Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis

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KEYWORDS

• Idiopathic pulmonary fibrosis • Progressive pulmonary fibrosis
• Interstitial lung disease • Diffuse parenchymal lung disease

KEY POINTS

- When diagnosing idiopathic pulmonary fibrosis (IPF), it is important to consider the demographic features of the patient, the physical examination, computed tomography (CT) chest results, and laboratory data.
- If a patient has a high pretest probability for IPF, chest CT is usually sufficient for the diagnosis without the need for a bronchoscopy or surgical biopsy.
- Disease progression should be tracked by clinical symptoms and pulmonary function testing, particularly forced vital capacity and diffusing capacity of the lungs for carbon monoxide values, and can guide when to start antifibrotic therapy.
- There is a formal definition of non-IPF progressive pulmonary fibrosis that incorporates symptoms, lung function data, and imaging changes.
- Treatment of IPF and progressive pulmonary fibrosis may involve nintedanib or pirfenidone and should follow a shared and informed decision-making process with the patient.

IDIOPATHIC PULMONARY FIBROSIS

Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of disorders that are classified together because of similar clinical, physiologic, radiographic, and pathologic manifestations.[1] ILDs are characterized by cellular proliferation, interstitial inflammation, and fibrosis within the wall of the alveolus, with findings not attributed to cancer or infection.[2] There are more than 200 types of known ILDs,[3] with interstitial fibrosis often predominating as a frequent phenotype. Among these, a large majority will receive a diagnosis of fibrotic hypersensitivity pneumonitis (sometimes attributable to an identified exposure), pulmonary sarcoidosis (granulomas as cause of fibrosis),

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connective tissue disease [CTD-ILD] related interstitial lung disease (autoimmune related), or idiopathic interstitial pneumonia (IIP, cause unknown).[2] Idiopathic pulmonary fibrosis (IPF) is the most common subtype among the different IIPs.[4] IPF is a specific form of chronic, progressive fibrosing interstitial pneumonia, with an unknown cause, and is limited to the lungs.[5] This book chapter explores the clinical manifestations, pathogenesis, treatment, and outcomes in IPF.

Clinical Manifestations and Diagnosis of Idiopathic Pulmonary Fibrosis

Epidemiology

The exact prevalence and incidence of IPF vary and depend on methodology as well as demographics of the geographic population from which the data are being collected. Both prevalence and incidence increase with age, and it is known that IPF most commonly occurs in the sixth and seventh decades of life. It is rare in patients younger than 50 years. Further, both the prevalence and incidence are higher in men compared with women.[5,6] Thus, the pretest probability of the disease can increase by using basic data such as age greater than 60 years and male sex.[7,8] In a recent systematic review,[9] the prevalence of IPF was 0.5 to 27.9/100,000 and the incidence ranged from 0.22 to 8.8/100,000.[10] US population estimates of IPF incidence ranged between 7 and 16/100,000. Comparatively, the Medicare population between 2000-2011 had an IPF yearly incidence of 93.7 cases per 100,000 person years.[11] In Europe, IPF prevalence ranges from 1.25 to 23.4 cases per 100,000 in the population and incidence of 0.22 to 7.9 cases per 100,000 population.[12] In a worldwide systematic review, the overall incidence of IPF is increasing, with conservative estimates revealing an incidence range from 3 to 9 per 100,000 per year for Europe and North America.[13]

The role that race/ethnicity plays in IPF diagnosis is less clear given variation in the pretest probabilities across demographic groups and geographic locations. One large study[14] evaluating IPF diagnoses among decedents in a national database found that Black patients are significantly less likely than White and Hispanic patients to be diagnosed with IPF at time of death, but among those Black patients diagnosed with IPF, death occurs at a younger age. Further Hispanic patients are more likely than White patients to have IPF present at time of death.[14] A more recent multicenter cohort study demonstrated that ILD diagnoses and death occurred at a much younger age among Black patients with diverse forms of fibrotic ILD.[15]

Pathogenesis and genetic predisposition

The pathogenesis of IPF is complex and likely related to cycles of epithelial cell injury and, subsequent, dysregulation in repair.[8] One prevailing theory proposes that IPF results from abnormal fibroblasts and epithelial cell function, along with abnormal epithelial-mesenchymal interactions with little to no inflammatory component.[16] This notion has been supported histologically with findings of fibroblastic foci directly beneath areas of damaged epithelium without the presence of inflammatory cells.[17] Initiation and progression of this fibrosis may depend on genetic factors, environmental triggers, an imbalance between oxidants and antioxidants, and an imbalance of certain cytokines.[18,19]

Although most cases of IPF are thought to be sporadic, familial cases have been described. Familial pulmonary fibrosis, Hermansky-Pudlak syndrome (HPS), and short telomere syndromes typically present at a younger age than IPF. Further, although a large number of genetic polymorphisms have been reported, few are well established.[5,20] Familial pulmonary fibrosis (FPF) is diagnosed when at least 2 relatives within the same family develop pulmonary fibrosis and seems to follow an autosomal dominant pattern.[21] A number of genetic factors have been attributed to FPF; some

notable genes include surfactant-associated proteins A (*SFTPA2*),[22] surfactant protein C (*SFTPC*),[23] and mucin 5B (*MUC5B*).[24] HPS is an autosomal recessive disorder characterized by oculocutaneous albinism and platelet abnormalities, which is a rare cause of usual interstitial pneumonia (UIP) often presenting at an earlier age.[25] Lastly, short telomere syndromes are caused by mutations in genes responsible for maintaining telomere length (eg, *TERT, TERC, PARN, DK1, TINF2, RTEL1*).[26] The disorder is characterized by severely short telomeres (often less than the first percentile for age and frequently less than the tenth percentile) along with dysfunction of one or more target organs. Short telomeres have been identified in about 25% of sporadic IPF and about 15% of families with FPF.[27]

Risk factors

Cigarette smoking has been identified as a potential risk factor for development of IPF with an odds ratio (OR) ranging from 1.6 to 2.9 for developing IPF in ever-smokers.[28,29] This relationship seems to be dose dependent, in that the odds of developing IPF increase with the number of pack-years smoked.[29] Further, chronic aspiration due to gastroesophageal reflux has been implicated in the development of pulmonary fibrosis; however, the direct relationship and degree to which chronic aspiration drives the pathogenesis of IPF remains unclear.[30] Environmental and occupational exposures to stone, metal, wood, and organic dusts has also been suggested as a risk factor.[31,32] Many viruses have been linked to the pathogenesis of IPF, but there is no clear evidence for a viral cause of the disease.[33] Hereditary factors may also contribute to IPF.

Clinical characteristics and diagnosis

History and physical examination. A common clinical presentation for IPF is dyspnea, which is usually progressive, debilitating, and persistent for greater than 6 months in an older adult. Dry cough, unrelieved with antitussives is also common. On physical examination crackles are detected on chest auscultation in more than 80% of patients.[5,8,34] These are often "dry," occur at end-inspiration, and have a "velcro" quality. Rales can also be heard, particularly with disease progression. Clubbing is present in up to half of all patients. Evidence of right-sided heart failure including an accentuated second pulmonic sound, right ventricular heave, and peripheral edema may be seen in the late stage of the disease and associated with cor pulmonale.

Laboratory and serologic tests. There are no laboratory tests to make the diagnosis of IPF, so the role of laboratory testing in patients with newly discovered ILD is to identify or exclude a cause for the disease.[5] These laboratory tests are usually looking for subclinical rheumatologic disease or hypersensitivity pneumonitis. They should, however, be interpreted cautiously, as an antinuclear antibody greater than or equal to 1:40 is present in 17% to 25% of patients with IPF and a positive rheumatoid factor is present in up to 18% of patients with IPF.[35]

Chest imaging. Most patients with IPF have an abnormal chest radiograph at the time of presentation.[36] Peripheral reticular opacities, most profuse at the lung bases, are typical findings on chest radiograph. The opacities are usually bilateral, often asymmetric, and associated with volume loss.[37]

High-resolution computed tomography scanning (HRCT) is the imaging modality of choice for diagnosing IPF and has changed the diagnostic evaluation by allowing for earlier diagnosis of IPF.[37–39] In a trained reviewer, the accuracy of a confident diagnosis of UIP made on HRCT is about 90%.[8,40] The common radiologic findings of IPF on HRCT are patchy, predominantly peripheral, subpleural, and bibasilar reticular

abnormalities.[5] There may be a variable, although usually limited, extent of ground-glass opacities (GGOs), and findings of extensive GGOs should prompt alternative diagnoses.[8] In areas of severe involvement there can be traction bronchiectasis and/or subpleural honeycombing.[5]

Pulmonary function testing. Complete pulmonary function testing (PFT with spirometry, lung volumes, diffusing capacity for carbon monoxide [DLCO]) is performed on all patients with suspected IPF.[41] PFTs often occur in conjunction with resting and ambulatory oxygen saturations as well and are done at baseline and at regular intervals to assess the degree of lung involvement and track disease progression. Commonly, IPF presents with a restrictive pattern on PFTs (often a reduced total lung capacity, reduced forced vital capacity [FVC]), a reduced DLCO, and oxygen desaturation or a decrease in 6-minunte walk distance with time and as the disease progresses.[41]

Flexible bronchoscopy. Although invaluable in many other pulmonary diseases, a bronchoalveolar lavage (BAL) has a limited role in evaluating a patient with an HRCT that is suggestive of UIP and is not guideline recommended[34]; this is because there are broad and overlapping range of cell counts that can be seen, none of which are sensitive or specific for IPF. However, when the clinical impression is consistent with IPF but the HRCT pattern is probable UIP or indeterminate then a cellular analysis may be helpful to exclude alternative diagnoses.

Transbronchial lung biopsy and transbronchial cryobiopsy. Transbronchial lung biopsy (TBLB) is a procedure that uses forceps to obtain transbronchial samples that are a few millimeters in size and can be helpful in some ILD diagnoses but often obtains a sample that is too small to definitively diagnose IPF.[41,42] Approximately one-third of TBLB done for new ILD of unknown cause will provide a clear diagnosis, with two-thirds requiring a subsequent lung biopsy.[43] Transbronchial cryobiopsy (TCBC) is a promising technique that is less invasive than a surgical lung biopsy (SLB) and can obtain biopsy samples that are better in size and quality compared with TBLB. Although some evidence suggests that the utility and safety of TBCB for diagnosing ILD in the context of a multidisciplinary discussion (MDD) is similar to that of an SLB, the role it plays in the diagnostic algorithm of ILD remains unestablished.[44,45]

Surgical lung biopsy. SLB remains the gold standard for obtaining histopathologic confirmation of a patient suspected of having IPF. The decision to perform an SLB requires assessing the benefits of making a definitive diagnosis relative to the surgical risks and should be done in the context of an MDD, ideally involving a pulmonologist, radiologist, pathologist, and rheumatologist with expertise in ILD. Per ATS/ERS/JRS/ALAT guidelines an SLB should be considered in a patient with newly detected ILD of uncertain cause and an HRCT pattern of probable UIP, indeterminate UIP, or an alternate diagnosis where the benefits of surgical lung biopsy outweigh the risk, unless the patient has significant hypoxia or medical comorbidities. However, in patients with newly detected ILD without a known cause, but with an HRCT pattern consistent with UIP, a lung biopsy will be unlikely to change management or diagnosis and is not worth the risk. SLB, whether done via a video-assisted thoracoscopic approach or a thoracotomy, leads to a definitive diagnosis (in conjunction with clinical assessment and HRCT) in 89% of patients.[34]

Diagnosis. The diagnosis of IPF is based on an algorithm that is highly reliant on HRCT scans and pathology data, if available, after exclusion of other known causes of ILD (eg, domestic and occupational exposures, CTD, and drug toxicity).[41] The features

on HRCT (**Table 1**) and histology patterns from lung biopsies (**Table 2**) can help diagnose IPF based on how similar the findings are to UIP. An algorithmic approach using these 2 diagnostic modalities (**Table 3**) can help determine how likely the diagnosis of IPF is.[8,41] Performance of an MDD is increasingly recommended for diagnosis ascertainment and crafting an optimal plan of management.[41]

Treatment

Nonpharmacotherapeutic and supportive care. The most important aspects of supportive care in IPF includes supplemental oxygen, education (including smoking cessation), pulmonary rehabilitation, management of comorbidities, and vaccinations. A large fraction of patients with IPF will require supplemental oxygen for symptoms and to prevent or delay the onset of secondary pulmonary hypertension due to hypoxemia. Improved education about the disease regarding diagnosis and management is an important component to patient's experience, and often this will include end-of-life discussions, particularly the avoidance of mechanical ventilation.[46] Pulmonary rehabilitation in ILD has resulted in a significant reduction in dyspnea and improvement in 6-minute walk distance.[47,48] Avoidance of pulmonary infections, and vaccinations against respiratory infections including *Streptococcus pneumoniae*, Influenza, *Bordetella pertussis*, and COVID-19, are also an important piece of care.[49,50] Lastly, prompt treatment of respiratory infections, including treatment of COVID-19 and preexposure prophylaxis for COVID-19 are also invaluable.[51]

Pharmacotherapy

Treatment available and target population There are 2 antifibrotic medications available to slow disease progression and reduce the frequency of exacerbations: nintedanib and pirfenidone.[5,52–54] In addition to slowing disease progression, these medications have also been shown to decrease the risk of all-cause mortality (pooled risk ratio [RR] 0.55, 95% confidence interval [CI] 0.45–0.66) and decrease risk of acute exacerbations of IPF (RR 0.63, 95% 0.53–0.76).[55] Between the 2 medications there is no clear agent of choice, but patient preference regarding side-effect profiles should be discussed (see further side-effect profiles in the following section).

In patients with mild-to-moderate disease with IPF without underlying liver disease the recommendation is to treat.[5] Further, in patients with more advanced IPF (FVC < 50% predicted and/or DLCO < 25% predicted) the recommendation is also to treat. Although those with advanced disease were not included in most major trials, studies suggest that both agents slow disease progression even at advanced stages.[56,57]

Nintedanib Nintedanib is a receptor antagonist for multiple tyrosine kinases that mediate the elaboration of fibrogenic growth factors and slows the rate of progression in IPF.[58,59] Based on clinical trials the efficacy of nintedanib is mostly due to a reduction in the rate of decline in lung function (particularly FVC) and a longer time to the first exacerbation of IPF.[56,59,60] The typical dose of nintedanib is 150 mg administered orally twice daily. Liver function testing (LFTs) should be assessed before initiation, and the medication should be avoided in patients with moderate or severe hepatic impairment (Child-Pugh B or C). After starting nintedanib, LFTs should be repeated monthly for 3 months and every 3 months thereafter. A pregnancy test should also be done and conception avoided until at least 3 months after last dose.

Most frequent adverse effects associated with nintedanib include diarrhea (62%), nausea (24%), vomiting (12%), and transaminitis (14%).[60] Diarrhea should be treated with hydration and antidiarrheal medications along with a potential dose reduction to 100 mg twice daily. Although clinical trials revealed that diarrhea leads to a dose reduction in 11% of patients and to discontinuation in 5%, observational/real world

Table 1
High-resolution computed tomography patterns in idiopathic pulmonary fibrosis

	HRCT Pattern			
	UIP Pattern	**Probable UIP Pattern**	**Indeterminate for UIP**	**CT Findings Suggestive of an Alternative Diagnosis**
Level of confidence for UIP histology	Confident (>90%)	Provisional high confidence (70%–89%)	Provisional low confidence (51%–69%)	Low to very low confidence (≤50%)
Distribution	• Subpleural and basal predominant • Often heterogeneous (areas of normal lung interspersed with fibrosis) • May be asymmetric	• Subpleural and basal predominant • Often heterogeneous (areas of normal lung interspersed with reticulation and traction bronchiectasis/ bronchiolectasis)	• Diffuse distribution without subpleural predominance	• Peribrochovascular predominant with subpleural sparing (consider NSIP) • Perilymphatic distribution (consider sarcoidosis) • Upper or mid lung (consider fibrotic HP,CTD-LID, and sarcoidosis) • Subpleural sparing (consider NSIP or smoking related IP)
CT features	• Honeycombing with or without traction bronchiectasis/ bronchiolectasis • Presence of irregular thickening of interlobular septa • Usually superimposed with a reticular pattern, mild GGO • May have pulmonary ossification	• Reticular pattern with traction bronchiectasis/ bronchiolectasis • May have mild GGO • Absence of subpleural sparing	• CT features of lung fibrosis that do not suggest any specific etiology	• Lung findings ○ Cysts (consider LAM,PLCH,LIP andDIP) ○ Mosaic attenuation or three-density sign (consider HP) ○ Predominant GGO (consider HP, smoking related disease, drug toxicity, and acute exacerbation of fibrosis) ○ Profuse centrilobular micronodules (consider HP or smoking-related disease)

- Nodules (consider sarcoidosis)
- Consolidation (consider organizing pneumonia, etc.)

- Mediastinal findings
  - Pleural plaques (consider) asbestosis
  - Dilated esophagus (consider CTD)

The previous term, "early UIP pattern," has been eliminated to avoid confusion with "interstitial lung abnormalities" described in the text. The term "indeterminate for UIP" has been retained for situations in which the HRCT features do not meet UIP or probable UIP criteria and do not explicitly suggest an alternative diagnosis.

Abbreviations: CT, computed tomography; CTD, connective tissue disease; DIP, desquamative interstitial pneumonia; GGO, ground-glass opacity; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IP, interstitial pneumonia; LAM, lymphangioleiomyomatosis; LIP, lymphoid interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; PLCH, pulmonary Langerhans cell histiocytosis; UIP, usual interstitial pneumonia.

Table 2
Histopathology patterns and features

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
• Dense fibrosis with architectural distortion (ie, destructive scarring and/or honeycombing) • Predominant subpleural and/or paraseptal distribution of fibrosis • Patchy involvement of lung parenchyma by fibrosis • Fibroblast foci • Absence of features to suggest an alternate diagnosis	• Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/PIF *And* • Absence of features to suggest an alternative diagnosis *Or* • Honeycombing	• Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause[a] • Some histologic features from column 1, but with other features suggesting an alternative diagnosis[b]	• Features of other histologic patterns of IPS (eg, absence of fibroblast foci or loose fibrosis) in all biopsies • Histologic findings indicative of other diseases (eg, hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)

Abbreviations: IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleiomyomatosis; UIP, usual interstitial pneumonia.

[a] Granulomas, hyaline membranes (other than when associated with acute exacerbation of IPF, which may be the presenting manifestation in some patients), prominent airway-centered changes, areas of interstitial inflammation lacking associated fibrosis, marked chronic fibrous pleuritis, organizing pneumonia. Such features may not be overt or easily seen to the untrained eye and often need to be specifically sought.

[b] Features that should raise concerns about the likelihood of an alternative diagnosis include a cellular inflammatory infiltrate away from areas of honeycombing, prominent lymphoid hyperplasia including secondary germinal centers, and a distinctly bronchiolocentric distribution that could include extensive peribronchiolar metaplasia.

Table 3
Idiopathic pulmonary fibrosis diagnosis based on high-resolution computed tomography and biopsy patterns, developed using consensus by discussion

IPF Suspected[a]		Histopathology Pattern[b]			
		UIP	Probable UIP	Indeterminate for UIP or Biopsy not Performed	Alternative Diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Portable UIP	IPF	IPF	IPF (Likely)[c]	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)[c]	Indeterminate[d]	Non-IPF dx
	Alternative diagnosis	IPF (Likely)[c]	Indeterminate[d]	Non-IPF dx	Non-IPF dx

Abbreviations: dx, diagnosis; UIP, usual interstitial pneumonia.

[a] "Clinically suspected of having IPF" is defined as unexplained patterns of bilateral pulmonary fibrosis on chest radiography or chest computed tomography, bibasilar inspiratory crackles, and age >60 y. Middle-aged adults (age >40 and < 60 years) can rarely present with otherwise similar clinical features, especially in patients with features suggesting familial pulmonary fibrosis.

[b] Diagnostic confidence may need to be downgraded if histopathological assessment is based on transbronchial lung cryobiopsy given the smaller biopsy size and greater potential for sampling error compared with surgical lung biopsy.

[c] IPF is the likely diagnosis when any of the following features are present: (1) moderate-to-severe traction bronchiectasis and/or bronchiolectasis (defined as mild traction bronchiectasis and/or bronchiolectasis in 4 or more lobes, including the lingula as a lobe, or moderate-to-severe traction bronchiectasis in 2 or more lobes) in a man >50 years old or in a woman >60 years old; (2) extensive (>30%) reticulation on HRCT and age > 70 years; (3) increased neutrophils and/or absence of lymphocytosis in BAL fluid; and (4) multidisciplinary discussion produces a confident diagnosis of IPF.

[d] Indeterminate for IPF (1) without an adequate biopsy remains indeterminate and (2) with an adequate biopsy may be reclassified to a more specific diagnosis after multidisciplinary discussion and/or additional consultation.

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studies suggest a much higher rate of dose reduction (20%–30%) or discontinuation (5%–25%) due to gastrointestinal (GI) side effects.[61,62]

Pirfenidone Pirfenidone is an antifibrotic that inhibits transforming growth factor beta–stimulated collagen synthesis, decreases the extracellular matrix, and blocks fibroblast proliferation in vitro (PMID: 31967851). The dose can be as high as 40 mg/kg/d with a maximum dose of 2403 mg/d, is taken in 3 divided doses, and always with food. It is initiated gradually with 1 capsule (267 mg) 3 times per day for 1 week, then 2 capsules, and then 3 capsules in a stepwise manner. Similar to nintedanib, LFTs should be monitored regularly with the medication, as drug-induced liver disease can range from mild to fatal. The efficacy of pirfenidone is in slowing the progression of IPF in patients with mild-to-moderate disease and a possible mortality benefit in pooled analysis.[63,64]

Most frequent adverse effects associated with pirfenidone include rash (30%), photosensitivity (9%), nausea (36%), diarrhea (26%), abdominal discomfort (24%), dyspepsia (19%), anorexia (13%), and fatigue (26%). Dose reduction or interruption for GI events was required in 18% of patients in the high-dose group, and 2% discontinued the medication. However, some of the GI adverse reactions can be mitigated by taking the medication with food.[65]

Prognosis and monitoring

Assessing disease severity and prognosis. The severity of IPF is assessed based on symptoms, HRCT findings, and PFTs. Although the typical progression is from mild → moderate → severe respiratory disease, the rate of the progression can vary. The median survival of IPF ranges from 2 to 5 years.[66,67] However, this estimate reflects the range of average life expectancies observed in cohorts of patients with IPF before effective therapies, rather than the limits of an individual patient's life expectancy. This is important, as the actual range of survival in IPF is broad, with up to 20% to 25% of patients living beyond 10 years.[66] Further, the role that antifibrotic agents have on potentially extending life expectancies remains unclear.

The Gender-Age-Physiology (GAP) model can be helpful in estimating the prognosis for patients.[67] This widely validated, clinical prediction model incorporates age, gender, FVC, and DLCO into a point system that is predictive of 1-, 2-, and 3-year mortality. When taken together, in conjunction with the patient's overall clinical picture, the GAP scores can help guide patient's prognosis.

Acute exacerbations. Acute exacerbations of IPF (AE-IPF) are defined as "an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality." They occur in 5% to 10% of patients with IPF annually, carry a poor prognosis with a median survival of only 3 to 4 months after an exacerbation, and have a high in-hospital mortality when presenting in respiratory failure (50% overall and 90% for those requiring mechanical ventilation).[68,69] The following diagnostic criteria for an AE-IPF, from the 2016 guidelines are as follows:[68]

- A known diagnosis of IPF (diagnosis may be made at the time of acute respiratory deterioration)
- Acute worsening, "typically less than 1-month duration"
- HRCT with new bilateral ground-glass opacification and/or consolidation superimposed on a background of findings consistent with UIP
- Heart failure or volume overload does not fully explain the worsening

Broadly speaking, multiple studies[63,64] have shown that worsening respiratory symptoms, regardless of whether or not they meet strict criteria for an acute

exacerbation, confer a high risk for subsequent mortality and thus should prompt a discussion of prognosis and goals of care. Treatment often consists of high-dose corticosteroids although data on their efficacy in exacerbations of IPF are lacking with a weak recommendation for their use in guidelines.[5]

Monitoring of disease. The primary reason to monitor the disease progression in patients with IPF is to assess for potential disease progression that may prompt a change in therapy including medication changes, referral to lung transplantation, and goals of care discussions. There is no clear guideline for frequency of monitoring although typically patients are seen every 3 to 6 months, with frequency dependent on clinical status. One of the key components to monitoring in IPF is following PFTs. Both declines in DLCO and FVC are strong predictors of mortality in IPF and may prompt referral to transplant. A decline in FVC or DLCO of at least 10% over 6 to 12 months predicts an increased risk of mortality, although changes as small as 5% over this same period also portend a worse prognosis.[70–73] In addition to PFTs, a decrease in 6-minute walk distance of 30 m is a clinically important change in IPF over 6 months and can predict mortality.[72,73] Further, worsening hypoxemia and increasing oxygen requirements are common indicators of disease progression and increase the risk of mortality.

Lung transplantation. IPF is the most common ILD referred for lung transplantation and is currently the most common disease process for which lung transplant is performed in the United States,[74] with a median survival following lung transplantation of 5.2 years.[75]

Guidelines for placing a referral for transplantation, in a patient with IPF, include the following:[76,77]

- DLCO less than 40% predicted
- FVC less than 80% predicted
- Any dyspnea or functional limitation due to disease
- A decrease in pulse oximetry of less than 89%, even if only on exertion

Criteria for placing a patient with IPF on the transplant list include the following:[76,77]

- Decline in FVC greater than or equal to 10% during 6 months of follow-up
- Decline in DLCO greater than or equal to 15% during 6 months of follow-up
- On 6-minute walk: oxygen desaturation to less than 88% or distance walked less than 250 m or greater than 50 m decline in distance walked over 6 months
- Pulmonary hypertension
- Hospitalization for respiratory decline, pneumothorax, or acute exacerbation

OTHER INTERSTITIAL LUNG DISEASES—PROGRESSIVE PULMONARY FIBROSIS

Introduction

Patients with a spectrum of lung disorders, including IPF, have a progressive fibrosing clinical phenotype that is characterized by an increasing extent of fibrosis on HRCT, decline in lung function, worsening symptoms, and early death.[41,78] These other ILDs include CTD-associated ILD (CTD-ILD), fibrotic hypersensitivity pneumonitis (HP), unclassifiable ILD, idiopathic nonspecific interstitial pneumonia (NSIP), and rarely sarcoidosis, organizing pneumonia, and ILD associated with occupational exposures.[79] (**Fig. 1**)

Based on clinical and pathophysiological similarities, it has been hypothesized that disorders with this progressive phenotype have a common mechanism, regardless of cause, and thus have a similar response to treatment.[78,80] This section aims to outline

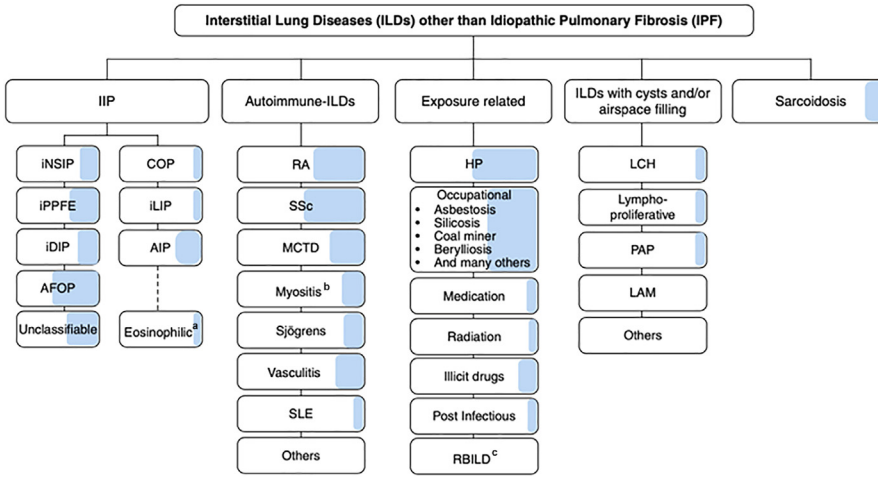

Fig. 1. Interstitial lung diseases (ILDs) manifesting progressive pulmonary fibrosis (PPF), developed using consensus by discussion. The shaded area represents the estimated proportion of patients with various types of ILD who manifest PPF. Note that idiopathic pulmonary fibrosis (IPF) is not included in the figure, because it is excluded from the definition of PPF. Although virtually all patients with IPF will manifest disease progression similar to PPF, the proportion of patients with ILDs other than IPF who manifest PPF is based on the consensus of opinions and the perception of the international committee. There are no data to provide the exact or estimated proportion of patients manifesting PPF in ILDs, other than IPF. [a]The committee acknowledges that eosinophilic pneumonia of unknown cause was not included in the IIP classification. [b]Myositis includes PM/DM/antisynthetase syndrome, which may be amyopathic. [c]Although respiratory bronchiolitis interstitial lung disease (RBILD) is acknowledged to be a consequence of exposure to cigarette smoke in virtually all patients with RBILD, RBILD and desquamative interstitial pneumonia (DIP) often coexist. Although DIP is also related to exposure to cigarette smoke in most of the patients, DIP is also seen in some patients with connective tissue disease, without exposure to cigarette smoke, and without a known cause. Antifibrotic treatment is indicated for patients diagnosed with IPF (3). Antifibrotic treatment of the other types of ILD upon manifesting PPF is as suggested/recommended in this guideline. AFOP, acute fibrinous and organizing pneumonia; AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; DM, dermatomyositis; HP, hypersensitivity pneumonitis; iDIP, idiopathic DIP; IIP, idiopathic interstitial pneumonia; iLIP, idiopathic lymphoid interstitial pneumonia; iNSIP, idiopathic nonspecific interstitial pneumonia; iPPFE, idiopathic pleuroparenchymal fibroelastosis; LAM, lymphangioleiomyomatosis; LCH, Langerhans cell histiocytosis; MCTD, mixed connective tissue disease; PAP, pulmonary alveolar proteinosis; PM, polymyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis. Reprinted with permission of the American Thoracic Society. Copyright © 2022 American Thoracic Society. All rights reserved. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2022;205(9):e18-e47. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

the diagnosis and treatment of progressive pulmonary fibrosis (PPF) in fibrotic ILD, other than IPF.

Although guidelines on PPF were being developed, there was a clinical trial (INBUILD trial, described in more detail in the later section[16]) reporting the beneficial effect of antifibrotic medication in ILDs other than IPF, which manifests with this

PPF phenotype. Given the significance of these findings, and the shift in treatment patterns toward a broader application of antifibrotics, a guideline committee was formed to define the diagnosis of PPF and decide on formal treatment recommendations. The guidelines,[41] established in 2022, for the diagnosis and treatment of PPF are a collaboration between ATS (American Thoracic Society), ERS (European Respiratory Society), JRS (Japanese Respiratory Society), and ALAT (Asociacion Latinoamericana de Torax) and are summarized below.

Definition of Progressive Pulmonary Fibrosis

In patients with ILD other than IPF, and who have radiological evidence of pulmonary fibrosis, PPF is defined as at least 2 of the following 3 criteria occurring within the past year with no alternative explanation.[70]

1. Worsening respiratory symptoms
2. Physiologic evidence of disease progression (either of the following; of note, much of these data have been extrapolated from data on IPF[81,82]):
   a. Absolute decline in FVC $\geq$ 5% predicted within 1 year of follow-up
   b. Absolute decline in DLCO (corrected for hemoglobin) $\geq$ 10% predicted within 1 year of follow-up
3. Radiological evidence of disease progression[83,84] (one or more of the following):
   a. Increased extent or severity of traction bronchiectasis and bronchiolectasis
   b. New GGO with traction bronchiectasis
   c. New fine reticulation
   d. Increased extent or increased coarseness of reticular abnormality
   e. New or increased honeycombing
   f. Increased lobar volume loss

As part of the diagnosis, it is important to exclude alternative explanations of worsening features with suspected progression; this is particularly true in those with worsened respiratory symptoms and/or a decline in DLCO, given the lower specificity of these features of PPF compared with FVC and chest CT.

It is important to highlight that PPF is defined separate from IPF (see **table 3**). Further PPF is not a diagnosis, and the definition is independent of the underlying condition. PPF has been associated only with prognosis, and it remains unclear if it also identifies patients best suited for antifibrotic therapy.[41]

Treatment of Progressive Pulmonary Fibrosis, Other than Idiopathic Pulmonary Fibrosis

Nintedanib

Available evidence for efficacy in progressive pulmonary fibrosis. As previously discussed, nintedanib has been shown to slow disease progression in IPF; as such, the guidelines looked to explore, based on evidence available, if it is a beneficial treatment of non-IPF PPF.[41] To guide this decision, investigators assessed data from a randomized clinical trial (RCT) (INBUILD)[78] that assigned 663 patients with progressive fibrosing ILD (PF-ILD) to nintedanib or placebo for 52 weeks, with a post hoc analysis that further broke down this relationship based on type of ILD. It should be noted that subtle differences in diagnostic criteria exist between the PF-ILD applied in the INBUILD study, and current PPF criteria.[41,78] Among all patients with PPF, FVC declined in both the treatment (nintedanib) and control (placebo) arms of the INBUILD trial, but the mean annual decline was significantly less (107 mL) in the nintedanib arm. The difference in the annual decline in FVC between nintedanib and placebo arms was 128 mL/y among patients who had a radiological UIP pattern, whereas it was 75.3 mL/

y in patients with a radiologic non-UIP pattern. More recent efforts assessing the PPF criteria identify the FVC decline of 10% points or greater as being integral to determination of outcomes among patients with PPF.[85,86] The trial further found that the adverse effect of "progression of ILD" was 2.4 times less likely in the nintedanib compared with the placebo arm. The INBUILD trial showed no significant difference in all-cause mortality or fatal acute exacerbations among all patients with PPF. Similarly, there was no difference in all-cause mortality among patients with PPF who had a radiological UIP pattern. Side effects from the medications were most commonly GI in nature, or transaminitis, as previously outlined in the section on IPF.

Guideline recommendations. Based on the earlier discussion, there is a conditional recommendation for nintedanib in patients with PPF based on 2 major factors:[41]

- There was a statistically significant reduction in disease progression, measured as the annual decline of FVC.
- The side effects are reversible with discontinuation of the medication.

Pirfenidone

Available evidence for efficacy in progressive pulmonary fibrosis. Pirfenidone, similarly, has been shown to slow disease progression in IPF; thus the committee looked to explore, based on evidence available, if it is a beneficial treatment of PPF. To guide this decision, the investigators primarily looked at 2 RCT that enrolled patients with PPF and evaluated the effects of pirfenidone or placebo.[87,88] One of the trials,[78] looking at patients with unclassifiable fibrotic ILD, randomly assigned 253 patients to receive pirfenidone or placebo with a 24-week follow-up period. The second trial,[77]randomly assigned 127 patients with PPF (chronic HP, CTD-ILD, NSIP, and asbestosis-induced lung disease) to receive pirfenidone or placebo with a 48-week follow-up period. Of note, the second trial was terminated early because of futility due to slow recruitment but imputations were made for the missing data.[41]

When the 2 RCTs were combined into a meta-analysis, pirfenidone was found to decrease FVC by 100 mL or by 2.3% over 24 weeks.[87,88] Pirfenidone reduced by 1.6 times the likelihood that percentage predicted of FVC would decline by greater than 5% and reduce by 1.9 times the likelihood that percentage predicted FVC would decline greater than 10%. Neither trial showed a statistically significant difference in progression-free survival, nor was there a difference in mortality.

Guideline recommendations. Based on the earlier discussion, and the fact that one-third of the committee abstained from voting for or against the use of pirfenidone, the committee made the following recommendation[41]:

- The recommendation is for further research into the efficacy, effectiveness, and safety of pirfenidone in both non-IPF PPF in general and specific types of non-IPF PPF.

CLINICS CARE POINTS

- IPF is defined by an UIP pattern after excluding other known causes of ILD.
- Indices of disease progression in IPF include lung function decline, worsening dyspnea, and greater extent of HRCT fibrosis. The GAP model can be helpful in prognosticating outcomes.
- Approach to management of IPF includes pharmacotherapy, nonpharmacotherapeutic interventions, and supportive care. Comorbidities should be addressed when present, and hypoxia treated with ambulatory O2.

- Consideration for antifibrotic therapy and lung transplantation evaluation should occur early.
- Patients with ILD other than IPF, and who have radiological evidence of pulmonary fibrosis, may have PPF with disease behavior similar to IPF.
- PPF is defined by the presence of 2 out of 3 criteria including worsening respiratory symptoms, physiologic evidence of disease progression, or radiological evidence of disease progression.

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CONFLICT OF INTEREST DISCLOSURES

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