidious onset of otherwise unexplained dyspnea on exertion
- Duration of illness  $\geq$  3 mo

- Bibasilar, inspiratory crackles (dry or "Velcro" type in quality)



## EPIDEMIOLOGY OF IPF

### Incidence and Prevalence

The precise incidence and prevalence of IPF are not known. Previous prevalence estimates for IPF varied from 3 to 6 cases per 100,000 in the general population ([5](#), [6](#)). A more recent population-based study for all interstitial lung diseases in the county population of Bernalillo, New Mexico revealed a prevalence of 20.2 cases per 100,000 for males and 13.2 cases per 100,000 for females with IPF ([7](#)).

Incidence estimates for IPF are quite limited. It has been estimated at 10.7 cases per 100,000 per year for males and 7.4 cases per 100,000 per year for females ([7](#)). However, the criteria that provided the basis for these data are not precisely defined.

### Sex and Age

More males have been reported with IPF than females ([5](#), [6](#), [8](#)). Patients with IPF are often middle aged, usually between 40 and 70 yr of age. Approximately two-thirds of patients with IPF are over the age of 60 yr at the time of presentation, with a mean age at diagnosis of 66 yr ([6](#), [9](#), [11](#)). The incidence of the disease increases with older age ([6](#), [10](#)). In one study, incident cases tended to be older than prevalent cases ([9](#)). Prevalence for adults 35 to 44 yr was 2.7 per 100,000; by contrast, prevalence exceeded 175 per 100,000 for individuals older than 75 yr ([7](#)). It is unclear if a syndrome similar to IPF occurs in children; if so, it is rare ([17](#), [18](#)).

### Geographical Location and Ethnicity

IPF has no distinct geographical distribution. It is reported worldwide in both rural and urban settings with no predilection by race or ethnicity. However, the age-adjusted mortality rates appear higher among whites and lower among blacks ([10](#)). The reason for this finding is unclear and likely relates to inadequate reporting rather than to differences in the disease course in whites compared with blacks.

There is geographic variation in the age-adjusted mortality from pulmonary fibrosis. This variation may reflect differences in occupational or environmental exposures. In the United States, age-adjusted mortality rates due to pulmonary fibrosis are lowest in the Midwest and Northeast, and highest in the West and Southeast ([10](#)). In the United Kingdom, the highest rates of mortality secondary to IPF occur in the industrialized central areas of England and Wales ([19](#)).

### Vital Statistics

Vital statistics on pulmonary fibrosis are scant and known to be of limited value. Deaths from pulmonary fibrosis increase with increasing age ([10](#)). The mortality rate for IPF per

100,000 population was estimated to be 3.3 in men and 2.5 in women, with an overall rate of 3.0 in both sexes in Japan (5). Similarly, in England and Wales, the annual number of deaths attributed to CFA has doubled between 1979 and 1988 (19). A summary of various studies reports that the mean length of survival from the time of diagnosis varied between 3.2 and 5 yr (20). In another study, the median survival was 28.2 mo from the onset of respiratory symptoms (21). Death certificates underreport the diagnosis of IPF as found in studies in Britain (15, 22, 23) and in the United States (24).



## POTENTIAL RISK FACTORS FOR IPF

### Cigarette Smoking

In case-control studies, cigarette smoking has been identified as a potential risk factor with the odds ratio (OR) from various regions of the world ranging from 1.6 to 2.9 for the development of IPF in ever-smokers (5, 9, 25). The odds of developing IPF increased with the pack-years of smoking in a study from the United Kingdom, but this effect was not significant (9); while a study in the United States revealed that those with a history of smoking for 21 to 40 pack-years had an OR of 2.3 (95% confidence interval [CI], 1.3 to 3.8) (25).

### Exposure to Commonly Prescribed Drugs

One case-control study has suggested an association between exposure to antidepressants and the risk of development of pulmonary fibrosis (26). The significance of this finding in the pathogenesis of IPF is unknown.

### Chronic Aspiration

Chronic aspiration secondary to gastroesophageal reflux has been implicated in development of pulmonary fibrosis (27). It is not clear what role chronic aspiration plays in the pathogenesis of IPF.

### Environmental Factors

Various environmental exposures in rural or agricultural areas and in urban and manufacturing settings have been linked to increasing risk of developing pulmonary fibrosis in patients where a defined pneumoconiosis was not present (5, 6, 9, 28). Metal dust and wood dust exposure show the most prominent association with increased risk for developing pulmonary fibrosis independent of cigarette smoking (6, 9, 28). The risk of developing pulmonary fibrosis increases with the number of work years of exposure. Dust containing steel, brass, lead, and pine wood are most specifically linked to developing lung fibrosis. Exposure to solvents (29), and atopy (30) have been suggested in the development of pulmonary fibrosis.

Unfortunately, many of the studies attempting to define the environmental risks for developing pulmonary fibrosis are limited by a reliance on the clinical diagnosis without performance of HRCT scanning or confirmation of the presence of UIP on lung biopsy. Therefore, these data must be considered with caution.

## Infectious Agents

Numerous viruses have been implicated in the pathogenesis of IPF, but there remains no clear evidence for a viral etiology (31, 32). Vergnon and coworkers found an association between Epstein-Barr virus (EBV) infection and IPF (33). EBV viral capsid antigen has also been demonstrated in lung tissue analyzed by immunofluorescent staining (34). A higher incidence of EBV (33), influenza (36), cytomegalovirus (CMV) (40), and hepatitis C (41) infection has also been reported in patients with IPF. The increased prevalence of hepatitis C in patients with IPF is not greater than that in other medical conditions (43). Parainfluenza 1 virus (Sendai) (31), human immunodeficiency virus 1 (HIV-1) (44), measles virus (45), parainfluenza 3 virus (46), herpesvirus 6 (47), *Mycoplasma* (48), and legionnaires' disease (49) have also been implicated as potential participants in the pathogenesis of IPF. However, these reports mainly show evidence of nonspecific pulmonary fibrosis and it is unclear the extent to which these sequelae mimic IPF.

## Genetic Predisposition to IPF

Hereditary factors may contribute to the risk of developing IPF (50) but no specific genetic markers have been identified (55). The most compelling evidence for participation of genetic factors is descriptions of familial cases of IPF. Familial IPF (FPF) is defined as at least two members of a primary biological family (parent, child, sibling) having clinical features of IPF that are confirmed histologically (55, 56). Review of medical records of family members with apparent breathing problems may actually identify more families with familial pulmonary fibrosis and other inherited ILDs. Familial IPF is probably inherited as an autosomal dominant trait with variable penetrance (54). Males and females are equally affected. There has been no clear association with human leukocyte antigen (HLA) (53, 57). Several investigators have reported an association between IPF and  $\alpha_1$ -antitrypsin inhibition (Pi) alleles present on chromosome 14 (60).



## APPROACH TO THE DIAGNOSIS OF IPF

The differential diagnosis of ILD is large and includes a heterogeneous group of acute and chronic processes. There have been many reviews that describe the differential diagnosis of ILD and provide a diagnostic algorithm useful in evaluating a patient with ILD (3). The diagnostic process for a patient with diffuse parenchymal lung disease must start with the elicitation of a thorough and extensive medical history that should include review of symptoms or signs suggestive of a systemic disorder, occupational and environmental exposures, use of medications and drugs, and family medical history.

## History and Physical Examination

While it is essential to make an accurate diagnosis for appropriate therapeutic interventions, the physician must realize that the key diagnostic procedure in the evaluation of ILD is a thorough

clinical assessment. The patient's age at the time of presentation may provide useful clues—for example, IPF is almost always an adult disorder, typically occurring in patients beyond 50 yr of age; sarcoidosis is more commonly seen in young and middle-aged adults, although it can manifest in the elderly patient; pulmonary histiocytosis X typically occurs in young cigarette smokers; respiratory bronchiolitis-associated interstitial lung disease (RBILD) occurs predominantly in heavy cigarette smokers of all ages; lymphangioleiomyomatosis (LAM) occurs predominantly in women who are premenopausal and is rare.

IPF usually presents insidiously, with the gradual onset of a nonproductive cough and dyspnea. Dyspnea is usually the most prominent and disabling symptom. It is usually progressive and in most patients it is reported to have been present for > 6 mo before presentation. Patients may also complain of paroxysmal dry cough that is refractory to antitussive agents.

On physical examination, crackles are detected on chest auscultation in more than 80% of patients. These are typically "dry," end-inspiratory, and "Velcro" in quality, and are most prevalent in the lung bases. With progression of the disease, rales extend toward the upper lung zones. Clubbing is noted in 25 to 50% of patients ([11](#), [15](#)). Cyanosis, cor pulmonale, an accentuated pulmonic second sound, right ventricular heave, and peripheral edema may be observed in the late phases of the disease ([11](#), [20](#)).

Extrapulmonary involvement does not occur, but weight loss, malaise, and fatigue may be noted. Fever is rare, and its presence suggests an alternative diagnosis. Symptoms or signs suggestive of a connective tissue disease (joint pains or swelling, musculoskeletal pain, weakness, fatigue, fever, photosensitivity, Raynaud's phenomenon, pleuritis, dry eyes, dry mouth) should be carefully elicited.

### **Laboratory and Serological Tests**

The routine laboratory evaluation of a patient suspected of having IPF is often not helpful except to "rule out" other causes of diffuse parenchymal lung disease. Polycythemia is rare despite the frequent presence of chronic hypoxemia. An elevated erythrocyte sedimentation rate and hypergammaglobulinemia may be found but are nondiagnostic. Elevation of lactate dehydrogenase (LDH) may be noted but is a nonspecific finding common to pulmonary disorders (e.g., alveolar proteinosis, idiopathic pulmonary fibrosis). An increase in the angiotensin-converting enzyme (ACE) level, or the presence of antibodies to organic antigens or anti-neutrophil cytoplasmic antibodies, although nondiagnostic, may be helpful in suggesting alternative diagnoses.

Positive circulating anti-nuclear antibodies (ANAs) or rheumatoid factor occur in 10 to 20% of patients with IPF, but rarely are titers high. The presence of high titers (> 1:160) would suggest the presence of a connective tissue disease (63- 70). Rarely, a patient may present with the clinical features of IPF and later develop a defined connective tissue disease. In these cases, the term IPF is not maintained since the illness is secondary to the underlying, previously undiagnosed connective tissue disease (e.g., "rheumatoid lung"). These various tests do not correlate with the extent or activity of pulmonary fibrosis, and do not predict therapeutic responsiveness ([20](#)).

The electrocardiogram is usually normal in the absence of pulmonary hypertension or concurrent cardiac disease.

## **Chest Radiograph**

Virtually all patients with IPF have an abnormal chest radiograph at the time of presentation (11). Indeed, basal reticular opacities are often visible on previous chest radiographs in retrospect for several years before the development of symptoms. In individuals with such asymptomatic abnormalities, investigation by physiologic evaluation or by high-resolution CT scanning could lead to earlier detection and treatment of IPF. Conversely, a normal chest radiograph cannot be used to exclude microscopic evidence of UIP on lung biopsy (71, 72). However, the HRCT scan will likely show evidence of disease in most of the cases with a normal chest radiograph.

Peripheral reticular opacities, most profuse at the lung bases, are characteristic findings on the chest radiograph of patients with IPF (73). These opacities are usually bilateral, often asymmetric, and are commonly associated with decreased lung volumes. Confluent alveolar opacities are rarely visible on the chest radiograph of patients with IPF, and, if present, suggest some other diagnosis, such as DIP or BOOP (73, 74). Patients with combined emphysema and IPF may have preserved or increased lung volumes, and may have upper lobe oligemia (i.e., apparent reduction in blood vessels). The differential diagnosis of the basal reticular pattern includes asbestosis and connective tissue diseases (such as scleroderma or rheumatoid arthritis). When a "confident" diagnosis of IPF is made on the basis of the chest radiograph (compared with an "uncertain" or "unlikely" diagnosis of IPF), it is correct in 48% (75) to 87% (76, 77) of cases. Radiographic evidence of pleural disease or lymphadenopathy is not usually found in IPF.

Given the indolent course of IPF, the clinical utility and optimal timing of follow-up chest radiographs are unclear. Radiographs are indicated if clinical deterioration occurs, to assess progression of disease, or to identify superimposed infection or malignancy. The profusion of lung opacities may be quantified visually, using a modification of the International Labor Organization (ILO) criteria for pneumoconiosis (78). However, this technique is time-consuming, and has not been proven to be clinically useful (79).

## **High Resolution CT Scanning**

High-resolution CT (HRCT) scanning has changed the diagnostic evaluation of patients with IPF (72, 80, 81). The technique of high-resolution CT allows detailed evaluation of the lung parenchyma by using 1- to 2-mm-thick slices, with a reconstruction algorithm that maximizes spatial resolution. HRCT allows earlier diagnosis of IPF, helps to narrow the differential diagnosis based on the CT pattern, and allows the identification of the extent of associated emphysema (72, 82, 83). HRCT can also help to increase the level of diagnostic confidence for IPF, when the clinical or radiologic features are uncertain.

*Radiologic pattern in IPF.* The HRCT pattern of IPF commonly shows patchy, predominantly peripheral, subpleural, bibasal reticular abnormalities. There may also be a variable amount of ground glass opacity that is usually limited in extent. In areas of more severe involvement there is often traction bronchiectasis and bronchiolectasis and/or subpleural honeycombing.

*Accuracy of HRCT diagnosis.* Studies that have evaluated the ability of CT scanning to accurately diagnose IPF have found that CT increases the level of diagnostic confidence compared with the chest radiograph. The accuracy of a confident diagnosis of UIP made on HRCT by a trained observer appears to be about 90% (75, 84). However, because a confident diagnosis of IPF is made by HRCT evaluation in only about two-thirds of patients with histologic UIP (85), about one-third of cases of UIP will be missed by relying on CT diagnosis alone. Less experienced observers are substantially less accurate than experienced observers (75).

*Differential diagnosis of the HRCT pattern.* Connective tissue diseases (particularly scleroderma and rheumatoid arthritis) (86, 87) and asbestosis (88) are commonly similar in CT appearance to IPF, except for the presence of parenchymal bands of fibrosis and pleural plaques in patients with asbestosis. Patients with subacute or chronic hypersensitivity pneumonitis can have similar reticular opacity or honeycombing, but often lack the bibasilar predominance seen in IPF (84). IPF may also be mimicked on CT by sarcoidosis (92) or idiopathic BOOP (77).

Extensive ground glass opacity on CT of the lung ( $\geq 30\%$  of lung is involved) should prompt consideration of another diagnosis rather than IPF, particularly desquamative interstitial pneumonitis (DIP) (93). Similar ground glass opacification, without basal or peripheral predominance, may be found in patients with respiratory bronchiolitis-interstitial lung disease (94), hypersensitivity pneumonitis (84, 95), idiopathic BOOP (77), or nonspecific interstitial pneumonia (NSIP) (96). The presence of centrilobular nodules, middle and upper lobe lung predominance, and absence of honeycombing favor hypersensitivity pneumonitis over IPF (84). Most importantly, the CT features must be interpreted in conjunction with a complete clinical evaluation.

*Role of HRCT in determining disease activity.* HRCT has been proposed as a technique for determining the "activity" of IPF (97). The CT finding of ground glass opacity (also called ground glass attenuation or hazy increase in lung density) refers to the presence of a diffuse homogeneous increase in density of the lung. When this finding occurs in association with reticular lines, and dilated bronchi or bronchioles (traction bronchiectasis or bronchiolectasis), it always indicates lung fibrosis. In conditions other than IPF, isolated ground glass density is usually associated with inflammatory cells in the alveolar septum or alveolar lumen (i.e., alveolitis) (98).

The ground glass opacity seen on HRCT in some patients with IPF can be associated with alveolar inflammation (97), but is predominantly associated with patchy fibrotic thickening of alveolar septa, and intraalveolar granulation tissue (99). Some studies have suggested that ground glass attenuation predicts physiologic improvement after steroid treatment (81). Ground glass opacity on CT often regresses on treatment in patients who have histologic DIP, but may not decrease as readily in those with histologic UIP (100). An area of ground glass opacity may progress to reticular opacity or honeycombing on follow-up evaluation (79). Patients with predominant reticular opacity or honeycombing usually progress despite treatment (81, 100). The extent of lung fibrosis on CT is an important predictor of survival (103).

*Role of HRCT in defining disease extent.* CT is increasingly used for quantification of disease extent. Subjective, semiquantitative assessment of disease extent by CT shows moderate

interobserver variability. This semiquantitative assessment correlates with evidence of physiologic impairment (104, 105). One study showed that the extent of overall lung involvement and the extent of ground glass pattern in the HRCT scans show a moderate correlation only with FVC and arterial PO<sub>2</sub> at peak exercise (103). Use of parameters derived from the digital CT data set may provide a more objective measure of disease extent (106).

For detection of early or mild infiltrative lung disease, HRCT is clearly more sensitive than the chest radiograph (107). However, in the early stages of any lung disease, including IPF, the degree of parenchymal infiltration may be too slight to cause any CT abnormality (72). Indeed, it has been shown that patients with biopsy-proven hypersensitivity pneumonitis (107), sarcoidosis (108), asbestosis (109), and IPF (72) may have normal high-resolution CT studies. Therefore, although it is quite rare, a normal HRCT cannot be used to exclude infiltrative lung disease.

### **Other Imaging Techniques**

The extreme inhomogeneity of magnetic susceptibility in the lung hampers the use of magnetic resonance to image the lung parenchyma. It may in future be useful as a tool for discriminating between lung inflammation and established fibrosis (110). Gallium imaging is not of any proven value for evaluation of IPF. Aerosols containing <sup>99m</sup>Tc-DTPA, a hydrophilic agent, are cleared more rapidly when there is increased capillary permeability, and may provide an index of lung inflammation (111). However, the clinical role of this agent remains unproven.

### **Pulmonary Function Testing**

The typical findings of pulmonary function tests are consistent with restrictive impairment (reduced vital capacity [VC] and total lung capacity [TLC]) by body plethysmography (114). Unless a complicating airways disease occurs, isovolume flow rates are well maintained. The DL<sub>CO</sub> corrected for hemoglobin is reduced frequently and the decline in DL<sub>CO</sub> may precede abnormalities in lung volume. The maximal breathing capacity is usually normal. The resting arterial blood gases may be normal or reveal hypoxemia (secondary to ventilation and perfusion mismatch) and respiratory alkalosis, and these abnormalities may be elicited or accentuated by exercise.

*Lung volumes.* The lung volumes (TLC, functional residual capacity [FRC], and residual volume [RV]) are reduced at some point in the course of disease in all patients with IPF. Early on, or more commonly in patients with superimposed chronic obstructive pulmonary disease, the lung volumes may be normal. Lung volumes are higher in smokers compared with never-smokers with IPF (115).

Pressure-volume studies often yield a curve that is shifted downward and to the right, consistent with a stiff noncompliant lung. In general, as the disease progresses, lung compliance decreases and lung volumes fall (116). Smokers have a shift of the pressure-volume curve upward and to the left and the transpulmonary pressure at any given lung volume is significantly lower than in nonsmokers with IPF. As a result, the coefficient of elastic retraction of the lungs is lower in smokers than in nonsmokers with IPF (115).

*Airways mechanics.* Patients with IPF are tachypneic; they develop more rapid shallow breaths as the disease progresses, and therefore the work of breathing is increased (123, 124). This rapid respiratory rate is felt to be secondary to altered mechanical reflexes, because of the increased elastic load and/or vagal mechanisms, since no defined chemical basis for the hyperventilation has been identified (125). Expiratory flow rates, forced expiratory volume in 1 s (FEV<sub>1</sub>), and forced vital capacity (FVC) are often decreased because of the reduction in lung volume, but the FEV<sub>1</sub>-to-FVC ratio is maintained or increased in IPF. However, because of the increased static elastic recoil found in these patients, flow rates when compared with lung volumes are often increased. Functional and pathologic alterations consistent with small airways disease have been described in patients with various interstitial pulmonary diseases, including IPF (116, 118, 133, 134). However, chronic airflow obstruction has been reported exclusively among smokers with IPF (123, 124, 135).

*Gas exchange at rest and during exercise.* The DL<sub>CO</sub> (corrected for hemoglobin level) is reduced and may actually precede the reduction of lung volume. The reduction in the DL<sub>CO</sub> is probably caused both by a contraction of the pulmonary capillary volume and by ventilation and perfusion abnormalities. The resting arterial blood gases may be normal initially or may reveal mild hypoxemia and respiratory alkalosis. The major cause of resting hypoxemia is ventilation and perfusion mismatching and is not due to either impaired oxygen diffusion, as was originally suspected, or by anatomic shunts. With exercise, the alveolar-arterial O<sub>2</sub> gradient (AaPO<sub>2</sub>) widens, and the arterial O<sub>2</sub> pressure (PaO<sub>2</sub>) and arterial O<sub>2</sub> saturation (SaO<sub>2</sub>) fall. During exercise, 20 to 30% of the exercise-induced widening of the AaPO<sub>2</sub> may be caused by some impairment of oxygen diffusion. Importantly, the abnormalities identified at rest do not accurately predict the magnitude of the abnormalities that may be seen with exercise. Although these abnormalities can be assessed by oximetry saturation, it has been demonstrated that this method may not yield as dramatic or significant a change as that obtained by arterial blood gases. Thus, formal cardiopulmonary exercise testing is more sensitive than resting physiologic testing in the detection of abnormalities in O<sub>2</sub> transfer, and exercise gas exchange has been demonstrated to be a sensitive parameter for monitoring the clinical course (122).

Patients with IPF increase their minute ventilation during exercise primarily by increasing their respiratory frequency. This method of increase differs from normal subjects in whom increased ventilation during mild exercise occurs by an increase in the VT rather than respiratory rate. Thus, patients with IPF have an elevated minute ventilation during exercise that is in part related to the increase in dead space (VD) ventilation. As well, the ratio of VD to VT is increased at rest and is maintained or decreases with exercise. On occasion, the VD to VT ratio may increase in interstitial lung disorders that have a prominent pulmonary vascular component, such as scleroderma. In patients with IPF, an increase in the VD/VT ratio should raise concern about pulmonary vascular disease, especially chronic pulmonary emboli, or associated emphysema.

*Pulmonary hemodynamics.* Pulmonary hypertension rarely occurs at rest in patients with early IPF. Nevertheless, pulmonary hypertension during exercise is common even during the early stages of IPF. When the VC is less than 50% of predicted or the DL<sub>CO</sub> falls below 45% of predicted, pulmonary hypertension at rest can be expected (136). In advanced pulmonary fibrosis, auscultatory findings consistent with pulmonary hypertension are present. The mean pulmonary artery pressure at rest ranges between 23 and 28 mm Hg and rarely exceeds 40 mm

Hg. A resting mean pulmonary artery pressure greater than 30 mm Hg is associated with a poor prognosis.

The exact mechanism(s) for the development of pulmonary hypertension in IPF is unknown. The pulmonary artery wedge pressure remains normal in IPF, and cor pulmonale is a late sequela. It has been demonstrated that oxygen therapy at rest and during exercise improves pulmonary hemodynamics and likely improves exercise capacity and prognosis. However, few data exist on the value of vasodilator therapy in the treatment of pulmonary hypertension in the interstitial lung diseases.

*Sleep disturbance.* Patients with IPF, especially those with daytime SaO<sub>2</sub> of less than 90% and/or a history of snoring during sleep, have been shown to develop sleep disturbances. These patients were found to have reduced rapid eye movement (REM) sleep, lighter and more fragmented sleep, and hypoxemia during REM sleep. Severe hypoxemia occurred even in the absence of obstructive or actual sleep apnea or changes in breathing pattern. Patients with tachypnea while awake maintain their tachypnea during sleep. This maintenance of rapid breathing during sleep suggested that the reflexes causing the rapid shallow breathing were active during the sleep phase as well. Thus, although definitive studies are lacking, identification and correction of the sleep disturbance and the use of supplemental oxygen during sleep are recommended because these may reduce morbidity and improve patient survival, especially regarding the pulmonary hypertension and cor pulmonale that develop in patients with IPF ([137](#), [138](#)).

### **Bronchoalveolar Lavage**

Bronchoalveolar lavage (BAL) has been enormously helpful in elucidating the key immune effector cells driving the inflammatory response in IPF ([139](#), [140](#)). Increases in polymorphonuclear leukocytes (PMNs), neutrophil products, eosinophils, eosinophil products, activated alveolar macrophages, alveolar macrophage products, cytokines, growth factors for fibroblasts, and immune complexes have been noted in BAL of patients with IPF.

Despite its value as a research tool, the diagnostic usefulness of BAL in IPF is limited. BAL may substantiate a variety of alternative specific diagnoses provided appropriate laboratory studies are performed to identify the key features (e.g., malignancy, infections, eosinophilic pneumonia, pulmonary histiocytosis X). In addition, the pattern of inflammatory cells identified may be helpful in narrowing the differential diagnosis of fibrosing interstitial pneumonias but is not diagnostic of IPF.

An increase in neutrophils (levels > 5%) is noted in 70 to 90% of patients, an associated increase in eosinophils (levels > 5%) is apparent in 40 to 60% of patients, and an additional increase in lymphocytes is noted in 10 to 20% of patients ([21](#)). However, these findings are seen in a wide variety of fibrosing lung conditions other than IPF. A lone increase in lymphocytes is uncommon in IPF (< 10% of patients), so when present, another disorder should be excluded (e.g., granulomatous infectious disease, sarcoidosis, hypersensitivity pneumonitis, idiopathic bronchiolitis obliterans organizing pneumonia [BOOP], nonspecific interstitial pneumonia [NSIP], or lymphocytic interstitial pneumonia [LIP]).

Provided its limitations are kept in mind, there appears to be a place for BAL in the evaluation of diffuse lung disease. The presence of a BAL neutrophilia increases the likelihood of an underlying fibrosing process (IPF, the fibrosing alveolitis of rheumatological disease, asbestosis, or fibrotic sarcoidosis). A BAL lymphocytosis is more suggestive of NSIP, granulomatous disease, or a drug-induced lung disease. Further BAL may reveal a number of alternative diagnoses, e.g., malignancy, infections, eosinophilic pneumonia, pulmonary histiocytosis X (with CD1 immunostain), or occupational dust exposure.

The clinical value of BAL to stage or monitor IPF is limited. Increases in the percentage of neutrophils or eosinophils (or both) in BAL fluid have been associated with a worse prognosis in some but not all studies ([12](#)). BAL lymphocytosis, found in fewer than 20% of patients with IPF, has been associated with a more cellular lung biopsy, less honeycombing, and a greater responsiveness to corticosteroid therapy ([14](#)). However, these relationships are too inconsistent in individual patients for BAL to be used as a reliable prognostic guide. Given its expense and invasiveness, serial bronchoscopy with BAL cannot be justified in the clinical management of patients with IPF. Cellular profiles obtained at the time of BAL as part of the initial diagnostic evaluation may be prognostically useful, but only in laboratories with a specific expertise in BAL analysis and where appropriate normal values and ranges have been established ([14](#), [139](#), [141](#)).

## Lung Biopsy

Usual interstitial pneumonia (UIP) is the histopathological pattern that identifies patients with IPF. Surgical lung biopsy, either open thoracotomy or preferentially by video-assisted thoracoscopy, provides the best tissue samples to distinguish UIP from other forms of idiopathic interstitial pneumonia and to exclude other processes that mimic IPF when identified in the setting of ILD of unknown etiology. The histopathologic patterns of desquamative interstitial pneumonia (DIP), respiratory bronchiolitis associated with interstitial lung disease (RBILD), nonspecific interstitial pneumonia (NSIP), lymphoid interstitial pneumonia (LIP), acute interstitial pneumonia (AIP), and BOOP are considered separate entities and are to be excluded from the group of patients with IPF. Thus, surgical lung biopsy is recommended in patients with suspected IPF and without contraindications to surgery. This recommendation is important in any patient with clinical or radiologic features that are not typical for IPF. In the instances when atypical clinical, radiographical, or physiological features of IPF are encountered, it has been shown that histopathological patterns other than UIP are more likely to be found, thereby often defining a process with a different prognosis or resulting in alternative approaches to management. The potential risks and cost associated with surgical lung biopsy need to be balanced against the accuracy of a clinical diagnosis, the likelihood of identifying a more treatable form of ILD, and the efficacy of the treatment ([149](#)). The potential benefits of surgical lung biopsy may be outweighed by increased risk for surgical complications (e.g., age > 70 yr, extreme obesity, concomitant cardiac disease, extreme impairment in pulmonary function). Video-assisted thoracoscopic (VATS) lung biopsy is the preferred technique, as this has been associated with less morbidity, less prolonged chest tube drainage, and reduced length of hospital stay compared with open lung biopsy ([150](#)).

Many clinicians believe transbronchial lung biopsies (TBBs) may be acceptable in the diagnosis of some processes that may mimic IPF ([3](#), [153](#)). Clearly, transbronchial biopsies are not helpful

in making the diagnosis of UIP ([101](#), [107](#)). Although TBBs are abnormal in many cases, they do not confirm UIP. Also, because of the small sample size (2 to 5 mm), TBBs should not be used to assess the degree of fibrosis or inflammation. TBB may exclude UIP by identifying an alternative specific diagnosis in the right clinical setting or with the use of special histopathological methods or stains, for example, malignancy, infections, sarcoidosis, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, eosinophilic pneumonia, or pulmonary histiocytosis X.

Open or video-assisted thoracoscopic surgical lung biopsy is performed in a minority of patients with chronic ILD, likely reflecting the pessimism that findings on lung biopsy will alter the proposed treatment plan ([150](#)). A review of 200 patients with IPF in the United Kingdom showed that transbronchial or open lung biopsies were performed in only 33% and 7.5% of patients, respectively; the diagnosis of IPF was made on clinical grounds in most cases ([153](#)). Clinical practice in the United States and other countries often mirrors this approach of relying largely on clinical and radiological features to make the diagnosis of IPF ([154](#), [155](#)). In most clinical series describing patients with presumed IPF, open or thoracoscopic lung biopsies were performed only in a minority of patients and many of these reports included patients with connective tissue disease or occupational exposures known to be associated with development of ILD ([7](#), [8](#), [11](#), [12](#), [15](#), [21](#), [22](#), [24](#), [80](#), [144](#), [153](#), [154](#), [156](#)). As discussed above, most studies show that expert observers will make a confident CT diagnosis of UIP in only about two-thirds of patients with histologic UIP ([85](#)). Therefore, one-third of cases of UIP would be missed by relying on CT diagnosis alone.

*Histopathological assessment.* The gross morphologic findings in IPF range from a normal appearance in early cases to diffuse honeycombing in the later stages of the disease process. Disease involvement is usually heterogeneous and worse in the lower lobes. A subpleural, peripheral, and paraseptal distribution of fibrosis is often seen. Areas of mildly involved or even normal pulmonary parenchyma may be interspersed throughout a background of extensive fibrosis and honeycombing.

Usual interstitial pneumonia (UIP) is the pathological abnormality essential to the diagnosis of IPF. The histologic hallmark and chief diagnostic criterion is a heterogeneous appearance at low magnification with alternating areas of normal lung, interstitial inflammation, fibrosis, and honeycomb change. These histological changes affect the peripheral subpleural parenchyma most severely. The interstitial inflammation is usually patchy and consists of an alveolar septal infiltrate of lymphocytes and plasma cells, associated with hyperplasia of type 2 pneumocytes. The fibrotic zones are composed mainly of dense collagen, although scattered foci of proliferating fibroblasts (so-called "fibroblastic foci") are a consistent finding. Areas of honeycomb change are composed of cystic fibrotic air spaces that are frequently lined by bronchiolar epithelium and filled with mucin.

Smooth muscle hyperplasia is commonly seen in areas of fibrosis and honeycomb change. Patients who are biopsied during an accelerated phase of their illness may show a combination of UIP and diffuse alveolar damage.

There is no single histologic finding that has shown a consistent correlation with treatment response or prognosis in UIP. Several investigators have shown a weak positive correlation between the degree of alveolar septal inflammation and steroid responsiveness, and a negative correlation between extent of fibrosis and response to steroid therapy. It is unclear if these studies included cases of DIP, RBILD or NSIP in their analysis.

The pathological differential diagnosis of UIP includes the following ([165](#), [166](#)):

*1. Desquamative interstitial pneumonia (DIP)* ([93](#), [100](#), [167](#), [168](#)). DIP is a rare entity (incidence, < 3% of all ILDs). It affects cigarette smokers in their fourth or fifth decade of life. Most patients present with a subacute (weeks to months) illness characterized by dyspnea and cough. The chest radiograph shows less severe changes compared with IPF and may be normal in up to 20% of cases. The chest radiograph and HRCT scan pattern show diffuse ground glass opacity in the middle and lower lung zones. Lung function testing shows a restrictive pattern with reduced DL<sub>CO</sub> and hypoxemia on blood gas analysis. Lung biopsy reveals a uniform, diffuse, intraalveolar macrophage accumulation. The macrophage accumulation may be accentuated around respiratory bronchioles; however, it extends diffusely throughout the lung parenchyma. There is little fibrosis with only mild or moderate thickening of alveolar walls. Unlike UIP, there is no scarring fibrosis causing remodeling of the lung architecture. Fibroblastic foci are absent or inconspicuous and the fibrous connective tissue that is present appears at about the same age. Interstitial inflammation is usually mild in extent and severity and consists of lymphocytes and a few plasma cells. Clinical recognition of DIP is important because the process is associated with a better prognosis than IPF, with an overall survival of about 70% after 10 yr.

*2. Respiratory bronchiolitis-associated interstitial lung disease (RBILD)* ([94](#), [169](#)). Like DIP, RBILD is a clinical syndrome found in current or former cigarette smokers. The clinical presentation resembles those of patients with other ILDs: cough and breathlessness with exertion, crackles on chest examine. Diffuse, fine reticular, or nodular interstitial opacities are found on chest radiograph usually with normal-appearing lung volumes. HRCT scanning often reveals hazy opacities. A mixed obstructive-restrictive pattern is common on lung function testing. An isolated increase in RV may be found. Arterial blood gases show mild hypoxemia. On lung biopsy, RBILD is defined by the presence of pigmented macrophages within the lumens of respiratory bronchioles. The changes are patchy at low magnification and have a bronchiolocentric distribution. Respiratory bronchioles, alveolar ducts, and peribronchiolar alveolar spaces contain clusters of these dusty brown macrophages accompanied by a patchy submucosal and peribronchiolar infiltrate of lymphocytes and histiocytes. Peribronchiolar fibrosis is also seen and expands to contiguous alveolar septa, which are lined by hyperplastic type 2 cells and cuboidal bronchiolar-type epithelium. The combination of alveolar septal thickening, epithelial hyperplasia, and pigmented intraluminal macrophages mimicks the appearance of DIP. The clinical course and prognosis of respiratory bronchiolitis are unknown but appear substantially better than IPF. Smoking cessation is important in the resolution of these lesions.

*3. Nonspecific interstitial pneumonias (NSIP)* ([96](#), [172](#), [173](#)). NSIP refers to a histologic appearance in ILD that does not conform to the previously established histologic patterns. The clinical presentation is similar to IPF. Cough and dyspnea are present for months to years. Chest

radiographic findings show primarily lower zone reticular opacities. Bilateral patchy opacities can also be seen. HRCT shows bilateral symmetric ground glass opacities or bilateral air space consolidation. It is extremely important that the pathologist not use "UIP" to refer to any nonclassifiable chronic interstitial pneumonia (172). The main histologic feature of NSIP is the homogeneous appearance of either inflammation or fibrosis as opposed to the heterogeneity seen in the other interstitial pneumonias. The changes are temporally uniform but the process may be patchy with intervening areas of unaffected lung. Honeycomb areas are rare. Unlike patients with UIP, the majority of patients with NSIP have a good prognosis, with most showing improvement after treatment with corticosteroids. Most cases of NSIP are of unknown etiology and are not associated with other processes, however, others appear to have an ill-defined connective tissue disease, drug-induced ILD, or chronic hypersensitivity pneumonitis as an underlying feature. There is an estimated 15-20% mortality in 5 yr.

4. *Acute interstitial pneumonia (Hamman-Rich syndrome) (174)*. Acute interstitial pneumonia (AIP) is a rare fulminant form of lung injury that presents acutely (days to weeks from onset of symptoms), usually in a previously healthy individual. The clinical signs and symptoms are most often fever, cough, and shortness of breath. Routine laboratory studies are nonspecific and generally not helpful. Diffuse, bilateral, airspace opacification is seen on chest radiograph. CT scans show bilateral, patchy, symmetric areas of ground glass attenuation. Bilateral areas of airspace consolidation may also be present. A predominantly subpleural distribution may be seen. These radiographic findings are similar to those seen in acute respiratory distress syndrome (ARDS). Most patients have moderate to severe hypoxemia and develop respiratory failure. The diagnosis of AIP requires the presence of a clinical syndrome of idiopathic ARDS and pathological confirmation of organizing diffuse alveolar damage (DAD). Lung biopsies from patients with AIP show histologic features identical to those of the exudative, proliferative, and/or fibrotic phases of DAD. The lung biopsy typically shows diffuse involvement although there may be variation in the severity of the changes among different histologic fields. The exudative phase shows edema, hyaline membranes, and interstitial acute inflammation. As the lesion progresses, type 2 pneumocyte hyperplasia becomes prominent. The pneumocytes may show cytologic atypia. Loose organizing fibrosis is mostly seen within alveolar septa, but it may also be seen within airspaces and this may be a prominent feature in more than one-third of cases. The connective tissue changes appear at about the same age. If the patient survives the lungs may resolve to normal. The lungs may also progress to end-stage honeycomb fibrosis. The mortality from AIP is high (> 60%) with the majority of patients dying within 6 mo of presentation. The main treatment is supportive care.

5. *Idiopathic bronchiolitis obliterans with organizing pneumonia (idiopathic BOOP) (73, 177)*. Idiopathic BOOP is a clinicopathological syndrome of unknown etiology. The disease onset occurs usually in the fifth and sixth decade and affects men and women equally. Almost three-fourths of the patients have their symptoms for less than 2 mo. A flulike illness, characterized by cough, fever, malaise, fatigue, and weight loss, heralds the onset of idiopathic BOOP in two-fifths of the patients. Inspiratory crackles are frequently present on chest examination.

Routine laboratory studies are nonspecific. Pulmonary function is usually impaired, with a restrictive defect being most common. Resting and exercise arterial hypoxemia is a common feature. The roentgenographic manifestations are quite distinctive. Bilateral, diffuse alveolar

opacities in the presence of normal lung volume constitute the characteristic radiographic appearance in patients with idiopathic BOOP. A peripheral distribution of the opacities, similar to that thought to be "virtually pathognomonic" for chronic eosinophilic pneumonia, is also seen in idiopathic BOOP. Rarely, the alveolar opacities may be unilateral. Recurrent and migratory pulmonary opacities are common. Irregular linear or nodular interstitial infiltrates or honeycombing are rarely seen at presentation. HRCT scans of the lung reveal patchy airspace consolidation, ground glass opacities, small nodular opacities and bronchial wall thickening and dilation. These patchy opacities occur more frequently in the periphery of the lung and are often in the lower lung zone. The CT scan may reveal much more extensive disease than is expected by review of the plain chest X-ray. The histopathologic lesions characteristic of idiopathic BOOP include an excessive proliferation of granulation tissue within small airways (proliferative bronchiolitis) and alveolar ducts associated with chronic inflammation in the surrounding alveoli. There are several other key features: there is a uniform, recent temporal appearance to the changes; the lung architecture is not severely disrupted; the distribution is patchy and peribronchiolar; the lesions are usually located within the airspace; foamy macrophages are common in the alveolar spaces, presumably secondary to the bronchiolar occlusion; the intraluminal buds of granulation tissue consist of loose collagen-embedding fibroblasts and myofibroblasts that extend from one alveolus to the adjacent one through the pores of Kohn, giving rise to the characteristic "butterfly" pattern; the bronchiolar lesions are secondary to intraluminal plugs of granulation tissue, always in association with plugs in the alveolar ducts and alveolar spaces; severe fibrotic changes, such as honeycombing, are unusual at the time of diagnosis; and giant cells are rare or absent, no granuloma or vasculitis is present. Corticosteroid therapy results in clinical recovery in two-thirds of the patients.

6. *Lymphocytic interstitial pneumonitis (LIP)* ([184](#), [185](#)). LIP is an uncommon cause of interstitial lung disease. It is distinguishable from DIP and UIP by the presence of monotonous sheets of lymphoplasmacytic cells that expand the interstitium. In addition, lymphocytes are found within alveolar spaces and lymphoid aggregates are distributed along lymphatic routes. Lymphocyte aggregates also appear in an angiocentric location. Other histologic features include type 2 epithelial cell hyperplasia, the presence of interstitial mononuclear cells, and the formation of interstitial noncaseating granulomas. The majority of cases are associated with some form of dysproteinemia (either a monoclonal or polyclonal gammopathy) or are found in association with Sjögren's syndrome (primary or secondary) or acquired immune deficiency syndrome (AIDS). The chest radiograph and HRCT are nonspecific, indicating bilateral, predominantly low-zone mixed alveolar- interstitial infiltrates. If a pleural effusion or mediastinal lymphadenopathy are present, the possibility of a low-grade lymphoma should be considered. Because of this tendency to progress to lymphoma most experts no longer include LIP among the idiopathic interstitial pneumonias.

7. *Pulmonary histiocytosis X* ([186](#)). Pulmonary histiocytosis X of the lung is a rare, smoking-related diffuse lung disease that primarily afflicts young adults between the ages of 20 and 40 yr. The clinical presentation is variable, from an asymptomatic state (approximately 16%) to a rapidly progressive condition.

The most common clinical manifestations at presentation are cough, dyspnea, chest pain, weight loss, and fever. Pneumothorax occurs in about 25% of patients and is occasionally the first

manifestation of the illness. Hemoptysis and diabetes insipidus are rare manifestations. The physical examination is usually normal and routine laboratory studies are not helpful. The radiographic features vary depending on the stage of the disease. The combination of ill-defined or stellate nodules (2-10 mm in size), reticular or nodular opacities, upper zone cysts or honeycombing, preservation of lung volume, and costophrenic angle sparing are felt to be highly specific for pulmonary histiocytosis X. CT lung scanning that reveals the combination of nodules and thin-walled cysts is virtually diagnostic of pulmonary histiocytosis X. Physiologically, the most prominent and frequent pulmonary function abnormality reported is a markedly reduced DL<sub>CO</sub>, although varying degrees of restrictive disease, airflow limitation, and diminished exercise capacity are described. Histiocytosis X is frequently associated with a "DIP-like" or RB pattern due to the strong association with cigarette smoking. However, histiocytosis X is predominantly an interstitial lesion characterized by the presence of centrally scarred stellate nodules seen well at low magnification, containing a polymorphic inflammatory infiltrate. Diagnosis of histiocytosis X is predicated on recognition of characteristic Langerhans cells within the inflammatory infiltrate in the appropriate histological context. Discontinuance of smoking is the key treatment, resulting in clinical improvement in 33% of the subjects. Most patients with pulmonary histiocytosis X suffer persistent or progressive disease. Death due to respiratory failure occurs in ~ 10% of patients.

8. A pattern of interstitial inflammation and fibrosis sometimes indistinguishable from UIP can occur in patients with asbestosis, connective tissue disease, chronic hypersensitivity pneumonitis, and certain drug-induced lung diseases. A histologic diagnosis of asbestosis requires demonstration of the offending fibers (usually in the form of ferruginous asbestos bodies) in the tissue specimen. Connective tissue disease, chronic hypersensitivity pneumonitis, and drug-induced lung diseases are distinguished by their clinical, serological, or radiographic manifestations.

9. Rarely, there are biopsies that cannot be classified into any of the recognized patterns, i.e., UIP, DIP, BOOP, AIP, or NSIP. These usually represent a sampling error as a result of an inadequate lung biopsy or a sample taken from a lesion that has only end-stage histopathological features. It is these cases that are referred to as "nonclassifiable" chronic interstitial pneumonia. It is important that the surgical biopsy include some areas of what appears to be "normal" lung to the surgeon, in order to exclude active lesions of other interstitial lung diseases.



## TREATMENT OF IPF

IPF progresses in a relentless and often insidious manner that may be difficult to detect using parameters such as symptomatology, chest radiographic findings, or spirometry alone. Spontaneous remissions do not occur. In earlier clinical studies, the clinical course of IPF was quite variable, with a mean survival ranging from 4 to 6 yr after the time of diagnosis. However, more recent clinical series of better defined cases of IPF have identified a much shorter survival, with mean survival among these studies ranging from 2 to 4 yr (5-yr survival range, 30 to 50%) ([11](#), [103](#), [163](#), [166](#), [191](#)).

### Rationale for Treatment

The treatment of IPF has been based on the concept that inflammation leads to injury and fibrosis (1). Initially, it is hypothesized that inflammatory and immune effector cells accumulate within the pulmonary parenchyma. As this alveolar and interstitial reaction is perpetuated, alveolar wall, vascular, and airway damage ensues; reparative processes are inadequate or impaired; and fibrosis develops. Eventually, the lung parenchyma is irreversibly deranged and gas exchange function impaired. When the ventilatory reserve is sufficiently diminished, symptoms of respiratory insufficiency become apparent. Although this conceptualization of the pathogenetic process suggests numerous theoretical points of therapeutic intervention, the practical treatment armamentarium has been largely restricted to antiinflammatory medications and, most recently, lung transplantation.

Optimal therapy for IPF is contentious (192). To date, most treatment strategies have been based on eliminating or suppressing the inflammatory component. No pharmacological therapy has been proven unequivocally to alter or reverse the inflammatory process of IPF. More importantly perhaps, little information has appeared supportive of the theory that the fibrotic process can be reversed. All currently available therapeutic trials in IPF are severely limited by the lack of clear understanding of the natural history of IPF, the presence of many different study designs; heterogeneous patient groups, disputable diagnostic certainty; variable study duration; differences in medication formulation, dosage, route of administration, and duration of treatment; lack of placebo controls; nonquantitative or differing types of assessment criteria; and variable intervals between evaluations.

### **Conventional Treatment Options**

Treatment options include corticosteroids (12, 20, 153, 193- 195), immunosuppressive/cytotoxic agents (e.g., azathioprine, cyclophosphamide) (12, 13, 158), and antifibrotic agents (e.g., colchicine or D-penicillamine) (12, 160, 161, 196) alone or in combination.

*Corticosteroids.* Despite their ubiquitous use, no prospective, randomized, double-blind, placebo-controlled trial has evaluated the efficacy of corticosteroids in the treatment of IPF (155). In three trials comparing corticosteroids with no treatment, none of the untreated patients with IPF improved (12, 16, 197). Given the limitations of existing studies that are based on defined quantitative assessment criteria, 10 to 30% of patients with IPF improve when treated with corticosteroids whereas up to 40% respond on the basis of subjective or undefined assessment criteria. Responses are usually partial and transient. Cures (i.e., sustained, complete remissions) are achieved in few patients. Even among responders, relapses or progression of the disease after an *initial* response suggests the need for prolonged treatment.

Historically, most investigators initiate therapy with high-dose corticosteroids (40 to 100 mg daily of prednisone or prednisolone) for 2 to 4 mo, with a subsequent gradual taper. However, no studies have compared differing dosages or duration of corticosteroid in appropriately matched or randomized patients. If responses are to occur with corticosteroids, improvement is usually noted within 3 mo. After 3 mo of corticosteroid therapy, objective clinical parameters (e.g., dyspnea scores, physiological studies, chest radiographs, HRCT) are required to gauge response. Subjective improvement is not adequate to gauge response, because of placebo effects or mood-enhancing effects of corticosteroids.

Common practice has been for maintenance corticosteroid therapy to be reserved for patients exhibiting *stabilization* or *objective* improvement. Corticosteroid-responsive patients are maintained on prednisone chronically (sometimes indefinitely), but in a gradually tapering dose. Relapses or deterioration warrant escalation of the dose or addition of an immunosuppressive agent. The dose of corticosteroid and rate of taper should be guided by clinical and physiological parameters. Since it is unlikely that corticosteroids completely eradicate the disease, prolonged treatment for a minimum of 1 to 2 yr (and sometimes indefinitely) is reasonable for patients exhibiting unequivocal responses to therapy. In this context, chronic low-dose prednisone (15 to 20 mg every other day) may be adequate as maintenance therapy. High-dose intravenous "pulse" methylprednisolone (1 to 2 g once weekly or biweekly) has been used, but has no proven advantage over oral corticosteroids ([198](#)).

*Cytotoxic treatment.* Immunosuppressive or cytotoxic agents (e.g., azathioprine or cyclophosphamide) are used among steroid nonresponders, patients experiencing serious adverse effects from corticosteroids, and patients at high risk for corticosteroid complications (e.g., age > 70 yr, poorly controlled diabetes mellitus or hypertension, severe osteoporosis, or peptic ulcer disease). Favorable responses have been noted in a few small treatment trials with cytotoxic agents (e.g., azathioprine or cyclophosphamide) in 15 to 50% of cases ([195](#), [199](#), [200](#)).

*Azathioprine.* Azathioprine has been used as therapy for IPF, primarily in patients failing or experiencing adverse effects from corticosteroids. Anecdotal responses were noted in uncontrolled studies ([200](#)). The combination of azathioprine plus corticosteroids was associated with modest improvement and enhanced survival in some patients ([195](#)).

*Cyclophosphamide.* No convincing data exist to show a superiority of cyclophosphamide over corticosteroids in treating IPF. In addition, no studies have directly compared cyclophosphamide with other immunosuppressive or cytotoxic agents ([158](#)). High-dose intravenous ("pulse") cyclophosphamide administered every 2 to 4 wk (dose range, 500 to 1,800 mg) has been tried in open trials of refractory IPF ([159](#), [201](#)). Results are generally unimpressive. The poor response to pulse cyclophosphamide likely reflects late course disease when treatment was instituted, rather than an intrinsic failure of cyclophosphamide therapy. No studies have compared oral with pulse cyclophosphamide for IPF. Toxicity associated with cyclophosphamide remains a major impediment to the routine use of this agent for IPF.

## **Potential Alternative Treatments**

A consensus conference on therapy for pulmonary fibrosis underscored the marginal benefit of existing therapies and suggested that major advances in survival awaited the development of novel therapies ([202](#)). Studies assessing novel therapeutic strategies require a better understanding of the pathogenesis of the disease.

Possible future (and completely untested) therapeutic strategies include: agents that inhibit cytokines, proteases, oxidants, or fibroblast growth factors; antifibrotic agents; dietary modifications; more efficient intrapulmonary delivery of drugs via liposomes; diphosphonates;

antioxidants; inhibitors of leukocyte integrins; and gene therapy (202). The following is a brief review of some of these potential novel treatments.

*Cyclosporin A.* Cyclosporin A has only rarely been used in IPF. Anecdotal responses have been noted but sustained remissions have been rare and toxicity is high (203). There are few data to support its use in IPF.

*Methotrexate.* Methotrexate has been successfully used as therapy for diverse immune-mediated pulmonary disorders. Published data evaluating methotrexate as therapy for IPF are lacking. The potential for pulmonary toxicity has dampened enthusiasm for using methotrexate to treat IPF.

*Chlorambucil.* Chlorambucil has been used by some investigators as a substitute for cyclophosphamide in the treatment of patients with IPF. Chlorambucil may cause gastrointestinal and bone marrow toxicity and may induce neoplasia (including leukemias). Given its toxicity and the lack of data as therapy for IPF, chlorambucil cannot be considered for treatment of IPF.

*Agents that alter collagen synthesis or fibrosis.* Since therapeutic results achieved with immunosuppressive or antiinflammatory agents have been disappointing, novel strategies employing antifibrotic agents have been advocated, but their value is unproven. Future therapies aimed at preventing or inhibiting the fibroproliferative response will be crucial in reducing the impact of this problem on the health of individuals afflicted with IPF.

*Colchicine.* Colchicine inhibits collagen formation and modulates the extracellular milieu *in vitro* and in animal models; it also suppresses the release of alveolar macrophage-derived growth factor and fibronectin by *in vitro*-cultured alveolar macrophages from patients with sarcoidosis or IPF (196). Although substantive data affirming the efficacy of colchicine as therapy for IPF are lacking, the efficacy appears similar to corticosteroids and the side effects attributed to colchicine are rarely severe (160, 161, 204). Thus, oral colchicine, 0.6 mg once or twice daily, may be considered as first line therapy or for patients refractory to corticosteroids, either alone or in combination with immunosuppressive/cytotoxic agents. Additional controlled trials are needed to determine the appropriate role for colchicine in the treatment of IPF.

*D-Penicillamine.* Anecdotal evidence of responses to D-penicillamine have been noted in idiopathic or connective tissue disease-associated pulmonary fibrosis but controlled studies have not been done (12, 193, 194, 204, 205). D-penicillamine is toxic, and significant adverse effects (e.g., loss of taste, nausea, vomiting, stomatitis, nephrotoxicity) complicate its use in up to 50% of patients. In view of its toxicity, and the lack of data affirming its efficacy, D-penicillamine has no proven value as therapy for IPF.

*Other antifibrotic agents.* Other antifibrotic agents are being tested in the treatment of lung fibrosis and include interferon  $\gamma$  (206), interferon  $\beta$ , relaxin (increases procollagenase), pirfenidone (207), halfuginone (inhibits collagen synthesis), suramin (profibrotic cytokine inhibition), and prostaglandin E<sub>2</sub> (inhibits collagen production).

*Other novel agents.* Because epithelial injury in IPF may be mediated by oxygen radicals (208) it has been suggested that *antioxidant* strategies might prove beneficial (209). Possible strategies

might include delivery of antioxidant enzymes to the lung parenchyma or even promoting increased genetic expression of antioxidant enzymes (202). *Glutathione* (an effective scavenger of toxic oxidants that suppresses lung fibroblast proliferation in response to mitogens), *taurine* (a natural free amino acid), and *niacin* inhibit the development of experimental fibrosis (better than either agent alone) in an animal model. High-dose *N-acetylcysteine*, as a glutathione precursor, has been suggested as an adjunct to maintenance immunosuppression therapy in patients with IPF (212).

Another potential strategy would be to interfere with the process of leukocyte retention in the lung (202). Leukocyte adhesion molecules play an important role in this process. Antibodies to such adhesion molecules have been shown to prevent collagen deposition in an animal model of lung injury (213). Agents that block the expression or function of adhesion molecules are rapidly becoming available and may some day prove clinically useful.

Although there is still much to be learned regarding the roles of various cytokines and growth factors in the complex process of pulmonary fibrosis, it is clear that these agents are critical (214). Inhibitors of specific fibrogenic cytokines or growth factors may help to retard the fibrotic process (215).

## ▶ STAGING AND PROGNOSIS

### Features Associated with Rate of Disease Progression

Several studies have identified features of IPF that are associated with an increased risk of more rapid disease progression (142, 146, 218). Unfortunately, it appears that many of the reported cases of IPF are in patients who present late in the course of their disease (218). This point is particularly important since many of the features of IPF that have been found to be associated with disease progression may only be relevant to the late or terminal phase of this disease process. Moreover, these findings suggest that efforts should be made to identify patients with IPF earlier in the course of their disease, when it is more likely that the clinical course may be altered by treatment.

Clinical deterioration is most frequently the result of disease progression; however, disease-associated complications and adverse effects of therapy are also important complications to be considered. Respiratory failure is the most frequent cause of death, accounting for approximately 40% of the deaths of patients with IPF. Other causes of death in patients with IPF include heart failure, ischemic heart disease, infection, and pulmonary emboli (20). Bronchogenic carcinoma has been identified with increased frequency (10 to 15% of patients) in advanced idiopathic pulmonary fibrosis. The prognosis for patients with idiopathic pulmonary fibrosis and lung cancer is poor.

Indicators of longer survival among patients with IPF include the following (12, 15, 21, 156, 157, 222, 223):

- Younger age (< 50 yr)

- Female sex,
- Shorter symptomatic period ( $\leq 1$  yr) with less dyspnea, relatively preserved lung function
- Presence of ground glass and reticular opacities on HRCT
- Increased proportion of lymphocytes (20 to 25%) in BAL fluid
- A beneficial response or stable disease 3 to 6 mo after initial corticosteroid therapy
- A history of "current" cigarette smoking at the time of diagnosis has been associated with improved survival- This finding remains unexplained

The degree of dyspnea and need for treatment with immunosuppressive agents (proxy measures of the extent and severity of disease) were found to be independently associated with progressive declines in both lung volumes and gas exchange ([218](#)). Excess neutrophils ( $> 5\%$ ) ([12](#)) and/or eosinophils ( $> 5\%$ ) ([146](#), [218](#), [226](#)) in the BAL fluid have been associated with a higher likelihood of disease progression and a failure to respond to immunosuppression. The extent of "fibrosis" on HRCT scan has been shown to be an important predictor of poorer survival ([103](#)). Risk stratification among patients with IPF appears to be feasible and could provide the basis for a clinical staging system.

### **Monitoring the Clinical Course of IPF**

Currently, there is no standard approach to stage IPF clinically or pathologically ([225](#)). Although IPF is a progressive form of interstitial lung disease, the extent and rate of progression vary markedly from one patient to the next. Thus, it is often difficult to determine if treatment is producing the desired effect. Objective, validated parameters to assess disease activity and response to therapy have varied among studies. Sadly, only a minority of patients with IPF respond to therapy. Subjective improvement occurs frequently (up to 70% of treated patients) and should not be the lone factor in determining whether to continue treatment. Objective improvement in physiologic abnormalities occurs in 20-30% of treated patients. Changes in pulmonary functional parameters used to identify "responders" (or "nonresponders") have not been uniform. Increases of only 10 to 15% from pretreatment baseline in even single parameters of pulmonary function (e.g., VC, DL<sub>CO</sub>) have been deemed favorable responses in some studies. Radiographic improvement (especially on chest radiograph) in patients with IPF has not been clearly documented and is considered quite uncommon. Lack of change or "stabilization" is considered by some investigators to represent a response among patients previously exhibiting a downhill course. This assessment of "response" may exaggerate the true impact of therapy in ameliorating the course of the disease, particularly when brief time periods (e.g., 3 to 6 mo) are analyzed. It is common during the management of an individual patient with IPF that some parameters used to assess the clinical course may improve while others show declines or no change.

Given this, a system to assess the stage of disease activity and the rate of progression is essential. A clinical, radiographic, and physiologic (CRP) scoring system that included seven clinical

variables (dyspnea, chest radiograph, spirometry, lung volume, diffusion capacity, resting alveolar-arterial O<sub>2</sub> difference, and exercise O<sub>2</sub> saturation) was shown to correlate with the degree of fibrosis and the cellular histopathological component of the open lung biopsy from patients with IPF (14). These findings suggested that a defined scoring system might be best in staging the extent of IPF and helpful in monitoring the clinical course. Although these results are encouraging, further internal and external validity testing is needed to develop a reliable staging system in IPF.

Repeated measurements of the following parameters are believed to be useful in assessing the clinical course of IPF:

- Assessment of dyspnea, using an established clinical scale for rating the impact of dyspnea on activities. (Also, it might also be useful to serially follow measures of "quality of life," using established instruments, but this requires additional study [226])
- Physiologic testing (227)
- Lung volumes
- DLCO
- Resting arterial blood gases (e.g., AaPO<sub>2</sub>)
- Cardiopulmonary exercise testing with measurement of gas exchange
- HRCT lung scans

## **RECOMMENDATIONS FOR TREATMENT**

To date we lack sufficient clinical evidence that any treatment improves survival or the quality of life for patients with IPF. However, the potential for a positive outcome has encouraged clinicians to treat these patients. Given the poor prognosis for patient with IPF, many experts have recommended that treatment be initiated in all patients with IPF who do not have contraindications to therapy. The committee believes that therapy is not indicated for all patients. Importantly, given the limited success of current treatments, the potential benefits of any treatment protocol for an individual patient with IPF may be outweighed by increased risk for treatment-related complications (e.g., age > 70 yr, extreme obesity, concomitant major illness such as cardiac disease, diabetes mellitus, or osteoporosis, severe impairment in pulmonary function, endstage honeycomb lung on radiographic evaluation).

The exact time that therapy should be started is unknown. The committee believes that response rates may be higher when treatment is initiated early in the course of the disease, before irreversible fibrosis has developed. Failures in some cases appear to reflect delays in initiating treatment.

Therefore, the committee recommends that if therapy will be offered to a patient, it should be started at the first identification of clinical or physiological evidence of impairment or documentation of decline in lung function.

Until adequate studies are conducted that define the best treatment for patients with IPF, this committee suggests the following *combined therapy* (corticosteroid and either azathioprine or cyclophosphamide) for those patients who have been given adequate information regarding the merits and pitfalls of treatment and who possess features consistent with a more likely favorable outcome (*see above*):

- *Corticosteroid* therapy (prednisone or equivalent) at a dose of 0.5 mg/kg (lean body weight [LBW]) per day orally for 4 wk, 0.25 mg/kg (LBW) per day for 8 wk, and then tapered to 0.125 mg/kg (ideal body weight [IBW]) daily or 0.25 mg/kg (LBW) every other day as initial therapy for IPF. (Lean body weight is the ideal weight expected for a patient of this age, sex, and height)
- *Azathioprine* at 2-3 mg/kg lean body weight (LBW) per day to a maximum dose of 150 mg/d orally. Dosing should begin at 25-50 mg/d and increase gradually, by 25-mg increments, every 7 to 14 d until the maximum dose is reached

or

- *Cyclophosphamide* at 2 mg/kg LBW per day to a maximum dose of 150 mg/d orally. Dosing should begin at 25- 50 mg/d and increase gradually, by 25-mg increments, every 7 to 14 d until the maximum dose is reached

### **Length of Therapy**

A discernible objective response to therapy may not be evident until the patient has received  $\geq$  3 mo of therapy. Consequently, in the absence of complications or adverse effects of the medications, combined therapy should be continued for at least 6 mo. At that time, repeat studies should be performed to determine the response to therapy (*see below*, MONITORING FOR ADVERSE EFFECTS OF TREATMENT).

*Six months after onset of therapy:*

- If the patient is found to be *worse* the therapy should be stopped or changed (e.g., continue prednisone at present dose and switch to different cytotoxic agent or consider an alternative therapy or lung transplantation)
- If the patient is found to be *improved or stable* the combined therapy should be continued, using the same doses of the medication(s)

*Twelve months after onset of therapy:*

- If the patient is found to be *worse* the therapy should be stopped or changed (e.g., consider an alternative therapy or lung transplantation)
- If the patient is found to be *improved or stable* the combined therapy should be continued, using the same doses of the medication(s)

*More than 18 mo after onset of therapy.* At this point, therapy should be individualized on the basis of the clinical response and tolerance of the patient to the therapy. The committee recommends that the therapy be continued indefinitely only in individuals with objective evidence of continued improvement or stabilization.

The committee recommends that a combination of factors be used to assess the response to treatment and clinical course of IPF:

*A favorable (or improved) response to therapy* is defined by two or more of the following, documented on two consecutive visits over a 3- to 6-mo period:

- A decrease in symptoms, specifically an increase in the level of exertion required before the patient must stop because of breathlessness or a decline in the frequency or severity of cough
- Reduction of parenchymal abnormalities on chest radiograph or HRCT scan
- Physiologic improvement defined by two or more of the following:
  - $\geq 10\%$  increase in TLC or VC (or at least  $\geq 200$ -ml change)
  - $\geq 15\%$  increase in single-breath DL<sub>CO</sub> (or at least  $\geq 3$  ml/min/mm Hg)
  - An improvement or normalization of O<sub>2</sub> saturation ( $\geq 4$  percentage point increase in the measured saturation) or PaO<sub>2</sub> ( $\geq 4$ -mm Hg increase from the previous measurement) achieved during a formal cardiopulmonary exercise test

*A stable (and presumed favorable) response to therapy* is defined by two or more of the following, documented on two consecutive visits over a 3- to 6-mo period:

- 10% change in TLC or VC, or  $< 200$ -ml change
- $< 15\%$  change in DL<sub>CO</sub>, or  $< 3$  ml/min/mm Hg
- No change in O<sub>2</sub> saturation ( $< 4\%$  increase) or PaO<sub>2</sub> ( $< 4$ -mm Hg increase) achieved during a formal cardiopulmonary exercise test

*A failure to respond to therapy* (e.g., after 6 mo of treatment) is defined as:

- An increase in symptoms, especially dyspnea or cough

- An increase in opacities on chest radiograph or HRCT scan, especially the development of honeycombing or signs of pulmonary hypertension
- Evidence of deterioration in lung function in two or more of the following:
  - $\geq 10\%$  decrease in TLC or VC ( or  $\geq 200$ -ml change)
  - $\geq 15\%$  decrease in single-breath DL<sub>CO</sub> (or at least  $\geq 3$ -ml/min/mm Hg change)
  - Worsening (greater fall) of O<sub>2</sub> saturation ( $\geq 4$  percentage point decrease in the measured saturation) or rise in the AaPO<sub>2</sub> at rest or during a formal cardiopulmonary exercise test ( $\geq 4$  mm Hg increase from the previous measurement)

### **Monitoring for Adverse Effects of Treatment**

Before starting therapy, patients should be informed about the potential risk and side effects of corticosteroid and cytotoxic therapy. Corticosteroid therapy is usually tolerated by patients; however, side effects are common and potentially disabling. Some patients develop side effects of corticosteroids more readily than others at equivalent doses. Efforts should be made to reduce or prevent side effects if possible. Peptic ulcer disease, posterior capsular cataracts, increased intraocular pressure, hypertension, endocrine and metabolic alterations (deposition and redistribution of fatty tissue with truncal obesity, moon facies, menstrual irregularities, impotence, hyperglycemia, hypokalemia, metabolic alkalosis, and secondary adrenal insufficiency) may occur. Potential musculoskeletal complications are osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, and myopathy. The latter may impair diaphragmatic and intercostal muscle strength and endurance, and these changes may complicate the assessment of therapeutic efficacy. Psychologic effects including euphoria, depression, or psychosis may also be encountered, especially in elderly patients (228). Methods to reduce the risk of steroid-induced osteoporosis should be instituted, especially in postmenopausal women, since even short-term therapy (3 to 6 mo) may cause reductions in bone mass. Unfortunately, the success of such regimens remains to be determined.

Azathioprine is less toxic than cyclophosphamide, as azathioprine does not induce bladder injury and has less oncogenic potential. The maximal dose of azathioprine or cyclophosphamide need not be adjusted according to the lowering of the white blood cell count. However, if the white blood cell count decreases to  $\leq 4,000/\text{mm}^3$  and the platelet counts fall below  $100,000/\text{mm}^3$  then the dose of azathioprine or cyclophosphamide should be stopped or lowered immediately by 50% of the current dose until these hematologic abnormalities recover. Recovery of the white blood cell (WBC) and platelet counts should be assessed weekly. If the counts do not recover, the medication should be completely discontinued until these abnormalities improve. On occasion the white blood cell count remains  $> 7,000/\text{mm}^3$  despite increases in the azathioprine or cyclophosphamide dose. In those instances, the dose should not exceed 150 mg/d. Patients taking azathioprine should also undergo monthly measurements of hepatocellular injury, and the dose of the medication should be reduced or stopped if abnormalities greater than three times the normal level are found. Forced diuresis,  $\geq 8$  glasses (8 oz. each) of water daily, and monthly monitoring

of the urine for red blood cells or other abnormality is recommended in an attempt to prevent clinically significant hemorrhagic cystitis in patients treated with cyclophosphamide.

Corticosteroid therapy may suppress the immune response to skin tests; therefore, when possible, tuberculin skin testing is advisable before the initiation of steroid therapy. The routine use of trimethoprim/sulfamethoxazole (one single-strength tablet three times weekly) as prophylaxis against *Pneumocystis carinii* or isoniazid as prophylaxis against *Mycobacterium tuberculosis* in patients receiving immunosuppressive therapy may be considered. Preventive therapy is recommended for persons with a positive tuberculin skin test or those at risk (e.g., individuals living in endemic areas), and in particular those patients taking > 15 mg of prednisone (or equivalent) daily for more than 3 wk. However, limited data exist to identify the risk of these infectious complications in this setting.

### **Other Management Issues**

Patients with IPF should be encouraged to enroll in a pulmonary physical rehabilitation program. These patients are usually so dyspneic with exertion that they discontinue any program of routine exercise. This discontinuation of exercise should not be encouraged since the primary goal is to restore patients to the highest possible functional state. No data from carefully defined studies of pulmonary rehabilitation in the management of patients with IPF have been reported. However, the panel recommends that for motivated patients a combination of exercise training, education, and psychosocial support may help, not by improvements in lung function, which are not likely to occur, but with improvement in exercise tolerance, together with decreased symptoms of breathlessness, improved quality of life, and less need for health care services ([229](#)). Daily walks or the use of a stationary bicycle are excellent routines. Severe hypoxemia ( $P_{aO_2}$  less than 55 mm Hg) at rest or during exercise should certainly be managed by supplemental  $O_2$ . Supplemental  $O_2$  during exercise may markedly improve exercise-induced hypoxemia and improve exercise performance ([228](#), [229](#)). Higher flow rates than that frequently used in chronic obstructive pulmonary disease may be required.

Severe paroxysms of cough may be among the most distressing features of IPF. A variety of antitussive agents have been used, but controlled studies assessing efficacy have not been done. Rib fractures secondary to protracted episodes of cough may occur in elderly individuals with severe osteoporosis. Oral codeine or other antitussives may be helpful in some patients and should be tried in patients with cough refractory to over-the-counter medications. Pulmonary hypertension may complicate IPF in the late phases of the disease ([20](#)). However, administration of vasodilators to reduce pulmonary arterial pressure has not been shown to be beneficial and may cause serious adverse effects (including systemic hypotension). Opioids have been used to reduce dyspnea in patients with severe chronic lung disease, but data affirming the efficacy of this practice are lacking. Low-dose (2.5 to 5 mg) nebulized morphine failed to improve dyspnea or exercise tolerance in patients with interstitial lung disease ([232](#)).

## Lung Transplantation

Transplantation should be considered for those patients who experience progressive physiologic deterioration despite optimal medical management and who meet the established criteria (233, 234). Single lung transplantation is currently the preferred surgical operation. Unless specific contraindications exist, patients with severe functional impairment, oxygen dependency, and a deteriorating course should be listed for lung transplantation. Relative contraindications to lung transplantation include unstable or inadequate psychosocial profile/stability, or significant extrapulmonary disorders (e.g., liver, renal, or cardiac dysfunction) that may negatively influence survival. Many centers limit lung transplantation candidates to those < 60 yr of age.

Owing to limited donor availability, early listing is important, as the waiting time for procuring a suitable donor organ may exceed 2 yr. Unfortunately, patients with rapidly progressive or severe IPF may die while awaiting transplantation. After successful transplantation, arterial oxygen tension is frequently sufficiently improved to alleviate the requirement for supplemental oxygen, lung volumes and DL<sub>CO</sub> are increased, and pulmonary hypertension and right ventricular dysfunction are reversed.

The decision to list patients for transplantation is sobering, as 5-yr survival after transplantation approximates 50 to 60%. Graft failure, infection, and heart failure are the most common causes of early mortality whereas bronchiolitis obliterans, infection, and malignancy are responsible for most late mortality.

### LIMITATIONS AND FUTURE GOALS

There are limited data on the full spectrum of cases of IPF. In fact, most of the reported studies suggest that patients with IPF generally present late in the course of their disease. This point is particularly important since many of the features of IPF that have been found to be associated with disease progression may be relevant only to the terminal phase of this disease process. Moreover, these findings indicate that efforts should be made to identify patients with IPF earlier in the course of their disease.

Case definition varies between studies; therefore, comparison of study populations is compromised. Selection bias exists, with the least selection bias occurring in population-based studies, although these studies are difficult to do and few are available for patients with IPF. As noted, there has been only one population-based study to date in the United States. In addition, many epidemiological studies rely on vital statistic data for information. These data have been shown repeatedly to be inaccurate and incomplete for the disease IPF. Cooperative interaction among investigators is necessary for population-based studies to claim the greatest degree of information and to learn more about the epidemiology of this disease. Obtaining historical information about occupational, environmental, and family history is critical to focus on the risk factors for the development of IPF. Improvement in tracking the disease on an international level needs to occur. Further studies of genetic predisposition to IPF are needed, with a challenge as to which gene(s) or marker(s) of susceptibility to focus investigations.

Prospective, controlled studies to critically evaluate the diverse immunosuppressive or antifibrotic agents available to the therapeutic armamentarium of IPF are required. Despite widespread clinical use of azathioprine and cyclophosphamide for patients with IPF who have failed corticosteroids, data directly comparing these agents are lacking. Further, many studies have employed these agents combined with corticosteroids. Despite anecdotal successes, the superiority of these alternative agents over corticosteroids has not convincingly been established. Owing to the rarity of IPF, and the heterogeneity of its clinical expression, prospective trials assessing specific agents will be fraught with difficulty. In addition to requiring a large number of clinical centers from which to draw an adequate number of subjects, it will be critical to match patients for severity, duration of illness, and activity of disease at entry, using objective, well-defined markers. The use of diagnostic tests such as HRCT scans or BAL to separate early inflammatory disease from late fibrosis may discriminate patient populations likely to benefit from aggressive antiinflammatory or antifibrotic therapy.

Given the lack of definitive data on therapeutic efficacy in the treatment of IPF, the committee strongly recommends the establishment of a multicenter, international consortium to allow the recruitment of sufficient numbers of subjects needed to determine the optimal treatment strategy for IPF. Mapel and colleagues estimated that if we assume a 5-yr survival of 50%, it would take at least 712 patients to detect a 20% improvement in survival (accrual time, 1 yr; follow-up time, 5 yr; type I error rate, 0.05; power, 0.80) ([155](#)). Given current estimates of the incidence of IPF, this would require a population base of approximately 7.7 million to capture, enroll, and randomize every incident case ([155](#)). Also, the studies should be randomized placebo-controlled trials. The use of a placebo group is attractive from a scientific viewpoint and is strongly encouraged but may discourage patients or physicians from participating in controlled trials largely because of the need to "do something" for this progressive, debilitating disease ([155](#)). However, a randomized placebo-controlled study would provide the most valuable data because it would overcome the bias and confounding effects of previous observational studies, allow identification of the natural history of IPF, and allow the identification of risk of complications of the therapy ([155](#)).

TALMADGE E. KING, JR., M.D., *Chair*

ULRICH COSTABEL, M.D.

JEAN-FRANÇOIS CORDIER, M.D.

GUILLERMO A. DO PICO, M.D.

ROLAND M. DU BOIS, M.D.

DAVID LYNCH, M.B.

JOSEPH P. LYNCH, III, M.D.

JEFFREY MYERS, M.D.

RALPH PANOS, M.D.

GANESH RAGHU, M.D.

DAVID SCHWARTZ, M.D.

CECILIA M. SMITH, D.O.

## ▶ Footnotes

**This statement was prepared by an ad-hoc committee of the Assembly on Clinical Problems. Members of the committee are:**

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## Examination

Select the *best* answer to each of the following items. Mark your responses on the Answer form.

1. The usual interstitial pneumonia (UIP) is the histopathological pattern that identifies patients with IPF.

- a. True
- b. False

2. The definite diagnosis of IPF in the presence of a surgical biopsy showing UIP includes the following \_\_\_\_\_.

- a. Exclusion of other known causes of interstitial lung disease such as drug toxicities, environmental exposures, and collagen vascular diseases.
- b. Abnormal pulmonary function studies that include evidence of restriction, and/or impaired gas exchange, with rest or exercise or decreased DL<sub>CO</sub>.
- c. Abnormalities on conventional chest radiographs or high-resolution computed tomography (HRCT) scans
- d. All or the above

3. Incidence estimates for IPF are quite limited. It has been estimated at 10.7 cases per 100,000 per year for males and \_\_\_\_\_ cases per 100,000 per year for females.

- a. 5.5
- b. 5.8
- c. 7.4
- d. None of the above

4. Approximately \_\_\_\_\_ of patients with IPF are over the age of 60 yr at the time of presentation, with a mean age at diagnosis of 66 yr. The incidence of the disease increases with older age.

- a. one third
- b. half
- c. two-thirds
- d. None of the above

5. There is geographic variation in the age-adjusted mortality from pulmonary fibrosis. This variation may reflect differences in occupational or environmental exposures. In the United States, age-adjusted mortality rates due to pulmonary fibrosis are lowest in the Midwest and Northeast, and highest in the West and Southeast.

- a. True
- b. False

6. In case-control studies, cigarette smoking has been identified as a potential risk factor with the odds ratio (OR) from various regions of the world ranging from \_\_\_\_\_ for the development of IPF in ever-smokers.

- a. 1.6 to 2.9
- b. 3.1 to 4.3
- c. 4.5 to 5.7
- d. None of the above

7. \_\_\_\_\_, parainfluenza 3 virus, herpesvirus 6, *Mycoplasma*, and legionnaires' disease have been implicated as potential participants in the pathogenesis of IPF.

- a. Parainfluenza 1 virus (Sendai),
- b. human immunodeficiency virus 1 (HIV-1),
- c. measles virus
- d. All of the above

8. On physical examination, crackles are detected on chest auscultation in more than \_\_\_\_\_% of patients.

- a. 69
- b. 76
- c. 80
- d. 92

9. The routine laboratory evaluation of a patient suspected of having IPF is often not helpful except to "rule out" other causes of diffuse parenchymal lung disease. Polycythemia is rare despite the frequent presence of chronic hypoxemia.

- a. True
- b. False

10. *Role of HRCT in determining disease activity.* HRCT has been proposed as a technique for determining the "activity" of IPF. The CT finding of ground glass opacity (also called ground glass attenuation or hazy increase in lung density) refers to the presence of a diffuse homogeneous increase in density of the lung. When this finding occurs in association with \_\_\_\_\_, it always indicates lung fibrosis.

- a. reticular lines
- b. dilated bronchi
- c. bronchioles (traction bronchiectasis or bronchiolectasis)
- d. All of the above

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