Idiopathic Pulmonary Fibrosis

Jason S. Zolak, MD[a], Joao A. de Andrade, MD[a,b,c,*]

KEYWORDS

• Idiopathic pulmonary fibrosis • Pathogenesis • Diagnosis • Management

KEY POINTS

- Progressive scarring of the lung parenchyma, and relentless loss of lung function leading to disabling dyspnea characterize idiopathic pulmonary fibrosis (IPF).
- The pathogenesis may be related to an aberrant wound healing process that starts in a genetically susceptible epithelium.
- The clinical course of IPF is unpredictable.
- No Food and Drug Administration approved therapies are available for IPF.
- Lung transplantation may be a viable option for a selected group of patients, and referral for evaluation should be considered at the time of diagnosis.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease of unknown cause characterized by progressive scarring of the lung parenchyma with a histologic pattern of usual interstitial pneumonia (UIP).[1] Clinically, it is manifested by progressive loss of lung function that leads to breathlessness and relentless functional limitation. It is a fatal disease with a median survival of only 3 years after the diagnosis,[2] and the incidence is estimated to be from 6.8 to 16.3 cases per 100 000 people.[3] IPF is more prevalent among older Caucasian men, with most cases being diagnosed in individuals older than 60 years.[3,4] To this date, no Food and Drug Administration–approved therapies are available for IPF.

The mortality rate associated with IPF has been increasing during the last few years, and a recent report estimates that it was approximately 50.8 deaths per million people between the years of 1992 and 2003.[5] If those numbers are correct, 40 000 people die

Funding sources: Dr Zolak: nil; Dr de Andrade: NIH/NHLBI (IPFnet), Intermune, Actelion, Fibrogen, Centocor, Immuneworks, Gilead, Boehringer-Ingelheim, and Celgene.
Conflict of interest: Nil.
[a] Division of Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, 1900 University Boulevard, THT 422, Birmingham, AL 35294-0006, USA; [b] Interstitial Lung Disease Program, Division of Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, 1900 University Boulevard, THT 422, Birmingham, AL 35294-0006, USA; [c] Medical Intensive Care Unit, Birmingham VA Medical Center, Birmingham, AL, USA
* Corresponding author.
E-mail address: joao@uab.edu

Immunol Allergy Clin N Am 32 (2012) 473–485
http://dx.doi.org/10.1016/j.iac.2012.08.006 **immunology.theclinics.com**
0889-8561/12/$ – see front matter Published by Elsevier Inc.

of IPF every year in the United States alone, which is comparable with the mortality rates attributed to breast cancer.

In this review article, the authors discuss evolving concepts regarding the pathogenesis of IPF, describe the most current diagnostic and management strategies, and discuss some of the recent clinical trials that explored novel therapies for IPF.

PATHOGENESIS

The factors that determine the onset and progression of IPF are not completely understood. The last few years have seen a shift in the paradigms regarding the pathogenesis of IPF from chronic inflammation leading to progressive fibrosis to an abnormal wound healing process in which multiple factors interplay.[6] Supporting that concept, studies of gene expression profile patterns have demonstrated that, when compared with lungs with chronic hypersensitivity pneumonitis, which is characterized by a significant inflammatory component, IPF lungs have a shift toward extracellular matrix turnover and epithelium development, growth, and differentiation.[7] Moreover, older reports exploring antiinflammatory agents have largely failed to demonstrate a treatment benefit in IPF.[8–10]

Alveolar epithelial cells and the myofibroblast are thought to be the key target cells in the pathogenesis of IPF; there is growing evidence that genetic susceptibility, cellular senescence, endoplasmic reticulum stress and oxidative stress, as well as epigenetic factors associated with micro-RNAs are critical factors for the injury continuum that ultimately leads to the extensive fibrotic changes and loss of lung function seen in IPF. The authors focus the discussion on those emerging concepts.

A genetic component for the development of IPF is suggested because up to 20% of cases are reported to occur in families.[11,12] Mutations both in the surfactant protein C and an isoform of the surfactant protein A genes have been reported.[13–16] Both mutations are linked to abnormal processing and protein misfolding in alveolar epithelial cells with subsequent endoplasmic reticulum alveolar stress that leads to an increased predisposition to fibrosis in response to injury.[16]

IPF is rarely diagnosed in individuals younger than 50 years,[3] suggesting that it may be, at least in part, a disease related to the aging process. Corroborating this hypothesis, studies of both familial and so-called sporadic cases of IPF demonstrated the presence of telomere shortening, which has been associated with cellular senescence and a reduced capacity for epithelial repair.[17–19]

Oxidative stress is defined as an imbalance between excessive generation of reactive oxygen species and diminished ability to scavenge them. Oxidative stress plays a role in the development of fibrosis in several different organ systems and it is a feature of IPF.[20,21] Transforming growth factor (TGF)-β1, which is considered to be the premier profibrotic cytokine, can stimulate the production of Reactive Oxygen Species and myofibroblast differentiation in human lung fibroblasts.[22] It has been demonstrated that the bronchoalveolar lavage fluid of patients with IPF has increased levels of reactive oxygen species as well as diminished levels of glutathione compared with controls.[23] Furthermore, there have been reports of evidence of oxidative stress and damage in the lung tissue of patients with IPF.[21,24] It has been demonstrated that oxidative stress can induce cellular senescence and apoptosis[25,26]; when fibroblasts become senescent, they acquire an apoptosis-resistant phenotype and secrete higher levels of reactive oxygen species.[27] Lung myofibroblasts do undergo similar changes[28] and are likely implicated in the formation of the positive feedback loop that helps perpetuate a proinjury and profibrotic microenvironment in the IPF lung.

The endoplasmic reticulum (ER) is an intracellular organelle that is responsible for proper folding, processing and trafficking of secreted proteins. Additionally, it is involved in the production of steroids, synthesis of lipids and calcium homeostasis.[29] Several factors, such as reduced energy stores, accumulation of improperly folded mutant proteins, and oxidative stress, may induce ER stress in the form of an adaptive process called unfolded protein response (UPR).[30] UPR is meant to facilitate ER protein folding and degradation; but if the triggering factor is persistent, it can lead to cell death through apoptosis. ER stress has been proposed as an important component of the pathogenesis of IPF because evidence of it has been found in lung tissue from patients with both familial and sporadic IPF.[22,31] Similar findings have been reported in epithelial cells in IPF.[31] Recent reports propose that ER stress is involved in the differentiation of lung fibroblasts into myofibroblasts, a process that is critical for the persistent collagen and matrix deposition that ultimately leads to remodeling of the IPF lung.[22] Furthermore, several stressors that have been implicated in the pathogenesis of IPF, such as viral infections, cigarette smoking, surfactant protein mutations, and oxidative stress, are also potential triggers of ER stress.[32]

MicroRNAs (miRs) are noncoding small RNAs that bind to the untranslated regions of target genes in response to several cellular stimuli and, in doing so, repress the translation of target genes or induce degradation of a given target gene mRNA. Abnormal expression of miRs have been linked to the pathogenesis of several common entities, such as diabetes, cancer, and cardiovascular disease,[33–35] and specifically to fibrosing processes in different organs, including IPF lungs.[35–38] It has been suggested that the role of miRs in the pathogenesis of fibrotic processes may be caused by its effect in the biology of TGF-β1.[37] A recent study presented evidence that 3 members of the miR-200 family (miR-200a, miR-200b, miR-200c) were downregulated in the lungs of mice with bleomycin-induced fibrosis. Levels of miR-200a and mi-RNA-200c were also decreased in the lungs of patients with IPF. Importantly, members of the miR-200 family inhibited epithelial-mesenchymal transformation of alveolar epithelial cells induced by TGF-β1 and actually reversed the fibrogenic activity of fibroblasts from both mice with bleomycin-induced fibrosis and patients with IPF.[39]

Taken together, these recent reports suggest that a dysfunctional alveolar epithelium, generated by genetic and perhaps epigenetic susceptibility, aging, and/or external noxious stimuli, may lead to abnormal epithelium-mesenchymal interactions that create a sustained and self-perpetuating loop of injury through oxidative stress and perhaps ER stress, thereby preventing normal epithelial repair with progressive fibrosis and ultimate loss of lung function.

CLINICAL PRESENTATION AND DIAGNOSIS

Patients with IPF typically present with the gradual onset of dyspnea on exertion and persistent nonproductive cough. Systemic symptoms, such as weight loss, fevers, arthralgias, and myalgias, are rare and suggest another process, such as collagen vascular disease. The median duration of illness before diagnosis is 24 months.[40] Physical examination usually reveals late, fine inspiratory crackles (Velcrolike [Velcro USA, Inc, Manchester, New Hampshire]) on auscultation, and digital clubbing is present in approximately half of patients. Cardiac examination often remains normal in the absence of pulmonary hypertension.

Pulmonary function tests (PFTs) demonstrate a normal forced expiratory volume in the first second of expiration/forced vital capacity (FVC) ratio with a restrictive ventilatory defect caused by poorly compliant parenchyma with reduced diffusion capacity for carbon monoxide (D_LCO) and abnormal gas exchange. The main mechanism for

hypoxemia at rest and with exercise in patients with IPF is ventilation-perfusion mismatch and not impaired diffusion as previously thought. Cardiopulmonary exercise testing may be more sensitive than resting PFTs in the detection of gas exchange abnormalities, and low maximum oxygen consumption on exercise testing correlates with an increased risk of death.[41]

In the appropriate clinical setting, a confident diagnosis of IPF can be made if a chest high-resolution CAT scan (HRCT) demonstrates bilateral and predominantly basal and subpleural reticulation, traction bronchiectasis, and honeycomb change (**Fig. 1**). Features that are inconsistent with IPF/UIP include upper/midlung predominance, peribronchovascular predominance, extensive ground-glass abnormality, profuse micronodules, discrete cysts, diffuse mosaic attenuation/air trapping, and consolidation in bronchopulmonary segments/lobes.[42] Unfortunately, a significant number of patients present with an HRCT that is atypical and require a surgical lung biopsy for a definitive diagnosis.[43,44]

The gross appearance of the lungs in IPF is characterized by a nodular pleural surface and the histopathology pattern is consistent with UIP. The histopathologic pattern of UIP includes the presence of temporal heterogeneity with areas of mature relatively acellular collagen bundles and areas of new fibrosis consisting of aggregates of fibroblasts in myxoid connective tissue called fibroblastic foci, honeycomb change, pleural involvement, and areas of normal lung (**Fig. 2**).

As one attempts to diagnose IPF and other types of interstitial lung disease, it is often helpful to think algorithmically. The evaluation begins with a careful and detailed history, physical examination, chest radiographs, pulmonary function testing, and serologic studies. This process should screen for systemic conditions associated with interstitial lung disease as well as environmental exposures and drug-related interstitial lung disease. The next step is obtaining an HRCT, and a confident diagnosis of UIP can be made if the typical features of UIP/IPF are present, abrogating the need for a surgical biopsy. If either the clinical presentation or the HRCT are atypical for IPF, then a surgical lung biopsy should be considered. Transbronchial biopsies are not thought to yield enough tissue and, therefore, are not usually indicated if IPF is suspected. A multidisciplinary discussion of the clinical information, radiographs, and histologic findings among experienced pulmonologists, radiologists, and pathologists

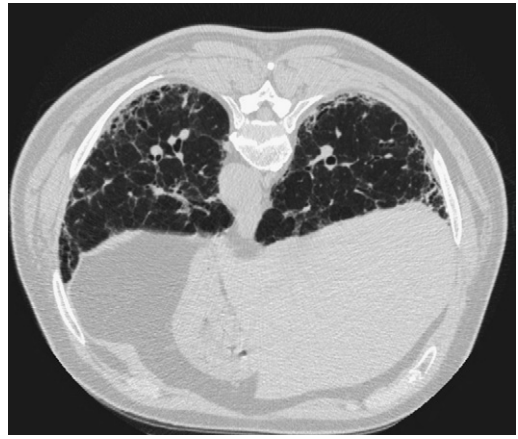

Fig. 1. Typical HRCT findings of IPF: pleural-based areas of honeycombing, coarse reticular opacities, and traction bronchiectasis.

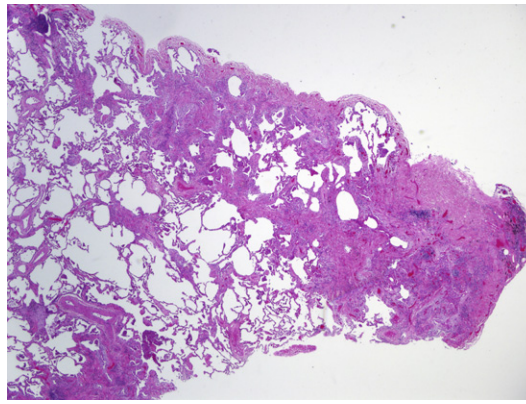

Fig. 2. Typical findings of usual interstitial pneumonia: temporal heterogeneity with areas of dense fibrosis (*right corner*), new fibrosis with fibroblast foci (*upper center, around airways*), bronchiolectasis, and early honeycombing (*upper center*), and areas of preserved alveolar architecture (*lower center*).

will increase diagnostic accuracy and is recommended as the method of choice for the diagnosis of IPF.[42,45]

CLINICAL TRIALS IN IPF

No approved therapies are available for IPF, and the process of drug discovery and drug development has been mired by several fundamental problems. Animal models of IPF using bleomycin-induced lung injury do not fully reproduce human disease, thereby making the interpretation of preclinical efficacy studies difficult. The scientific community continues to debate which outcome measures are clinically meaningful. Although all-cause mortality is clearly a meaningful end point for a clinical trial, those studies require larger numbers of patients, longer periods for enrollment and follow-up, and carry significant cost. Other measures, such as change in lung function over time, have been suggested as adequate surrogates for mortality but are yet to be rigorously validated.[46]

During the last 20 years, more than 3000 patients have been enrolled in clinical trials exploring novel therapies for IPF and most used different measures of change in lung physiology as the primary end point (**Table 1**). A few studies met their primary end point but none thus far have demonstrated a survival advantage or a clinically meaningful benefit in IPF. Another factor to consider as one interprets the results of the past IPF clinical trials is that most allowed the use of corticosteroids in the placebo arm.

To this date, only 3 phase III clinical trials in IPF have met their primary end point. The Study of the Effects of High-Dose N-Acetylcysteine (NAC) in Idiopathic Pulmonary Fibrosis (IFIGENIA) compared the effectiveness of 1-year combined antiinflammatory therapy of azathioprine and prednisone with or without the antioxidant NAC.[47] At the end of 1 year, patients randomized to the triple therapy arm had a statistically significant lower rate of decline in FVC and D_LCO compared with patients who took only prednisone and azathioprine. Although this study has been widely criticized for the lack of a placebo-only group and the significant rate of dropouts, it was used to inform a 3-arm (prednisone, azathioprine, NAC vs NAC alone vs placebo alone) randomized trial sponsored by the National Heart, Lung, and Blood Institute IPF Clinical Research Network (IPFnet), the Prednisone, Azathioprine, and N-Acetylcysteine (PANTHER)-IPF trial.

Table 1
Recent randomized clinical trials in IPF

Study	Drug	Entry Criteria	Primary End Point	n	Corticosteroids (CS) Allowed	Results
Raghu[77]	Interferon γ 1b	FVC >50, D_LCO >25	Progression-free survival	330	Yes	Negative
Azuma[52]	Pirfenidone	Age, oxygen saturation measured using pulse oximetry (SpO_2)	ΔSpO_2 six-minute walked test(6MWT)	109	Yes	Negative
Demedts[47]	Prednisone(Pred)/ azathioprine(AZA) $\pm$ NAC	FVC $\leq$80, D_LCO <80	Absolute (Abs) ΔFVC, D_LCO	182	Yes	Less deterioration in FVC and D_LCO with triple therapy
Kubo[50]	CS $\pm$ Anticoagulant	Decline with CS	Survival/time to death	56	Yes	Better survival in the anticoagulant group
King[78]	Bosentan	FVC $\geq$50, D_LCO $\geq$30	six-minute walk distance (6MWD)	158	Yes	Negative
Raghu[79]	Etanercept	FVC $\geq$45, D_LCO $\geq$25	Δ%FVC, D_LCO, A-a	88	No	Negative
King[80]	Interferon γ 1b	FVC $\geq$55, D_LCO $\geq$35	Survival	826	Yes	Negative
Daniels[81]	Imatinib	FVC $\geq$55, D_LCO $\geq$35	Disease progression/death	119	No	Negative
Noble[54]	Pirfenidone	FVC $\geq$50, D_LCO $\geq$35	Δ%FVC	435	Yes	Lower decline in FVC
Noble[54]	Pirfenidone	FVC $\geq$50, D_LCO $\geq$35	Δ%FVC	344	Yes	Negative
Taniguchi[53]	Pirfenidone	SpO_2 on 6MWT	ΔFVC	275	Yes	Lower decline in FVC for the group randomized to the higher dose of pirfenidone
Zisman[82]	Sildenafil	D_LCO <35	6MWD	180	Yes	Negative
Noth[51]	Warfarin	Progressive disease	Death/hospitalization/ decline in %FVC $\geq$10	145	Yes	Harmful
Raghu[48]	Pred/Aza/NAC	FVC $\geq$50, D_LCO $\geq$30	Δ%FVC	155	Yes	Harmful
Richeldi[83]	BIBF-1120	FVC $\geq$50, D_LCO 30–79	Rate of decline in FVC	432	Yes	Negative

Abbreviations: Abs, absolute; AZA, azathioprine; CS, corticosteroids; 6MWD, six-minute walked distance; 6MWT, six-minute walk test; NAC, N-acetylcysteine; SpO2, oxygen saturation measured using pulse oximetry.

PANTHER-IPF is a randomized, double-blind, placebo-controlled trial that enrolled patients with mild to moderate IPF in a 1:1:1 ratio. An interim analysis conducted when approximately 50% of the data had been collected demonstrated a statistically significant increased risk of death and hospitalizations for patients randomized to the triple-therapy arm compared with those randomized to placebo. This finding prompted the data safety monitoring board to stop enrollment in the triple-therapy arm.[48] The study continued to recruit patients to both NAC and placebo arms and is expected to complete the follow-up in the fall of 2013. The results of PANTHER-IPF provide strong evidence against the use of antiinflammatory therapy for patients with IPF.

Many animal and human studies have supported the importance of the coagulation cascade in the pathogenesis of IPF.[49] Kubo and colleagues[50] conducted a prospective, randomized, open-label study of 64 patients with IPF with mild physiologic impairment recruited at the time of hospitalization. All patients had evidence of prior clinic deterioration and were taking corticosteroids at the time of enrollment. Patients were randomized to receive either corticosteroids alone (n = 33) or corticosteroids plus anticoagulation (n = 31), which consisted of either outpatient warfarin titrated to international normalized ratio (INR) of 2 to 3 or intravenous low molecular heparin during periods of hospitalization for disease exacerbation. There was a statistically significant improvement in both survival and mortality associated with acute exacerbation of IPF in the anticoagulant-treated group. Several methodological concerns have been raised about this study. Survival in the control group was much lower than reported in some contemporary IPF clinical trials. Furthermore, 8 out of 31 patients randomized to the anticoagulant group withdrew consent before receiving the study drug, but an intent-to-treat analysis of the whole randomized patient cohort was not conducted. This study, however, suggested a potential role for anticoagulation as a treatment strategy for IPF and informed the Anticoagulant Effectiveness in Idiopathic Pulmonary Fibrosis (ACE-IPF) trial of the IPFnet. ACE-IPF was a randomized, double-blind, controlled study of patients with progressive IPF that were randomized to either placebo or warfarin targeting an INR of 2 to 3 in a 1:1 ratio. The primary end point of ACE-IPF was a composite of time to death, nonbleeding/nonelective hospitalization, or a 10% or greater reduction in FVC. The planned treatment duration was 48 weeks, but after 145 of the planned 245 patients had been enrolled, the data safety monitoring board recommended stopping the study because of a low probability of benefit and, more importantly, a statistically significant increase in mortality among patients randomized to warfarin.[51] The results of both PANTHER-IPF and ACE-IPF illustrate the importance to confirm promising preliminary results with adequately powered placebo-controlled, randomized, clinical trials.

Pirfenidone is a molecule that has been demonstrated to have antifibrotic properties in preclinical studies using animal models of pulmonary fibrosis. In 2005, Azuma and collaborators[52] published a study conducted in Japan in which 107 patients with IPF were randomized to either placebo or pirfenidone. This study largely failed to meet its primary end point but was stopped early by the data safety monitoring board because more patients in the placebo group experienced acute exacerbations of IPF. Subsequently, Taniguchi and collaborators[53] conducted a 3-arm trial of 275 patients with IPF randomized to 2 different doses of pirfenidone (1800 mg or 1200 mg) or placebo. Patients randomized to the higher-dose group had a significant reduction in the rate of decline in vital capacity and improved progression-free survival, which was a secondary end point. Although these results were largely encouraging, it is concerning that the primary end point was changed after the trial was started and that the method chosen to handle missing data might have magnified the treatment effect of pirfenidone. More recently, Noble and colleagues[54] reported the results of 2

concomitant, large, placebo-controlled, randomized trials of pirfenidone that recruited most patients with IPF from centers in the United States. The primary end point of both studies was a change in predicted FVC at week 72. Study 004 randomized 435 patients in a 2:2:1 model to a higher-dose group, a placebo group, or a lower-dose group. Study 006 enrolled 334 patients in a 1:1 model to either a high dose of pirfenidone or placebo. Study 004 met its primary end point but study 006 did not. Overall, both studies demonstrated that pirfenidone has a very good safety profile, but questions remain regarding its efficacy. Pirfenidone is not yet approved for use in the United States but has been approved for the treatment of IPF in the European Union and in Japan.

MANAGING PATIENTS WITH IPF

Recent clinical trials in IPF have largely failed to identify effective therapies for IPF but have given us much-needed insights into the natural history of the disease. Analysis of the placebo arm of a large, multicenter, randomized, clinical trial of interferon-γ-1b in patients with moderate IPF demonstrated that lung physiology had only a minimal decline during the first 12 months following randomization. Approximately half of the deaths that occurred acutely were preceded by a period of rapid deterioration that did not have an identifiable cause. There was an overall trend toward worsening dyspnea and lung physiology before death, but there was great variability among patients and, more importantly, the initial FVC was not a reliable predictor of outcomes.[55] These findings are significant because they emphasize the fact that the clinical course of IPF is unpredictable.[42]

Lung transplantation is the only option to prolong the life of patients with advanced IPF[56] but it has considerable limitations. It is a costly treatment available to only a very selected few and has a 5-year median survival of only 50%.[57]

Because no effective pharmacologic therapies are available, the management of patients with IPF focuses on measures to preserve quality of life, mobility, and independence. Patients with IPF have diminished exercise capacity, significant fatigue, breathlessness, depression, diminished cognitive function, and diminished quality-of-life measures compared with the general population.[58,59]

Pulmonary rehabilitation has been shown to have a positive impact on those elements in patients with chronic obstructive pulmonary disease and is recommended for patients with IPF.[42] Although well-designed prospective and controlled studies exploring the role of pulmonary rehabilitation in IPF are lacking, retrospective cohort studies have suggested that pulmonary rehabilitation is largely beneficial, especially for patients with more advanced disease.[60]

Hypoxemia is often seen in patients with advanced IPF and may be a harbinger of shorter survival[40]; however, no conclusive studies have been performed on the effects of long-term oxygen therapy on survival or level of breathlessness.[61] A few small studies suggest a favorable impact of oxygen therapy on exercise capacity and quality of life.[62,63]

Severe, nonproductive cough is another problem commonly reported in IPF; it is important to consider that about half the cases of persistent cough in patients with interstitial lung diseases may be related to factors, such as upper airway cough syndrome and gastroesophageal reflux.[64]

Gastroesophageal reflux is prevalent in IPF and it has been suggested that it is involved in the pathogenesis as both the initial insult or later as a promoter of recurrent lung injury.[65–67] Supporting this hypothesis, a recent retrospective cohort study reported that the use of antireflux medications was associated with decreased radiologic fibrotic findings and was an independent predictor of longer survival.[68]

Sleep-disordered breathing has been reported to be common in IPF, causing a negative impact in quality of life.[69,70] No studies have explored the impact of nocturnal noninvasive ventilation for IPF patients with sleep-disordered breathing.

A subset of patients, especially those with a significant smoking history, has disease that is characterized by the simultaneous presence of pulmonary fibrosis and emphysema. This combined pulmonary fibrosis and emphysema phenotype occurs more commonly in men, with a mean age of 65 years. It is associated with a relative preservation of lung volumes and marked reductions in D_LCO on PFTs.[71] Such patients are more likely to require oxygen therapy and develop pulmonary hypertension and may have worse outcomes compared with those with only pulmonary fibrosis.[72]

Pulmonary hypertension is often seen in IPF and may be associated with disease progression and poor survival,[73,74] but the best strategies for the diagnosis and management of pulmonary hypertension in IPF remains to be defined.

IPF is typically a gradually progressive disease, but 5% to 10% of patients experience episodic worsening of symptoms and lung function termed acute exacerbations of IPF. Acute exacerbation of IPF has been defined as an unexplained clinical decline within 30 days associated with new bilateral ground-glass opacities or consolidation on imaging on a background of UIP, lack of evidence for infection and exclusion of heart failure, pulmonary thromboembolism, or other known causes of acute lung injury.[75] Acute exacerbations are associated with a high mortality and poor 6-month prognosis among those who survive the episode. Patients who are experiencing acute exacerbations are often treated with high doses of corticosteroids, but there is no evidence that such strategy impacts outcomes.[76]

In summary, patients with IPF ought to receive aggressive treatment of reflux and be referred for pulmonary rehabilitation. If sleep-disordered breathing is present, noninvasive positive pressure ventilation can be considered if no contraindication is present. Most importantly, patients with IPF should be referred early to tertiary care centers to be evaluated for lung transplantation and to be considered for participation in clinical trials.[42]

REFERENCES

1. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med 1998;157(4 Pt 1):1301–15.
2. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;157(1): 199–203.
3. Raghu G, Weycker D, Edelsberg J, et al. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2006;174(7):810–6.
4. de Andrade JA, Daniel N, Wille KM, et al. Racial disparities in idiopathic pulmonary fibrosis. Data from a Southeastern U.S. Center. Proc Am Thorac Soc 2008; 2008:A249.
5. Olson AL, Swigris JJ, Lezotte DC, et al. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. Am J Respir Crit Care Med 2007;176(3):277–84.
6. Selman M, King TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. Ann Intern Med 2001;134(2):136–51.
7. Selman M, Pardo A, Barrera L, et al. Gene expression profiles distinguish idiopathic pulmonary fibrosis from hypersensitivity pneumonitis. Am J Respir Crit Care Med 2006;173(2):188–98.

8. Selman M, Carrillo G, Salas J, et al. Colchicine, D-penicillamine, and prednisone in the treatment of idiopathic pulmonary fibrosis: a controlled clinical trial. Chest 1998;114(2):507–12.
9. Collard HR, Ryu JH, Douglas WW, et al. Combined corticosteroid and cyclophosphamide therapy does not alter survival in idiopathic pulmonary fibrosis. Chest 2004;125(6):2169–74.
10. Douglas WW, Ryu JH, Swensen SJ, et al. Colchicine versus prednisone in the treatment of idiopathic pulmonary fibrosis. A randomized prospective study. Members of the Lung Study Group. Am J Respir Crit Care Med 1998;158(1):220–5.
11. Hodgson U, Laitinen T, Tukiainen P. Nationwide prevalence of sporadic and familial idiopathic pulmonary fibrosis: evidence of founder effect among multiplex families in Finland. Thorax 2002;57(4):338–42.
12. Marshall RP, Puddicombe A, Cookson WO, et al. Adult familial cryptogenic fibrosing alveolitis in the United Kingdom. Thorax 2000;55(2):143–6.
13. Nogee LM, Dunbar AE 3rd, Wert SE, et al. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med 2001;344(8):573–9.
14. Thomas AQ, Lane K, Phillips J 3rd, et al. Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. Am J Respir Crit Care Med 2002;165(9):1322–8.
15. Wang Y, Kuan PJ, Xing C, et al. Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer. Am J Hum Genet 2009;84(1):52–9.
16. Lawson WE, Cheng DS, Degryse AL, et al. Endoplasmic reticulum stress enhances fibrotic remodeling in the lungs. Proc Natl Acad Sci U S A 2011;108(26):10562–7.
17. Alder JK, Chen JJ, Lancaster L, et al. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. Proc Natl Acad Sci U S A 2008;105(35):13051–6.
18. Cronkhite JT, Xing C, Raghu G, et al. Telomere shortening in familial and sporadic pulmonary fibrosis. Am J Respir Crit Care Med 2008;178(7):729–37.
19. Tsakiri KD, Cronkhite JT, Kuan PJ, et al. Adult-onset pulmonary fibrosis caused by mutations in telomerase. Proc Natl Acad Sci U S A 2007;104(18):7552–7.
20. Brenner DA. Molecular pathogenesis of liver fibrosis. Trans Am Clin Climatol Assoc 2009;120:361–8.
21. Kinnula VL, Fattman CL, Tan RJ, et al. Oxidative stress in pulmonary fibrosis: a possible role for redox modulatory therapy. Am J Respir Crit Care Med 2005;172(4):417–22.
22. Baek HA, Kim do S, Park HS, et al. Involvement of endoplasmic reticulum stress in myofibroblastic differentiation of lung fibroblasts. Am J Respir Cell Mol Biol 2012;46(6):731–9.
23. Cantin AM, Hubbard RC, Crystal RG. Glutathione deficiency in the epithelial lining fluid of the lower respiratory tract in idiopathic pulmonary fibrosis. Am Rev Respir Dis 1989;139(2):370–2.
24. Kuwano K, Nakashima N, Inoshima I, et al. Oxidative stress in lung epithelial cells from patients with idiopathic interstitial pneumonias. Eur Respir J 2003;21(2):232–40.
25. Dasari A, Bartholomew JN, Volonte D, et al. Oxidative stress induces premature senescence by stimulating caveolin-1 gene transcription through p38 mitogen-activated protein kinase/Sp1-mediated activation of two GC-rich promoter elements. Cancer Res 2006;66(22):10805–14.

26. MacNee W. Accelerated lung aging: a novel pathogenic mechanism of chronic obstructive pulmonary disease (COPD). Biochem Soc Trans 2009;37(Pt 4): 819–23.
27. Toussaint O, Medrano EE, von Zglinicki T. Cellular and molecular mechanisms of stress-induced premature senescence (SIPS) of human diploid fibroblasts and melanocytes. Exp Gerontol 2000;35(8):927–45.
28. Waghray M, Cui Z, Horowitz JC, et al. Hydrogen peroxide is a diffusible paracrine signal for the induction of epithelial cell death by activated myofibroblasts. FASEB J 2005;19(7):854–6.
29. Lin JH, Walter P, Yen TS. Endoplasmic reticulum stress in disease pathogenesis. Annu Rev Pathol 2008;3:399–425.
30. Xu C, Bailly-Maitre B, Reed JC. Endoplasmic reticulum stress: cell life and death decisions. J Clin Invest 2005;115(10):2656–64.
31. Lawson WE, Crossno PF, Polosukhin VV, et al. Endoplasmic reticulum stress in alveolar epithelial cells is prominent in IPF: association with altered surfactant protein processing and herpesvirus infection. Am J Physiol Lung Cell Mol Physiol 2008;294(6):L1119–26.
32. Tanjore H, Blackwell TS, Lawson WE. Emerging evidence for endoplasmic reticulum stress in the pathogenesis of idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol 2012;302(8):L721–9.
33. Croce CM. Causes and consequences of microRNA dysregulation in cancer. Nat Rev Genet 2009;10(10):704–14.
34. Latronico MV, Condorelli G. MicroRNAs and cardiac pathology. Nat Rev Cardiol 2009;6(6):419–29.
35. Thum T, Gross C, Fiedler J, et al. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. Nature 2008;456(7224):980–4.
36. van Rooij E, Sutherland LB, Thatcher JE, et al. Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis. Proc Natl Acad Sci U S A 2008;105(35):13027–32.
37. Liu G, Friggeri A, Yang Y, et al. miR-21 mediates fibrogenic activation of pulmonary fibroblasts and lung fibrosis. J Exp Med 2010;207(8):1589–97.
38. Kato M, Zhang J, Wang M, et al. MicroRNA-192 in diabetic kidney glomeruli and its function in TGF-beta-induced collagen expression via inhibition of E-box repressors. Proc Natl Acad Sci U S A 2007;104(9):3432–7.
39. Yang S, Banerjee S, de Freitas A, et al. Participation of miR-200 in pulmonary fibrosis. Am J Pathol 2012;180(2):484–93.
40. King TE Jr, Tooze JA, Schwarz MI, et al. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med 2001;164(7):1171–81.
41. Fell CD, Liu LX, Motika C, et al. The prognostic value of cardiopulmonary exercise testing in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2009;179(5): 402–7.
42. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183(6):788–824.
43. Raghu G, Mageto YN, Lockhart D, et al. The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease: a prospective study. Chest 1999;116(5):1168–74.
44. Hunninghake GW, Zimmerman MB, Schwartz DA, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2001; 164(2):193–6.

45. Flaherty KR, King TE Jr, Raghu G, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med 2004;170(8):904–10.
46. Raghu G, Collard HR, Anstrom KJ, et al. Idiopathic pulmonary fibrosis: clinically meaningful primary endpoints in phase 3 clinical trials. Am J Respir Crit Care Med 2012;185(10):1044–8.
47. Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med 2005;353(21):2229–42.
48. Raghu G, Anstrom KJ, King TE Jr, et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012;366(21):1968–77.
49. de Andrade JA, Olman MA. Coagulation and fibrinolysis in the pathogenesis of pulmonary fibrosis. In: Schwarz M, King TE, editors. Interstitial lung disease. 5th edition. Shelton (CT): People's Medical Publishing House; 2011. p. 315–34.
50. Kubo H, Nakayama K, Yanai M, et al. Anticoagulant therapy for idiopathic pulmonary fibrosis. Chest 2005;128(3):1475–82.
51. Noth I, Anstrom KJ, Calvert SB, et al. A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2012; 186(1):88–95.
52. Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2005;171(9):1040–7.
53. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010;35(4):821–9.
54. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011;377(9779): 1760–9.
55. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. Ann Intern Med 2005;142(12 Pt 1):963–7.
56. Grossman RF, Frost A, Zamel N, et al. Results of single-lung transplantation for bilateral pulmonary fibrosis. The Toronto Lung Transplant Group. N Engl J Med 1990;322(11):727–33.
57. Christie JD, Edwards LB, Kucheryavaya AY, et al. The registry of the international society for heart and lung transplantation: twenty-eighth adult lung and heart-lung transplant report–2011. J Heart Lung Transplant 2011;30(10):1104–22.
58. Adams M, Williams A, Fell J. Exercise in the fight against thrombosis: friend or foe? Semin Thromb Hemost 2009;35(3):261–8.
59. Kaser A, Martinelli M, Feller M, et al. Heart rate response determines long term exercise capacity after heart transplantation. Swiss Med Wkly 2009;139(21–22): 308–12.
60. Ferreira A, Garvey C, Connors GL, et al. Pulmonary rehabilitation in interstitial lung disease: benefits and predictors of response. Chest 2009;135(2):442–7.
61. Crockett AJ, Cranston JM, Antic N. Domiciliary oxygen for interstitial lung disease. Cochrane Database Syst Rev 2001;(3):CD002883.
62. Tzanakis N, Samiou M, Lambiri I, et al. Evaluation of health-related quality-of-life and dyspnea scales in patients with idiopathic pulmonary fibrosis. Correlation with pulmonary function tests. Eur J Intern Med 2005;16(2):105–12.
63. Harris-Eze AO, Sridhar G, Clemens RE, et al. Oxygen improves maximal exercise performance in interstitial lung disease. Am J Respir Crit Care Med 1994;150(6 Pt 1):1616–22.
64. Madison JM, Irwin RS. Chronic cough in adults with interstitial lung disease. Curr Opin Pulm Med 2005;11(5):412–6.

65. Tobin RW, Pope CE 2nd, Pellegrini CA, et al. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;158(6):1804–8.
66. Raghu G, Freudenberger TD, Yang S, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J 2006; 27(1):136–42.
67. Raghu G, Yang ST, Spada C, et al. Sole treatment of acid gastroesophageal reflux in idiopathic pulmonary fibrosis: a case series. Chest 2006;129(3):794–800.
68. Lee JS, Ryu JH, Elicker BM, et al. Gastroesophageal reflux therapy is associated with longer survival in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;184(12):1390–4.
69. Lancaster LH, Mason WR, Parnell JA, et al. Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. Chest 2009;136(3):772–8.
70. Krishnan V, McCormack MC, Mathai SC, et al. Sleep quality and health-related quality of life in idiopathic pulmonary fibrosis. Chest 2008;134(4):693–8.
71. Jankowich MD, Polsky M, Klein M, et al. Heterogeneity in combined pulmonary fibrosis and emphysema. Respiration 2008;75(4):411–7.
72. Mejia M, Carrillo G, Rojas-Serrano J, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest 2009;136(1):10–5.
73. Lettieri CJ, Nathan SD, Barnett SD, et al. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006; 129(3):746–52.
74. Nadrous HF, Pellikka PA, Krowka MJ, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest 2005;128(4):2393–9.
75. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007;176(7):636–43.
76. Hajari AS, de Andrade JA. Acute exacerbations of interstitial lung disease. Clin Pulm Med 2011;18(3):113.
77. Raghu G, Brown KK, Bradford WZ, et al. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med 2004; 350(2):125–33.
78. King TE Jr, Behr J, Brown KK, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2008;177(1):75–81.
79. Raghu G, Brown KK, Costabel U, et al. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. Am J Respir Crit Care Med 2008;178(9):948–55.
80. King TE Jr, Albera C, Bradford WZ, et al. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. Lancet 2009;374(9685):222–8.
81. Daniels CE, Lasky JA, Limper AH, et al. Imatinib treatment for idiopathic pulmonary fibrosis: randomized placebo-controlled trial results. Am J Respir Crit Care Med 2010;181(6):604–10.
82. Zisman DA, Schwarz M, Anstrom KJ, et al. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 2010;363(7):620–8.
83. Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011;365(12):1079–87.