Steven D Nathan · A Whitney Brown
Christopher S King

Guide to Clinical Management of Idiopathic Pulmonary Fibrosis

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Preface

When contemplating and collaborating on this book, the three of us jokingly referred to it as the *50 shades of IPF*. Indeed, there are many gray zones in the diagnosis and management of idiopathic pulmonary fibrosis (IPF) and more often than not nothing is black or white. The hope with this handbook is to provide practical tips and guidance for practitioners while demystifying this emerging disease entity. We set out to accomplish this by drawing on our own clinical experience; having seen many patients with IPF and other conditions that tend to mimic IPF. Through our accrued experience, shaded with our synthesis of the existing literature, we hope to provide an easy read that can serve as a resource to all clinical providers. This book is intended for anyone involved in the care of patients with possible IPF, including students, residents, fellows, primary care providers, and pulmonologists, as well as patients themselves. In other words, we just want to sell as many copies of this book as possible. This is obviously stated in jest, but the three of us have directed all royalties from this book to the William and Catherine Goodrum Pulmonary Fibrosis Fund, the mission of which is to fund pulmonary fibrosis research at our institution. We dedicate this book to all patients with interstitial lung disease who have molded our collective experience and helped shed light on the shaded areas that are frequently encountered in medicine.

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Dr. Nathan has authored over 400 publications including original research manuscripts, abstracts, reviews, electronic publications, book chapters, and a book on idiopathic pulmonary fibrosis (IPF) that he co-edited. He is a reviewer for multiple journals, is an Associate Editor for *Pulmonary Year in Review*, and is on the editorial board of *Thorax*. He has served on multiple committees, including FDA Advisory Boards as well as steering committees for clinical trials in IPF and pulmonary hypertension, where he has also served as chair. He is also chairperson of Pilot for IPF, an international educational initiative for pulmonary fibrosis.

Abbreviations

5-LO	5-Lipoxygenase
6MWT	6-Minute walk test
ABCA3	Adenosine triphosphate-binding cassette transporter A3
ACS	Acute coronary syndrome
AEC	Alveolar epithelial cell
AE-IPF	Acute exacerbation of idiopathic pulmonary fibrosis
AIP	Acute interstitial pneumonia
ANA	Anti-nuclear antibody
ARDS	Adult respiratory distress syndrome
ATP	Adenosine triphosphate
αvβ6	Alpha v beta 6
BNP	Brain natriuretic peptide
bpm	Beats per minute
CAD	Coronary artery disease
CCP	Cyclic citrullinated peptide
CK	Creatinine kinase
COP	Cryptogenic organizing pneumonia
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPFE	Combined pulmonary fibrosis/emphysema
CPI	Composite physiologic
CTD	Connective tissue disease
CTD-ILD	Connective tissue disease-associated interstitial lung disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CTGF	Connective tissue growth factor
CYP	Cytochrome P450

DAH	Diffuse alveolar hemorrhage
DIP	Desquamative interstitial pneumonia
D_{Lco}	Diffusing capacity of the lungs for carbon monoxide
dsDNA	Double stranded DNA
EMT	Epithelial-mesenchymal transition
FEV_1	Forced expiratory volume in the first one second
FGF	Fibroblast growth factor
FiO_2	Fraction of inspired oxygen
FPF	Familial pulmonary fibrosis
FVC	Forced vital capacity
GAP	Gender, age, physiology
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
HP	Hypersensitivity pneumonitis
HRCT	High resolution computed tomography
IIPs	Idiopathic interstitial pneumonias
IL-13	Interleukin-13
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
KL-6	Krebs von der Lungen-6
LAM	Lymphangiolyomyomatosis
LIP	Lymphocytic interstitial pneumonia
LT	Leukotriene
MCTD	Mixed connective tissue disease
mPAP	Mean pulmonary artery pressure
mTOR	Mammalian target of rapamycin
NSIP	Non-specific interstitial pneumonia
NT-proBNP	N-terminal pro brain natriuretic peptide
OP	Organizing pneumonia
OR	Odds ratio
OSA	Obstructive sleep apnea
PA	Pulmonary artery
PDGF	Platelet derived growth factor
PFT	Pulmonary function testing
P-gp	P-glycoprotein
PH	Pulmonary hypertension
PLCH	Pulmonary Langerhans' cell histocytosis
PPFE	Pleuroparenchymal fibroelastosis

PRR	Pulse rate recovery
PRR=Δ	Max pulse – pulse 1 minute after cessation of walk
RA	Rheumatoid arthritis
RB-ILD	Respiratory bronchiolitis associated interstitial lung disease
RCT	Randomized controlled trial
RDW	Red cell distribution width
RF	Rheumatoid factor
RVSP	Right ventricular systolic pressure
SLE	Systemic lupus erythematosus
SNPs	Single nucleotide polymorphisms
sPAP	Systolic pulmonary artery pressure
SpO_2	Arterial oxygen saturation
TGF-β	Transforming growth factor-beta
TLC	Total lung capacity
TNF-α	Tumor necrosis factor-alpha
U1-RNP	U1-ribonuclear protein
UIP	Usual interstitial pneumonia
VATS	Video-assisted thoracoscopic surgery
VEGF	Vascular endothelial growth factor

Chapter 1
Overview of Idiopathic Pulmonary Fibrosis

1.1 History

Interstitial lung diseases (ILDs) represent a broad category of diseases affecting the interstitium of the lung in a diffuse fashion. Idiopathic pulmonary fibrosis (IPF) is a distinct subtype and one of the most common forms of ILD. It is a chronic fibrosing condition that is limited to the lungs, tends to be progressive in nature, and results in significant morbidity and mortality. IPF needs to be differentiated from the many other causes ILDs. Table 1.1 categorizes all the ILDs by a simple mnemonic of five 'I's, a 'C', and an 'N' [1].

IPF was formerly referred to as cryptogenic fibrosing alveolitis, but this term has since been abandoned. Indeed, the definition of IPF has evolved over the past two decades [2]. IPF used to be a 'wastebasket' term that encompassed many of the idiopathic fibrosing conditions; this group of disorders is now referred to as the idiopathic interstitial pneumonias (IIPs) [3] (Table 1.2).

The 'pneumonia' or 'pneumonitis' aspect of this broad category of diseases is somewhat of a misnomer; none of these entities are infectious in etiology and many lack a significant inflammatory component. Indeed, it used to be commonly thought that IPF was an inflammatory disease and that the fibrosis was the end product of chronic inflammation. This paradigm evolved from bronchoalveolar lavage studies in the

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Table 1.1 Categories of interstitial lung disease. N/A, not applicable

Category	Diseases	Sub-categories/examples
Idiopathic	Idiopathic interstitial pneumonias (IIPs)	**Major IIPs:** Idiopathic pulmonary fibrosis (IPF) Non-specific interstitial pneumonia (NSIP) Respiratory bronchiolitis associated interstitial lung disease (RB-ILD) Desquamative interstitial pneumonia (DIP) Cryptogenic organizing pneumonia (COP) Acute interstitial pneumonia (AIP) **Rare IIPs:** Lymphocytic interstitial pneumonia (LIP) Pleuroparenchymal fibroelastosis (PPFE) Unclassifiable IIP
	Sarcoidosis	
	Amyloidosis	
	Lymphangiolyomyomatosis (LAM)	
	Pulmonary Langerhans' cell histocytosis (PLCH)	
	Eosinophilic pneumonia	
	Neurofibromatosis	
	Diffuse alveolar hemorrhage (DAH)	
Immunologic	Connective tissue disorders	Scleroderma, rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, Sjogren's Syndrome, inflammatory myositis

Inhalational	Inorganic	Asbestosis, silicosis, coal miners, pneumoconiosis, hard metal lung disease, berylliosis, siderosis
	Organic: chronic hypersensitivity pneumonitis	Bird fanciers disease, farmer's lung
Iatrogenic	Antiarrhythmics, antimicrobials, chemotherapy agents, biologics, radiation	Amiodarone, nitrofurantoin, bleomycin, busulfan, cyclophosphamide, rituximab, interferon (alpha, beta)
Infectious	Viral	CMV, influenza
	Fungal	*Pneumocystis carinii*
Congestive heart failure	N/A	N/A
Neoplastic	Lymphangitic carcinomatosis Bronchoalveolar carcinoma	N/A

Table 1.2 The idiopathic interstitial pneumonias. N/A, not applicable

Idiopathic interstitial pneumonias	Acronym	Mnemonic	Category of idiopathic interstitial pneumonia
Idiopathic pulmonary fibrosis	IPF	I	Major
Non-specific interstitial pneumonia	NSIP	N	Major
Cryptogenic organizing pneumonia	COP	C	Major
Respiratory bronchiolitis-associated interstitial lung disease	RB-ILD	R	Major
Acute interstitial pneumonia	AIP	A	Major
Pleuroparenchymal fibroelastosis	PPFE	P	Rare
Desquamative interstitial pneumonia	DIP	D	Major
Unclassifiable	N/A	U	Unclassifiable
Lymphoid interstitial pneumonia	LIP	L	Rare

late 1970s that described an excess of inflammatory cells [4–6]. It has since been learned that the inflammatory milieu is mostly a secondary phenomenon. Nonetheless, this did lead to the notion that therapy for IPF should be aimed at managing inflammation. Accordingly, the wide-spread use of steroids and cytotoxic agents, such as azathioprine and cyclophosphamide, was common practice. It is only recently that azathioprine and prednisone have been shown to not only be ineffective, but also possibly harmful to patients with IPF [7].

Until recently, there were no effective medical therapies to treat IPF. The only recourse for patients was to be evaluated

for enrollment in a clinical trial or to undergo lung transplantation; unfortunately, both of these options are not readily available to the majority of patients. Other ancillary management tools include participation in pulmonary rehabilitation and implementation of supplemental oxygen for those with resting, nocturnal, or exercise-induced hypoxemia. Recently, two drugs (pirfenidone and nintedanib) have been shown to slow the rate of deterioration or loss of lung function in patients with IPF [8]. Pirfenidone and nintedanib are available in many countries around the world (approved in 2014 and 2015, respectively, by the US Food and Drug Administration for use in patients with IPF) [9]. While neither of these drugs are a cure or panacea, their availability has heralded a new era in the management of patients with IPF and resulted in renewed interest and hope for this otherwise deadly disease.

The pathologic correlate of IPF is referred to as usual interstitial pneumonia (UIP), which has now also crept its way into the radiographic lexicon in the context of high resolution computed tomographic (HRCT) image patterns. The name UIP evolved very simply because this was the pattern of injury most commonly seen by pathologists in IPF. It is important to note that this pathologic pattern is not synonymous with the clinical entity of IPF and can be seen in other lung diseases (such as connective tissue disease related ILD, occupational lung disease, and chronic hypersensitivity pneumonitis) [3].

1.2 Incidence and Prevalence

IPF tends to be a disease of the elderly and affects males more often than females [2]. There is evidence to suggest that the prevalence of IPF is increasing [10]. It is estimated that there are approximately 120,000 cases in the US and probably equivalent numbers in Europe [2], although the true prevalence is likely higher than this. There is no apparent ethnic or racial predilection for IPF, but the estimated prevalence of the

Table 1.3 Common occupational causes of interstitial lung disease

Exposure	Lung disease	Associated occupations
Asbestos	Asbestosis	Shipbuilding Building maintenance Mining Milling Automobile mechanic Railroad worker Electrician
Coal dust	Coal miner's pneumoconiosis	Coal mining
Rock and sand	Silicosis	Mining Sandblasting Quarrying Construction Foundry work
Beryllium	Berylliosis	Mining Aerospace manufacturing Electronics manufacturing
Cobalt (from hard metal tools used for cutting/drilling)	Hard metal lung disease	Diamond polishing Dental laboratories Manufacturing of cutting/drilling tools

disease in other countries remains poorly defined. The course of the disease is similar in patients from diverse geographic areas; in general, males and the elderly tend to have a worse prognosis [11]. Interestingly, patients with higher body mass index and active smokers appear to have better outcomes, however, this could be due to lead time bias with these patients presenting and being diagnosed earlier in their disease course [12, 13]. Most patients (60–70 %) with IPF have been or are current smokers [14]. Other risk factors include various occupational exposures (Table 1.3), which have been associated with a higher incidence of the disease [15]. It therefore seems likely that significant (especially long-term exposure) to any noxious inhaled substance may heighten the risk for IPF.

1.3 Genetics

Familial pulmonary fibrosis (FPF) accounts for 0.5–3.7 % of IPF cases [16] and is defined by a history of pulmonary fibrosis in at least two first degree relatives. The clinical presentation of FPF is similar to that of sporadic IPF, although the age of onset tends to be younger [17], therefore FPF should be suspected in patients who present at an earlier age. Additionally, any family history of IPF or unknown lung disease may provide a clue to the familial variant. There are a number of genetic variants that have been linked to FPF [16, 18–29]; each of which has a variable influence on the development of pulmonary fibrosis. For example, within families not all persons with the same mutation will develop pulmonary fibrosis, suggesting that epigenetics are important. In other words, there seems to be variability in the way in which an individual's genetic predisposition interacts with the environment and other factors [18, 23, 26, 30].

In addition to the typical Mendelian inheritance pattern in the familial variant, potential genetic factors in all afflicted patients are being investigated. Single nucleotide polymorphisms (SNPs) — elucidated through gene-wide association studies — that have been shown to be important in the predilection for IPF include:

- *MUC5B* — a polymorphism in the promoter region of *MUC5B*, the mucin gene, has been found in approximately 34 % of patients with FPF versus 9 % of healthy controls [22, 27]. This variant of *MUC5B* has been found to be associated with the development of IPF (odds ratios [OR] of developing disease: 9.0 and 21.8 for heterozygotes and homozygotes, respectively) [31]. It also holds prognostic information, paradoxically conferring a twofold survival advantage to patients with IPF who carry the polymorphism [32].
- *TERT* and *TERC* — mutations in *TERC* and *TERT*, the genes encoding telomerase, may also increase risk for the development of IPF [29, 33]. Telomeres are regions of repetitive, non-coding nucleotide sequences at the end of chromosomes, and telomerase

is a polymerase (enzyme) that adds telomere repeats to chromosomes. Mutations in *TERC* and *TERT* affect telomerase function. In a study by Tsakiri et al. [34] it was demonstrated that individuals with IPF have shorter telomeres in comparison to age-matched family members. Progressive telomere shortening ultimately leads to apoptosis or cell-cycle arrest and may play a role in the pathogenesis of IPF [29].

  - Heterozygous *TERT* mutations are present in approximately 18 % of FPF and 3 % of sporadic IPF cases [35].
  - *TERC* mutations have a rare association with IPF [34].

- A2 and C surfactant proteins — pulmonary surfactant reduces surface tension within the lungs and prevents end-expiratory atelectasis. Mutations in surfactant protein A2 and C impair surfactant function leading to pulmonary fibrosis in affected individuals [20, 21].
- Adenosine triphosphate (ATP)-binding cassette transporter A3 (ABCA3) — ABCA3 is produced in the lung by type II pneumocytes, where it transports surfactant lipids into lamellar bodies and is essential in the maintenance of pulmonary surfactant lipid homeostasis. Recessive mutations in the *ABCA3* gene are increasingly being recognized as a cause of ILD (specifically in IPF) in older children and young adults [36].

The above mentioned genetic abnormalities account for a small minority of cases of IPF; there are likely a number of as yet unrecognized genetic abnormalities that contribute to the development of IPF. Improved understanding of the genetics of IPF will be essential to the development of more effective treatment strategies. In the future, the hope is that genetic testing will allow for phenotyping and individualized targeted therapy of this deadly disease. Given the current uncertainty regarding the clinical significance of the identified common genotypes, routine genotyping in IPF is not recommended.

1.4 Course and Prognosis

The course of IPF is notoriously difficult to predict on a case-by-case basis. Some patients remain stable for many years, some have an inextricable downhill course, while others have periods of stability punctuated by episodes of deterioration with progression in a so-called 'stepwise' pattern (Fig. 1.1) [2, 11]. Acute exacerbations (clinical worsening that occurs over 30 days or less without identifiable cause) may also occur unpredictably in these patients. Acute exacerbations tend to occur at a rate of about 5–15 % per patient year and invariably are accompanied by a very poor prognosis [37]. Some patients may present with an acute exacerbation as their heralding event. This should always be borne in mind for patients who present with an adult respiratory distress syndrome (ARDS)-like picture with no apparent precipitating factor. The pathologic findings of acute exacerbation in IPF are indistinguishable

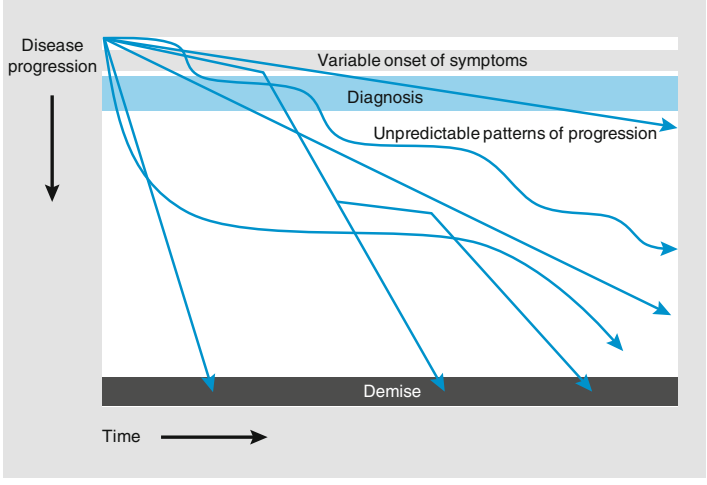

FIGURE 1.1 Course and prognosis of idiopathic pulmonary fibrosis (Adapted from Raghu et al. [2] and Ley et al. [11])

from ARDS, with a diffuse alveolar damage pattern, but superimposed on a background of UIP [38].

The prognosis of IPF is poor, with an estimated average survival of 2.5–4 years from the time of diagnosis [39]. Patients with IPF also have a propensity for comorbidities, likely due to advanced age, and some patients may succumb with their IPF, rather than from their IPF. Comorbidities that may lead to death include cardiovascular disease, thromboembolic disease, and lung cancer (more common in patients with IPF compared to age-matched controls) [40]. Other common comorbidities include obstructive sleep apnea and gastroesophageal reflux disease (GERD). These will be discussed in Chap. 6.

Key Points

- IPF has a typical pattern on HRCT such that lung biopsy is usually not necessary for diagnosis.
- Other identifiable causes of ILD must be excluded.
- A very small percentage of IPF cases are familial (defined as 2 or more first degree relatives with pulmonary fibrosis).
- Mutations in *MUC5B* and certain telomerase mutations appear to be associated with a higher risk of IPF, but account for the minority of cases.
- Prognosis, although heterogeneous, is generally poor, with an average of survival of 2.5–4 years from the time of diagnosis.
- The first treatments for IPF, pirfenidone and nintedanib, were approved in 2014 and 2015, respectively.

References

1. Wallis A, Spinks K. The diagnosis and management of interstitial lung diseases. BMJ. 2015;350:h2072.
2. 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;183:788–824.

3. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733–48.
4. Hunninghake GW, Gadek JE, Kawanami O, Ferrans VJ, Crystal RG. Inflammatory and immune processes in the human lung in health and disease: evaluation by bronchoalveolar lavage. Am J Pathol. 1979;97:149–206.
5. Reynolds HY, Fulmer JD, Kazmierowski JA, Roberts WC, Frank MM, Crystal RG. Analysis of cellular and protein content of broncho-alveolar lavage fluid from patients with idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis. J Clin Invest. 1977;59:165–75.
6. Weinberger SE, Kelman JA, Elson NA, et al. Bronchoalveolar lavage in interstitial lung disease. Ann Intern Med. 1978;89:459–66.
7. Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King Jr TE, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366:1968–77.
8. King CS, Nathan SD. Practical considerations in the pharmacologic treatment of idiopathic pulmonary fibrosis. Curr Opin Pulm Med. 2015;21:479–89.
9. Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis–FDA review of pirfenidone and nintedanib. N Engl J Med. 2015;372:1189–91.
10. Raghu G, Chen SY, Yeh WS, et al. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001–11. Lancet Respir Med. 2014;2:566–72.
11. Ley B, Collard HR, King Jr TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;183:431–40.
12. Alakhras M, Decker PA, Nadrous HF, Collazo-Clavell M, Ryu JH. Body mass index and mortality in patients with idiopathic pulmonary fibrosis. Chest. 2007;131:1448–53.
13. Antoniou KM, Hansell DM, Rubens MB, et al. Idiopathic pulmonary fibrosis: outcome in relation to smoking status. Am J Respir Crit Care Med. 2008;177:190–4.
14. Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1997;155:242–8.
15. Miyake Y, Sasaki S, Yokoyama T, et al. Occupational and environmental factors and idiopathic pulmonary fibrosis in Japan. Ann Occup Hyg. 2005;49:259–65.

16. Lawson WE, Grant SW, Ambrosini V, et al. Genetic mutations in surfactant protein C are a rare cause of sporadic cases of IPF. Thorax. 2004;59:977–80.
17. Garcia CK. Idiopathic pulmonary fibrosis: update on genetic discoveries. Proc Am Thorac Soc. 2011;8:158–62.
18. Chibbar R, Shih F, Baga M, et al. Nonspecific interstitial pneumonia and usual interstitial pneumonia with mutation in surfactant protein C in familial pulmonary fibrosis. Mod Pathol. 2004;17:973–80.
19. Guillot L, Epaud R, Thouvenin G, et al. New surfactant protein C gene mutations associated with diffuse lung disease. J Med Genet. 2009;46:490–4.
20. Maitra M, Wang Y, Gerard RD, Mendelson CR, Garcia CK. Surfactant protein A2 mutations associated with pulmonary fibrosis lead to protein instability and endoplasmic reticulum stress. J Biol Chem. 2010;285:22103–13.
21. Nogee LM, Dunbar 3rd AE, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med. 2001;344:573–9.
22. Seibold MA, Wise AL, Speer MC, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med. 2011;364:1503–12.
23. Thomas AQ, Lane K, Phillips 3rd J, 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;165:1322–8.
24. van Moorsel CH, van Oosterhout MF, Barlo NP, et al. Surfactant protein C mutations are the basis of a significant portion of adult familial pulmonary fibrosis in a dutch cohort. Am J Respir Crit Care Med. 2010;182:1419–25.
25. Verleden GM, du Bois RM, Bouros D, et al. Genetic predisposition and pathogenetic mechanisms of interstitial lung diseases of unknown origin. Eur Respir J Suppl. 2001;32:17–29s.
26. 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;84:52–9.
27. Zhang Y, Noth I, Garcia JG, Kaminski N. A variant in the promoter of MUC5B and idiopathic pulmonary fibrosis. N Engl J Med. 2011;364:1576–7.
28. Ono S, Tanaka T, Ishida M. Surfactant protein C G100S mutation causes familial pulmonary fibrosis in Japanese kindred. Eur Respir J. 2011;38:861–9.

29. Armanios MY, Chen JJ, Cogan JD, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med. 2007;356:1317–26.
30. Lawson WE, Loyd JE, Degryse AL. Genetics in pulmonary fibrosis–familial cases provide clues to the pathogenesis of idiopathic pulmonary fibrosis. Am J Med Sci. 2011;341:439–43.
31. Mathai SK, Yang IV, Schwarz MI, Schwartz DA. Incorporating genetics into the identification and treatment of idiopathic pulmonary fibrosis. BMC Med. 2015;13:191.
32. Peljto AL, Zhang Y, Fingerlin TE, et al. Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. JAMA. 2013;309:2232–9.
33. Diaz de Leon A, Cronkhite JT, Yilmaz C, et al. Subclinical lung disease, macrocytosis, and premature graying in kindreds with telomerase (TERT) mutations. Chest. 2011;140:753–63.
34. 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;104:7552–7.
35. Diaz de Leon A, Cronkhite JT, Katzenstein AL, et al. Telomere lengths, pulmonary fibrosis and telomerase (TERT) mutations. PLoS One. 2010;5:e10680.
36. Young LR, Nogee LM, Barnett B, Panos RJ, Colby TV, Deutsch GH. Usual interstitial pneumonia in an adolescent with ABCA3 mutations. Chest. 2008;134:192–5.
37. Sgalla G, Biffi A, Richeldi L. Idiopathic pulmonary fibrosis: diagnosis, epidemiology and natural history. Respirology. 2015. doi:10.1111/resp.12683. [Epub ahead of print].
38. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2007;176:636–43.
39. Nathan SD, Shlobin OA, Weir N, et al. Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. Chest. 2011;140:221–9.
40. King C, Nathan SD. Identification and treatment of comorbidities in idiopathic pulmonary fibrosis and other fibrotic lung diseases. Curr Opin Pulm Med. 2013;19:466–73.

Chapter 2
Clinical Presentation and Diagnosis

2.1 Symptoms

Patients typically present with insidious onset of shortness of breath. This may or may not be accompanied by a chronic dry cough. Cough is the presenting symptom in approximately 12 % of patients [1]. Patients who are physically more active and robust in their daily lives or who exercise regularly are more likely to notice the onset of their symptoms sooner compared to those patients who are more sedentary. Given the non-specific symptoms of idiopathic pulmonary fibrosis (IPF), patients are frequently misdiagnosed initially. Non-specific symptoms include:

- shortness of breath;
- dry cough;
- tiredness;
- loss of appetite; and
- weight loss.

Some patients may be diagnosed while still asymptomatic, either based on findings from physical examination or chest imaging. An astute clinician may hear inspiratory crackles (present in 96.8 % of symptomatic patients [1]) on routine auscultation of the lung bases and initiate an evaluation with imaging. Alternatively, pulmonary fibrosis may be initially detected as an incidental finding on imaging carried out for

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other reasons. Chest imaging tends to be ubiquitous and frequently unrelated to any specific pulmonary condition or symptoms. Some examples include:

- routine chest X-ray performed for other reasons (e.g., a preoperative assessment prior to surgery for an unrelated condition);
- computed tomographic (CT) scan of the chest for lung cancer screening;
- abdominal CT obtained for gastrointestinal (GI) complaints with abnormalities noted at the lung bases (which are captured with upper abdominal cuts); and
- fluoroscopy during cardiac catheterizations to diagnose coronary artery disease (CAD) in patients presenting with shortness of breath.

2.2 Patient History

A detailed patient history is mandatory to evaluate for risk factors of IPF as well as to exclude other conditions that may be in the differential. Patient history should ascertain whether any of the following are present:

- Predisposing factors:
  - smoking (former or current); and
  - family history of interstitial lung disease (ILD) or IPF.
- Professions at higher risk for IPF:
  - farmers;
  - hairdressers;
  - wood workers; and
  - metal workers.
- Clues to alternative causes of ILD:
  - pet bird exposure, frequent hot tub use, mold exposure (chronic hypersensitivity pneumonitis [HP]);

- occupational exposures: asbestos (asbestosis), silica (silicosis), tin (stannosis), coal (coal miners' pneumoconiosis); and
- stigmata of an underlying connective tissue disease (CTD) including gastroesophageal reflux disease (GERD) symptoms, Raynaud's phenomenon, joint pain, skin rash, and muscle weakness (Table 2.1).

2.3 Physical Examination

Vital signs are almost invariably normal, with the exception of pulse oximetry, which may be low at rest. However, a normal pulse oximetry reading does not rule out IPF or any other pulmonary condition. A minority of patients may have digital clubbing at presentation. Chest auscultation may reveal inspiratory coarse crackles at the bases of the lungs; these crackles have been described as 'Velcro®' in nature since their sound is very similar to that of Velcro® being pulled apart. In more advanced disease, crackles may progress so that they can be heard throughout the lung fields, both posteriorly and anteriorly. Pulmonary hypertension (PH) may complicate the course of IPF, so clinicians should look for signs of this complication on physical exam. A clinical clue to its presence may be an increased P_2 heart sound. Overt evidence of right heart failure, including jugular venous distention, ascites, and lower extremity edema, is very unusual even in the presence of advanced IPF.

2.4 Pulmonary Function Tests

All patients with suspected lung disease should undergo pulmonary function testing (PFT). In IPF, spirometry usually shows a restrictive pattern, with the forced vital capacity (FVC) and the forced expiratory volume in the first one second (FEV_1) both reduced, resulting in a normal

TABLE 2.1 Signs and symptoms of connective tissue disease

Disease and most common radiographic/ pathologic patterns	Presentation/symptoms of possible underlying CTD	Signs of CTD
Scleroderma ■ -NSIP -UIP -Unclassifiable -Rare: OP, DAH	**Demographics:** Female Young age (especially <50 years) GERD symptoms ■ ■ Dysphagia ■ Early satiety ■ Diarrhea or constipation ■	Telangiectasia ■ Dilated esophagus on CT ■ Sclerodactyly ■
Rheumatoid arthritis ■ -UIP -NSIP -OP	Joint pains ■ ■	Arthritic changes-hands ■
MCTD ■ -NSIP -Rare: AIP, DAH	Morning hand joint stiffness ■ Raynaud's Phenomenon ■ ■ ■	Arthritic changes of small and large joints ■
SLE ■ -Acute pneumonitis -DAH -OP -NSIP -UIP	Alopecia ■ Photosensitivity ■ ■	Oral ulceration ■ ■ Maculopapular rash ■ ■
Sjogren's syndrome ■ -LIP -Bronchiolitis -OP -NSIP -UIP -Lymphoma	Dry mouth, dry eyes ■ ■	Uveitis ■
Polymyositis/ dermatomyositis ■ -NSIP -UIP -OP -Rare: AIP, DAH	Skin rash ■ ■ Muscle pains, weakness ■	Heliotrope rash ■ Proximal muscle weakness ■ Mechanic's hands ■ Gottron's nodules ■

The colored squares indicate a specific disease entity, features of scleroderma are marked in blue; rheumatoid arthritis in green; mixed connective tissue disease in gray; systemic lupus erythematosus in red; Sjogren's syndrome in purple; and polymyositis/dermatomyositis in yellow

AIP acute interstitial pneumonia, *CT* computed tomography, *CTD* connective tissue disease, *DAH* diffuse alveolar hemorrhage, *GERD* gastroesophageal reflux disease, *LIP* lymphoid interstitial pneumonia, *MCTD* mixed connective tissue disease, *NSIP* non-specific interstitial pneumonitis, *OP* organizing pneumonia, *UIP* usual interstitial pneumonia

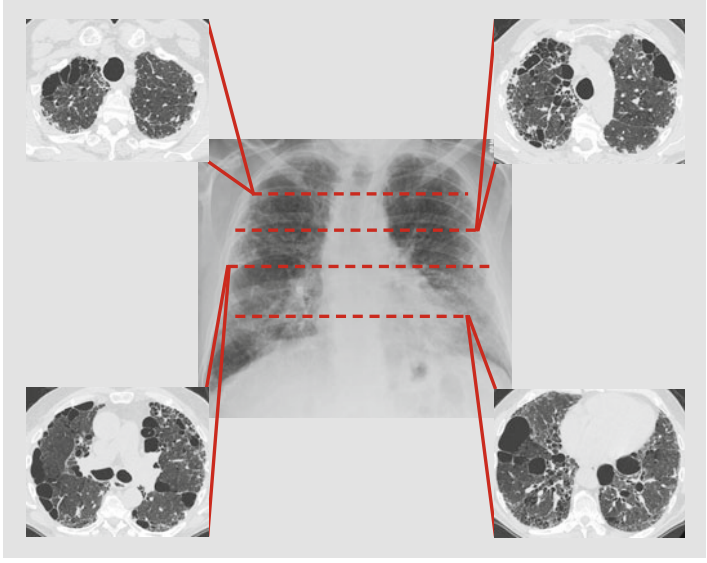


FIGURE 2.1 Chest X-ray and computed tomographic imaging demonstrating combined pulmonary fibrosis and emphysema. The computed tomography scan demonstrates typical subpleural fibrosis as well as bullous disease that are characteristic of emphysema

FEV_1/FVC ratio. This preserved ratio differentiates the ILDs from the obstructive lung diseases (which typically manifest with a reduced FEV_1/FVC ratio). Some cases of restrictive lung disease, IPF included, can have increased FEV_1/FVC ratios that reflect the 'snappiness' of the non-compliant or stiff lungs, which results in more of the lung volume being expelled in the first one second. On the other end of the spectrum, a slightly reduced or normal FEV_1/FVC ratio may be present when IPF occurs in combination with emphysema. This is a distinct entity that is referred to as combined pulmonary fibrosis/emphysema (CPFE) (Fig. 2.1). Normal spirometry and lung volumes do not exclude IPF, with approximately 14 % of patients presenting with FVC >80 % predicted (commonly regarded as the lower limit of normal) [1]. The single breath diffusing capacity (D_{Lco}) is commonly reduced, usually more so than the FVC, reflecting loss of the pulmonary capillary bed.

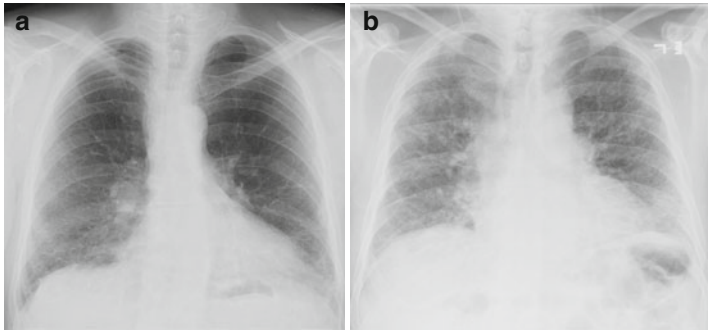


FIGURE 2.2 Chest X-rays showing (**a**), early and (**b**), advanced interstitial changes

2.5 Chest X-Ray

Plain chest film typically demonstrates increased interstitial markings at the bases of the lungs in the early stages of disease (Fig. 2.2a). IPF is a disease that typically involves the lower lobes first, with abnormalities most notable on the periphery of the lungs. As the disease progresses these abnormalities extend and involve other regions of the lung. Similarly, as the disease progresses, the lung volumes on chest X-rays become progressively smaller (Fig. 2.2b).

2.6 Laboratory Tests

There is no specific diagnostic marker for IPF, however, laboratory testing is important to exclude other conditions that may mimic IPF (including the various connective tissue disorders and chronic HP). Most patients should, at a minimum, have a screening test for anti-nuclear antibody (ANA) and rheumatoid factor (RF), or ANA and anti-cyclic citrullinated peptide (CCP). Depending on the clinical presentation, especially for younger patients, a full CTD panel should be considered. Autoimmune serologic testing should be

Table 2.2 Serologic tests to consider when evaluating a patient with interstitial lung disease

Serologic test	Associated diseases
Hypersensitivity pneumonitis panel	Hypersensitivity pneumonitis
Anti-nuclear antibody (ANA) Double stranded DNA (dsDNA) Anti-Smith	Systemic lupus erythematosus
Anti-Ro (Sjögren's-syndrome-related antigen A) Anti-La (Sjögren's-syndrome-related antigen B)	Sjogren's syndrome
U1-ribonuclear protein (U1-RNP)	Mixed connective tissue disease
Anti-centromere, topoisomerase I (SCL-70)	Scleroderma
Creatinine kinase (CK), aldolase, Jo-1 Comprehensive myositis panel	Myositis
Rheumatoid factor, cyclic citrillunated peptide	Rheumatoid arthritis

considered when evaluating patients with ILD (Table 2.2). In addition to the anti-Jo antibody test, which may be positive in patients with polymyositis, there are also other antibodies that may be present in the anti-synthetase syndrome. A comprehensive myositis panel is only available at certain reference labs and is normally ordered only when clinical suspicion is high.

The utility of a hypersensitivity panel is uncertain since a positive test to a specific antigen does not necessarily infer causation, similarly a negative test does not rule out chronic HP. The decision to obtain such testing is left to the discretion of the physician, but can be helpful in diagnosing chronic HP given the right constellation of exposure history, CT changes, and lung biopsy findings.

2.7 Chest Computed Tomography Scan

The cornerstone of IPF diagnosis is high resolution computed tomography (HRCT). The high resolution of this technique (≤2.5 mm cuts) enables greater detail of the lung parenchyma compared to the standard technique (5 mm cuts). In addition, prone imaging can be helpful in more subtle cases to distinguish between atelectasis and true changes of ILD. Expiratory images, in addition to inspiratory images, should be requested to assess for air trapping that can accompany chronic HP and other kinds of lung disease. Distinctive radiographic changes seen in IPF include:

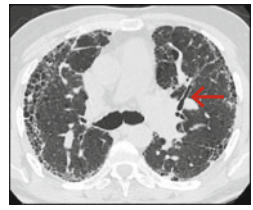
- bilateral sub-pleural reticular infiltrates;
- honeycombing;
- traction bronchiectasis; and
- the absence of atypical features that suggest other forms of ILD (consolidation, alveolar or ground glass infiltrates, air trapping and areas of hyperlucency [may be seen in chronic HP], and cysts).

If a patient has all four of the above radiographic features in the appropriate clinical context, this is usually sufficient to make the diagnosis of IPF. If patients lack one or more of the features, then the patient may be categorized as having probable, possible, or unlikely IPF. Figure 2.3 provides example of an inconsistent usual interstitial pneumonia (UIP) pattern (unlikely to be IPF), a possible UIP pattern (could possibly be IPF), and a typical UIP pattern (which in the right clinical context is very likely to be IPF). In the first two scenarios, a lung biopsy may be required to make the diagnosis. CT imaging of the chest has additional benefit beyond the lung parenchyma; it enables visualization of other structures that may provide clues to the diagnosis, presence of comorbidities, and potentially even prognosis.

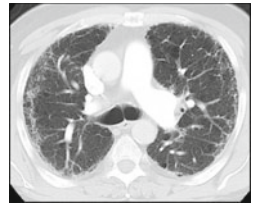
Extra-pulmonary findings are important to note, and can include the following (Fig. 2.4):

- Esophagus — an enlarged patulous esophagus can be a clue to the presence of comorbid GERD and/or the presence of scleroderma. An air-fluid level within the esophagus may provide additional evidence for aspiration risk.

a UIP pattern
Subpleural, basal predominance
Reticular abnormality
Honeycombing with or without traction bronchiectasis (red arrow)
Absence of inconsistent features



b Possible UIP pattern
Subpleural, basal predominance
Reticular abnormality
Absence of inconsistent features



c Inconsistent UIP pattern
Upper or mid-lung predominance
Peribronchovascular predominance
Extensive ground glass abnormality (extent > reticular abnormality)
Profuse micronodules
Discrete cysts (multiple, bilateral, away from areas of honeycombing)
Diffuse mosaic attenuation/air-trapping (bilateral in 3 or more lobes)
Consolidation in bronchopulmonary segment(s)/lobe(s)

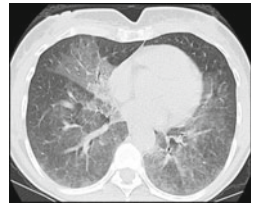


FIGURE 2.3 High resolution computed tomography examples of (**a**), typical usual interstitial pneumonia (*UIP*) pattern, (**b**) possible UIP pattern, and (**c**) inconsistent with UIP pattern

- Coronary calcification — can be seen on the mediastinal images and may indicate underlying coronary artery disease [2].
- Pleura — thickening of the pleura may be seen as a residual after prior pleuritis (possible underlying CTD), while pleural plaques might indicate underlying asbestosis.
- Mediastinal adenopathy — enlarged nodes (up to 1 cm in diameter) can be seen in IPF, but more prominent adenopathy should raise the suspicion for other entities, the most common being sarcoidosis.
- Pulmonary artery segment — an enlarged pulmonary artery with a diameter greater than that of the adjacent aorta is associated with the presence of pulmonary hypertension and attenuated survival (see Chap. 5) [3].

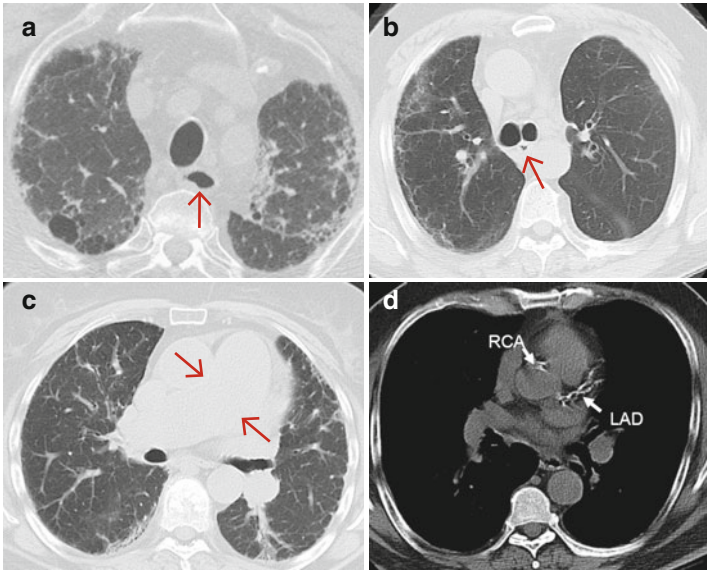


FIGURE 2.4 Extra-pulmonary structures to evaluate on computed tomography scans: (**a**) patulous esophagus, (**b**) thickened esophagus, (**c**) enlarged pulmonary artery (*red arrow*), and (**d**) coronary artery calcifications. *LAD* left anterior descending artery, *RCA* right coronary artery

2.8 Lung Biopsy

A confirmatory lung biopsy is required to confirm the diagnosis in some cases (approximately 30 %) [1]. The types of procedures that may be employed to obtain lung tissue are outlined in the following sections.

2.8.1 Bronchoscopy

The pieces of tissue obtained with transbronchial biopsies are usually too small and inadequate to make the diagnosis of IPF. If tissue is needed for pathological evaluation, standard bronchoscopy is typically not recommended.

2.8.2 Cryobiopsy via Bronchoscopy

The pieces of tissue obtained by cryobiopsy are typically larger than those obtained with standard transbronchial forceps and therefore may be sufficient to make the diagnosis of IPF at experienced centers [4].

2.8.3 Video-Assisted Thoracoscopic Surgical Lung Biopsy

Video-assisted thoracoscopic surgical (VATS) lung biopsy is the gold-standard in terms of obtaining tissue for the diagnosis of IPF. The decision to proceed with this should take into consideration the age and comorbidities of the patient and the likelihood of an IPF diagnosis (versus another entity). If there is a very good chance that the patient has IPF (based on clinical features) then a surgical lung biopsy is usually not necessary for confirmation. Similarly, if the patient has a documented CTD or features consistent with another cause of ILD (e.g., pleural plaques in someone with a history of asbestos exposure) then a lung biopsy may not be needed. Lung biopsies are most helpful when there is true diagnostic uncertainty and biopsy results will influence clinical management.

2.8.3.1 Tips for the VATS Surgeon

Biopsy samples should be obtained from at least two, preferably three areas of the lung. Biopsies from the most diseased looking areas of the lung should be avoided. These typically show non-specific 'end-stage' fibrosis and may not provide the necessary features to make an accurate diagnosis. Areas adjacent to obvious fibrotic lung should be targeted. Even areas of grossly appearing normal lung will usually show changes typical of IPF.

The anesthesiologist should be instructed to limit the fraction of inspired oxygen (FiO_2) and only give sufficient oxygen to maintain adequate oxygen saturation. Use of high oxygen

concentrations and high tidal volumes in the setting of single lung ventilation may induce lung injury and precipitate an acute exacerbation of IPF [5]. Additionally, judicious use of intravenous fluids intraoperatively may reduce the risk for acute exacerbations [6].

Patients with severe disease and/or evidence of PH are usually not good candidates for VATS lung biopsies. The relative risks and benefits of the procedure need to be weighed carefully in such cases.

2.9 Making the Diagnosis

There is no single gold-standard test for the diagnosis of IPF. What is typically regarded as the gold-standard is a multidisciplinary consensus, including a clinician (usually a pulmonologist), a radiologist (ideally a thoracic radiologist), and a pathologist [7]. However, in most instances, the diagnosis can be made without a tissue diagnosis and therefore this multidisciplinary approach in reality may be bi-disciplinary between the pulmonologist and radiologist. The diagnosis requires the exclusion of other conditions as a cause of the ILD in the context of a HRCT that is typical or probable for IPF. A simple mnemonic to remember other causes of ILD is shown in Table 1.1 (see Chap. 1). The conditions that are most difficult to differentiate from IPF include non-specific interstitial pneumonia (NSIP), chronic HP, underlying connective tissue disorders, and the newly described entity of interstitial pneumonia with autoimmune features [8].

A thorough history is an essential first step. Particular attention to possible occupational exposures, hobbies that might involve organic or inorganic particles, and exposure to birds are especially important. Inhalational agents that may cause other forms of lung disease or increase the risk for IPF or other types of ILD are listed in Table 2.3.

Patients with IPF may demonstrate clubbing of their digits and typically have bibasilar inspiratory 'Velcro®' crackles,

Table 2.3 Inhalational exposures/activities that increase the risk for interstitial lung disease

Exposure	Occupations/industries	Disease associations
Tobacco smoke	N/A	IPF, COPD, CPFE, lung cancer
Aerosols	Hairdressers	IPF
Dusts	Farmers	IPF, chronic HP
Wood dust	Wood workers	IPF
Metal dust	Metal workers	IPF
Silica	Mining, foundries, sandblasting	Silicosis
Asbestos	Mining, ship building, building maintenance, milling, automobile mechanics, railroad workers, electricians	Asbestosis
Coal	Mining	Coal miner's pneumoconiosis
Beryllium	Aerospace, automotive, electronics	Berylliosis

COPD combined obstructive pulmonary disease, *CPFE* combined pulmonary fibrosis and emphysema, *HP* hypersensitivity pneumonitis, *IPF* idiopathic pulmonary fibrosis, *N/A* not applicable

however, the absence of these does not rule out IPF. Physical examination may yield signs that are suggestive of conditions that may mimic IPF, specifically signs of an underlying connective tissue disorder (Table 2.1). Tests that should be considered to exclude other conditions, primarily connective tissue disorders, are shown in Table 2.2.

Radiographic imaging, in particular the HRCT, is integral and necessary to establish the diagnosis of IPF. The HRCT of the chest should be placed in the context of the clinical picture. Older age, in particular, increases the pretest

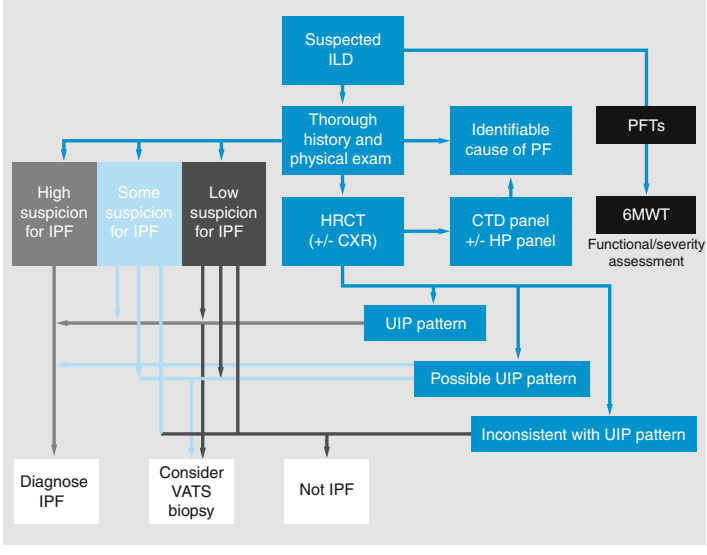


FIGURE 2.5 Diagnostic algorithm for idiopathic pulmonary fibrosis. *6MWT* 6-min walk test, *CTD* connective tissue disease, *CXR* chest X-ray, *HP* hypersensitivity pneumonitis, *HRCT* high resolution computed tomography, *ILD* interstitial lung disease, *IPF* idiopathic pulmonary fibrosis, *PFT* pulmonary function test, *UIP* usual interstitial pneumonia, *VATS* video-assisted thoracoscopic surgery

probability of IPF. The likelihood of a patient having IPF is much higher with increasing age (for example >70 years) versus a younger patient (for example <50 years) with the same clinical presentation.

The results of surgical lung biopsy do not provide a default diagnosis and the pathologic findings need to be interpreted in the context of the clinical and radiographic presentations. There can be instances in which the HRCT pattern may 'trump' the pathologic pattern in determining the final diagnosis. A recommended diagnostic algorithm is shown in Fig. 2.5. HRCT findings and histopathological findings can be incorporated to determine the probability of IPF (Table 2.4).

In some cases, the diagnosis of IPF may be a dynamic one, for example, a patient could be diagnosed with IPF, but

TABLE 2.4 Idiopathic pulmonary fibrosis diagnosis, incorporating histopathology and high resolution computed tomography

HRCT	**Inconsistent with UIP pattern** • Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality • Profuse micronodules • Discrete cysts • Mosaic attenuation/air trapping • Consolidation	**Possible UIP pattern** • Subpleural, basal predominance • Reticular abnormality • Absence of inconsistent features	**UIP pattern** • Subpleural, basal predominance • Reticular abnormality • Honeycombing +/- traction bronchiectasis • Absence of inconsistent features
Histopathology	**Biopsy indicated or to be considered**		**Biopsy generally not indicated**
UIP pattern • Marked fibrosis/architectural distortion • +/-honeycombing, predominantly • Subpleural/paraseptal • Patchy fibrosis • Fibroblastic foci • Absence of atypical features	IPF probable	IPF yes	IPF yes
Probable UIP pattern • Marked fibrosis/architectural distortion • +/- honeycombing • Absence of either patchy fibrosis or fibroblastic foci • Absence of atypical features • Honeycomb changes only	IPF no	IPF yes	
Possible UIP pattern • Patchy or diffuse fibrosis • +/-interstitial inflammation • Absence of other criteria for UIP • Absence of features suggesting alternate diagnosis	IPF no	IPF probable	
Non-classifiable fibrosis **Not UIP pattern (any of 6)** • Hyaline membranes • Organizing pneumonia • Granulomas • Marked interstitial inflammation • Predominant airway centered changes • Other features suggestive of alternate diagnosis	IPF no	IPF no	IPF no*

HRCT high resolution computed tomography, *IPF* idiopathic pulmonary fibrosis, *UIP* usual interstitial pneumonia

[a]Histopathology dominates over HRCT

months or years later manifest signs of an underlying CTD. In such a case, the diagnosis may change from IPF to CTD-associated ILD (CTD-ILD) as the clinical picture evolves.

Key Points

- IPF diagnosis requires thorough patient history to assess for risk factors or alternative diagnoses.
- Diagnosis should include blood-work to assess for other causes of UIP pattern (such as CTD or hypersensitivity pneumonitis).
- IPF is more common in men than women and increases with age (>65–70 years of age).
- Typical physical exam findings are dry 'Velcro®' crackles at lung bases +/– digital clubbing.
- Diagnosis can be made on HRCT alone if radiographic diagnostic criteria are met.
- If HRCT is inconclusive, VATS lung biopsy may be advised (if the patient is suitable for surgery).
- Bronchoscopy is not generally recommended as it is likely to be non-diagnostic.
- The standard of care for diagnosis is a multidisciplinary approach with radiologic and pathologic (if applicable) findings considered in clinical context.

References

1. Nathan SD, Shlobin OA, Weir N, et al. Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. Chest. 2011;140:221–9.
2. Nathan SD, Basavaraj A, Reichner C, et al. Prevalence and impact of coronary artery disease in idiopathic pulmonary fibrosis. Respir Med. 2010;104:1035–41.
3. Shin S, King CS, Brown AW, et al. Pulmonary artery size as a predictor of pulmonary hypertension and outcomes in patients with chronic obstructive pulmonary disease. Respir Med. 2014;108:1626–32.

4. Hernández-González F, Lucena CM, Ramírez J, et al. Cryobiopsy in the diagnosis of diffuse interstitial lung disease: yield and cost-effectiveness analysis. Arch Bronconeumol. 2015;51:261–7.
5. Sakamoto S, Homma S, Mun M, Fujii T, Kurosaki A, Yoshimura K. Acute exacerbation of idiopathic interstitial pneumonia following lung surgery in 3 of 68 consecutive patients: a retrospective study. Intern Med. 2011;50:77–85.
6. Mizuno Y, Iwata H, Shirahashi K, et al. The importance of intraoperative fluid balance for the prevention of postoperative acute exacerbation of idiopathic pulmonary fibrosis after pulmonary resection for primary lung cancer. Eur J Cardiothorac Surg. 2012;41:e161–5.
7. 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;183:788–824.
8. Vij R, Noth I, Strek ME. Autoimmune-featured interstitial lung disease: a distinct entity. Chest. 2011;140:1292–9.

Chapter 3
Diseases that Mimic Idiopathic Pulmonary Fibrosis

There are number of conditions that may commonly be confused and difficult to differentiate from idiopathic pulmonary fibrosis (IPF). This chapter discusses these conditions in more detail.

3.1 Non-specific Interstitial Pneumonia

Non-specific interstitial pneumonia (NSIP) is a pathologic entity that was first described in 1994 [1]. It is the second most common of the idiopathic interstitial pneumonias (IIPs) and can be difficult to differentiate from IPF [2]. The diagnosis of NSIP should only be made pathologically and, unlike IPF, is never a diagnosis that can be made based upon radiography alone. Pathologically, NSIP is characterized by diffuse homogenous fibrotic and/or cellular infiltrates, and therefore, can be further subcategorized into fibrotic NSIP, cellular NSIP, or mixed cellular fibrotic NSIP [3]. This pathologic pattern of injury may be idiopathic in nature or result from other causes of interstitial lung disease (ILD) including chronic hypersensitivity pneumonitis (HP), connective tissue diseases (CTDs), or autoimmune featured ILD. NSIP is the pathologic entity that is most commonly seen in all of the CTDs [4], not including rheumatoid arthritis where usual interstitial pneumonia (UIP) is the most

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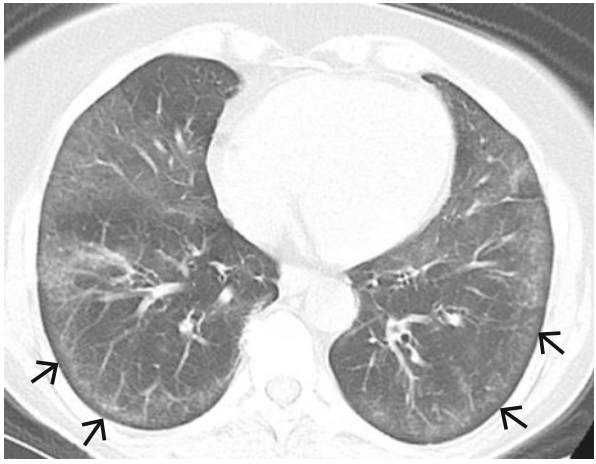

FIGURE 3.1 The radiographic appearance of non-specific interstitial pneumonia with characteristic rim of subpleural sparing, as indicated by the arrows

common [5]. Therefore, when the diagnosis of NSIP is made pathologically, it is incumbent on the clinician to make sure that there is no identifiable cause before the diagnosis of idiopathic NSIP can be made. It is a condition that has a distinctly better course than IPF, with a 5-year survival of approximately 80 % of patients [6]. However, patients with severe functional impairment have a grim prognosis similar to those with IPF [7]. Given the prognostic implications, it is important to differentiate NSIP from IPF. Idiopathic NSIP tends to occur in younger patients and tends to be more predominant in females, in contrast to IPF, which has a male predominance [8]. The clinical presentation is very similar to that of IPF, with insidious onset of shortness of breath, and sometimes associated with a chronic non-productive cough [8]. Unlike IPF, there is no characteristic radiographic appearance, hence why this diagnosis always requires the pathologic specimen [3]. One radiographic finding that has some measure of specificity for NSIP is a rim of subpleural sparing (unaffected lung in the subpleural space), a finding reported in 21–64 % of cases [6, 9] (Fig. 3.1).

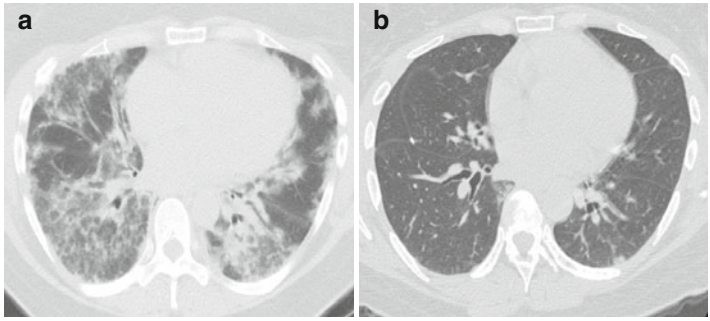

FIGURE 3.2 High resolution computed tomographic images showing the cellular variant of non-specific interstitial pneumonia. (**a**) Before treatment, and (**b**) improvement in infiltrates after treatment with corticosteroids

The treatment approach for NSIP is also quite different to that of IPF, with immunosuppressive therapy commonly regarded as standard of care, although studies attesting to this are lacking [8]. The cellular variant of NSIP (less common) is felt to be more responsive to immunosuppressive therapy (Fig. 3.2). Whether fibrotic NSIP is a disease that may be responsive to anti-fibrotic therapy is unknown and requires independent studies.

3.2 Connective Tissue Disease-Associated Interstitial Lung Disease

ILD is commonly present in many of the CTDs. The prevalence of connective tissue disease-associated interstitial lung disease (CTD-ILD) for the various CTDs is estimated to be [10]:

- scleroderma 40–100 %;
- rheumatoid arthritis 20–30 %;
- polymyositis/dermatomyositis 20–50 %;
- systemic lupus erythematosus 2–8 %; and
- Sjogren's syndrome up to 25 %.

CTD-ILD is a relatively easy diagnosis to make in the context of a patient with pre-existing CTD. In such situations a diagnosis of idiopathic interstitial pneumonitis (such as IPF or idiopathic NSIP) cannot be made being that there is a pre-existing identifiable etiology for the ILD. A thorough patient history and physical examination may provide important clues to an underlying CTD since, in many cases, the onset of respiratory symptoms and ILD may herald the onset of the underlying CTD. In rarer instances, patients may present without any CTD features, which might only manifest months to years after the diagnosis of the underlying ILD [11]. Therefore, patients who are initially diagnosed with an IIP can have their diagnosis evolve over time if an underlying CTD subsequently manifests. The radiographic features of CTD-ILD tend to be non-specific and, in many cases, a UIP pattern occurs [11]. Various radiographic examples are shown in Fig. 3.3. Table 2.1 (see Chap. 2) summarizes the major pathologic entities and presenting signs and symptoms of the more common CTDs.

3.3 Chronic Hypersensitivity Pneumonitis

Chronic HP is perhaps the one disease that is most difficult to differentiate from IPF. HP can present acutely, subacutely, or chronically. Patients who develop chronic HP do not necessarily have a history of either acute or subacute HP or a documented history to a known allergen. Chronic HP can occur as a result of exposure in either an occupational or home setting following long-term inhalation of a wide spectrum of organic antigens from mammalian and avian proteins, fungi, thermophilic bacteria, and certain chemical compounds [12]. Chronic HP occurs most commonly in those with some type of exposure to birds, especially bird droppings (Bird fancier's lung), among farmers (Farmer's lung), or after exposure to moldy hay grain or silage, or contaminated forced-air systems and water reservoirs [12]. There are many other potential exposures that can result in chronic HP, underscoring the need for

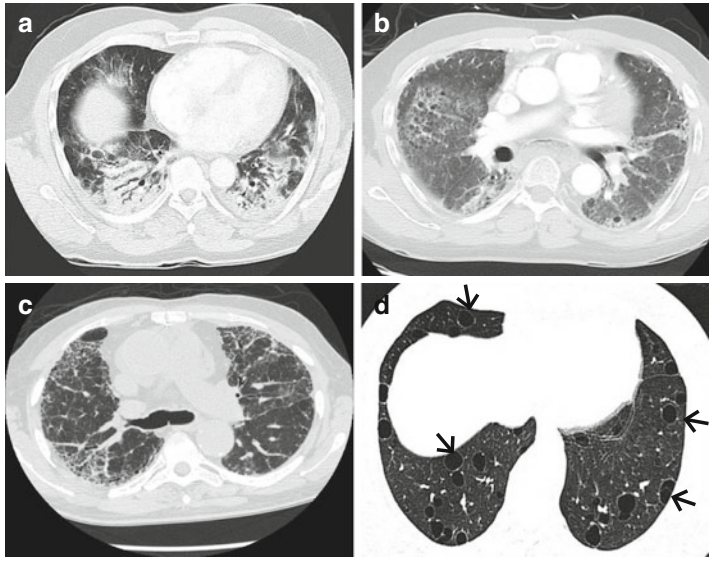

FIGURE 3.3 High resolution computed tomographic images demonstrating the heterogeneous radiographic appearance of connective tissue disease-interstitial lung disease. (**a**) Organizing pneumonia (rheumatoid arthritis), (**b**) fibrotic non-specific interstitial pneumonia (mixed connective tissue disease), (**c**) usual interstitial pneumonia (systemic lupus erythematosus), and (**d**) lymphocytic interstitial pneumonia (Sjögren's) with characteristic cystic changes as indicated by the arrows

a thorough social and occupational history in anyone presenting with ILD. Patients can present very similarly to those with IPF with chronic insidious onset of shortness of breath. An important clinical clue is if shortness of breath and cough worsen in any specific environment, either at work or at home. However, this is more likely to indicate acute or subacute HP and is not very sensitive for chronic HP. Chest imaging may demonstrate distinct changes, including poorly formed small nodules, ground-glass attenuation (either patchy or diffuse), peribronchiolar infiltrates, or areas of air trapping that are best seen on expiratory computed tomography (CT) imaging (Fig. 3.4) [13]. Pathologically, the presence of poorly formed

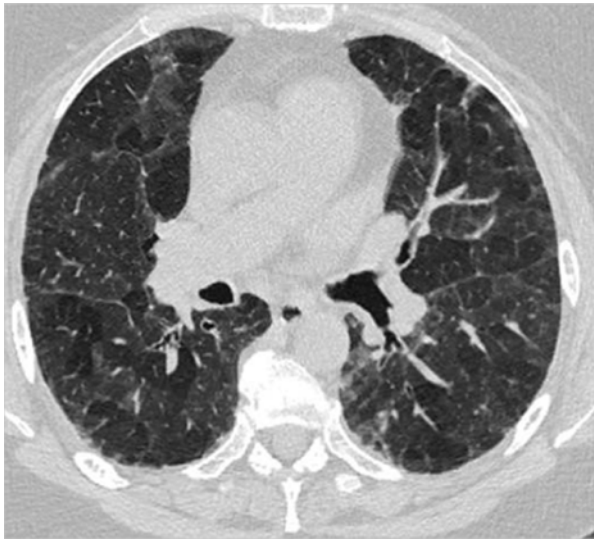

FIGURE 3.4 The typical radiographic appearance of chronic hypersensitivity pneumonitis with peribronchiolar infiltrates and mosaic appearance from air trapping

granulomas, especially in a peribronchiolar distribution, are suggestive of HP. Peribronchiolar fibrosis should also raise the index of suspicion for chronic HP. Treatment includes identification and avoidance of the offending antigen and in some cases immunosuppressive therapy with steroids ± a cytotoxic agent [12]. At present there are no firm guidelines for the diagnosis or treatment of chronic HP.

3.4 Unclassifiable Interstitial Lung Disease

Even in the best hands, under the best circumstances, and despite everyone's best efforts, there are number of patients with ILD that remains unclassifiable. This represents approximately 10 % of patients with ILD [14]. Patients with unclassifiable disease likely represent a mix of ILDs, including IPF, NSIP, and chronic HP. It makes sense therefore, that these

patients tend to have an unpredictable disease course [14, 15]. One of the main reasons patients remain unclassifiable is due to the lack of a surgical lung biopsy, which may be contraindicated because of patient comorbidities or severity of illness. However, there are some patients who remain unclassifiable despite a surgical lung biopsy that may show changes that are non-specific or unclassifiable, including 'end-stage fibrotic lung disease.' There are also patients who have conflicting clinical, radiographic, and pathologic changes and therefore a specific clinical diagnosis is unattainable.

Key Points

- **NSIP:**
  - Can be idiopathic or more commonly secondary to CTD.
  - Diagnosis requires lung biopsy.
  - Treatment is with immunosuppressive therapy in most cases.
- **CTD-ILD**
  - ILD can be the presenting symptom in some cases.
  - Diagnosis can be made on clinical history and positive serologies.
  - If lung biopsy is obtained, it can show NSIP, UIP, OP, pleuritis, or any combination thereof.
  - Treatment is with immunosuppressive therapy in most cases.
- **Chronic HP**
  - Can occur in the absence of an identifiable exposure.
  - Chest imaging may show poorly formed small nodules, ground-glass attenuation, peribronchiolar infiltrates, or areas of air trapping.

- Histopathologic findings include granulomas, NSIP, and/or UIP pattern in peribronchiolar distribution.
- Treatment is withdrawal of exposure (if known) and immunosuppression in some cases.

- **Unclassifiable ILD**
  - Specific diagnosis may not be possible in a minority of ILD cases.
  - Frequently results from inability to safely perform lung biopsy or non-specific findings on lung biopsy.

References

1. Katzenstein AL, Fiorelli RF. Nonspecific interstitial pneumonia/fibrosis. Histologic features and clinical significance. Am J Surg Pathol. 1994;18:136–47.
2. Kligerman SJ, Groshong S, Brown KK, Lynch DA. Nonspecific interstitial pneumonia: radiologic, clinical, and pathologic considerations. Radiographics. 2009;29:73–87.
3. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733–48.
4. Kim EJ, Collard HR, King Jr TE. Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. Chest. 2009;136:1397–405.
5. Gutsche M, Rosen GD, Swigris JJ. Connective tissue disease-associated interstitial lung disease: a review. Curr Respir Care Rep. 2012;21(1):224–32.
6. Travis WD, Hunninghake G, King Jr TE, et al. Idiopathic nonspecific interstitial pneumonia: report of an American Thoracic Society project. Am J Respir Crit Care Med. 2008;177:1338–47.
7. Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med. 2003;168:531–7.

8. Glaspole I, Goh NS. Differentiating between IPF and NSIP. Chron Respir Dis. 2010;7:187–95.
9. Silva CI, Müller NL, Lynch DA, et al. Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. Radiology. 2008;246:288–97.
10. Castelino FV, Varga J. Interstitial lung disease in connective tissue diseases: evolving concepts of pathogenesis and management. Arthritis Res Ther. 2010;12:213.
11. Vij R, Strek ME. Diagnosis and treatment of connective tissue disease-associated interstitial lung disease. Chest. 2013;143: 814–24.
12. Selman M, Buendía-Roldán I. Immunopathology, diagnosis, and management of hypersensitivity pneumonitis. Semin Respir Crit Care Med. 2012;33:543–54.
13. Wuyts W, Sterclova M, Vasakova M. Pitfalls in diagnosis and management of hypersensitivity pneumonitis. Curr Opin Pulm Med. 2015;21:490–8.
14. Ryerson CJ, Urbania TH, Richeldi L, et al. Prevalence and prognosis of unclassifiable interstitial lung disease. Eur Respir J. 2013;42:750–7.
15. Skolnik K, Ryerson CJ. Unclassifiable interstitial lung disease: a review. Respirology. 2016;21:51–6.

Chapter 4
Pathogenesis of Idiopathic Pulmonary Fibrosis

4.1 Etiology

The etiology of idiopathic pulmonary fibrosis (IPF) remains incompletely understood. Historically, IPF was thought to be a condition characterized by inflammation, leading to fibrosis. The current understanding is based on the concept of repetitive injury with an abnormal wound healing response in a genetically susceptible host [1]. The initial injury appears to be to the alveolar epithelial cells (AECs), particularly type II AECs. The current understanding of the pathogenesis of IPF is depicted in Fig. 4.1 [2].

4.2 Alveolar Epithelial Cell Injury

There are two types of AECs, type I and type II. Type I AECs are extremely thin squamous cells that facilitate gas exchange between the alveoli and the blood stream. Type II AECs produce, secrete, and recycle pulmonary surfactant [3]. Additionally, AECs assist in regulating fluid balance in the lung and produce compounds of the innate immune system [3]. Injury to AECs results not only in AEC death, but also in phenotypic transformation of the surviving cells, which potentiates further injury. The downstream consequences of injury to the AECs include [2]:

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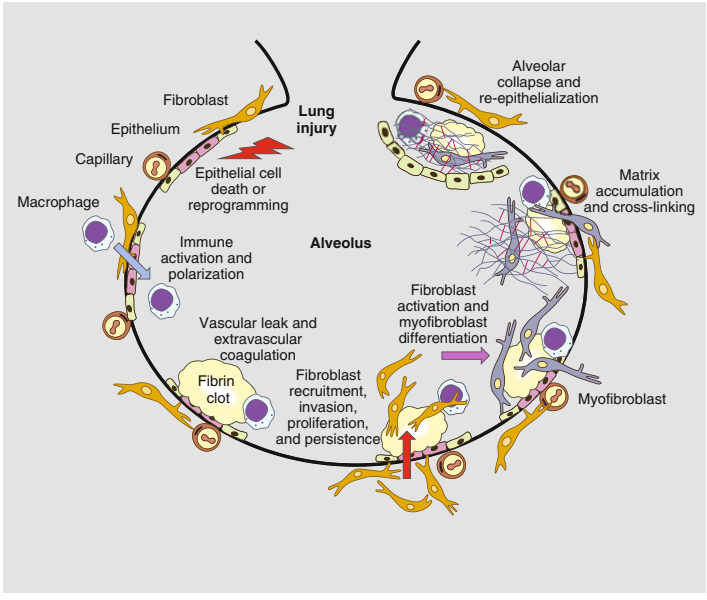

FIGURE 4.1 Pathogenesis of idiopathic pulmonary fibrosis [2]. Injury to alveolar epithelial cells triggers a cascade of aberrant healing, which results in fibrosis (Reproduced with permission from © The American Thoracic Society)

- vascular leak;
- extravascular coagulation;
- fibroblast recruitment and activation; and
- activation of the innate immune system.

4.3 Disease Heterogeneity

The repetitive injury concept parallels the heterogeneous nature of the disease in its distribution and progression. In a single lung, or even a biopsy from a lobe of one lung, there is temporal and spatial gradation of injury, from 'burnt-out' or 'end-stage' fibrotic changes (that usually manifest pathologically as areas of microscopic honeycombing), to areas of fresh

collagen deposition and thickened or fibrotic alveolar septae, to areas of normal, uninvolved lung. The demarcation between abnormal and normal lung can be fairly abrupt. The spatial heterogeneity pathologic pattern mimics what is typically noted radiographically, in that the disease tends to start at the periphery where more of the advanced changes are noted and 'marches' medially to the more central areas of the lung. This pattern of progression also tends to occur in a caudo-cranial direction with the most diseased areas present at the lung bases.

4.4 The Role of the Fibroblast

At the interface of abnormal–normal lung, the presence of fibroblasts (spindle-shaped cells) in clusters (or foci) can be noted. The prevailing paradigm is that fibroblasts are central to the propagation of the disease. Specifically, the fibroblasts proliferate in a disinhibited or unchecked fashion. Whereas a fibroblastic response is normal in the context of any injury in any tissues, for reasons unknown, the fibroblasts are stimulated and fail to be 'turned off' in patients with IPF. Whether this is inherent to the fibroblast itself or a result of the local lung milieu remains to be determined. Potential sources of fibroblasts include any or all of the following:

- endogenous lung fibroblasts;
- circulating bone marrow-derived fibrocytes [4];
- epithelial cells that undergo transformation to mesenchymal cells, so-called epithelial-mesenchymal transition (EMT) [5]; and
- pleural mesothelial cells (this is an attractive hypothesis and could explain the peripheral predilection of the disease) [6].

4.4.1 Inciting Events

The following may play a role in the initiation or perpetuation of the disease [2]:

- gastroesophageal contents: acid, non-acid, food;
- infections;
- cigarette smoke;
- other volitional inhalants;
- environmental inhalants (see Table 2.3 in Chap. 2 for risk factors for IPF);
- high FiO_2;
- lung 'stretch' (i.e., high tidal volumes) in the context of mechanical ventilation; and
- aging.

4.4.2 Collagen Deposition

Collagen deposition and extracellular matrix formation results from the persistently activated fibroblasts. This may take place within the interstitium or the alveoli. Collagen deposition provides the scaffold for the fibrosis that eventually evolves.

4.5 Cytokines

There are multiple cytokine derangements that have been found in patients with IPF. Presently, the role of these cytokines remains investigational and has not been incorporated into routine clinical practice. The major cytokine culprits thought to play a pivotal role in the genesis and perpetuation of IPF include [2]:

- transforming growth factor-beta (TGF-β);
- platelet derived growth factor (PDGF);
- connective tissue growth factor (CTGF);
- vascular endothelial growth factor (VEGF); and
- fibroblast growth factor (FGF).

Other important cytokines include:

- endothelin;
- tumor necrosis factor-alpha (TNF-α); and
- interleukin-13 (IL-13).

4.6 Pathways and Mechanisms

Several potential signaling pathways may be activated and drive the development of fibrosis. These include the Wnt and lysyl oxidase-like 2 (LOXL2) pathway. Telomere shortening may predispose cells to type II AECs to apotosis, setting the stage for the aberrant pathways leading to progressive fibrosis. These mechanisms are discussed in more detail below.

4.6.1 Wnt Pathway

The Wnt pathway is an evolutionarily conserved pathway crucial to cell-fate determination and organogenesis during embryological development [7]. The best characterized pathway, the canonical/β-catenin pathway, appears essential to lung development, as deletion of β-catenin prevents formation of distal airways in animal models [8]. Nuclear accumulation of β-catenin has been found in fibroblastic foci of IPF lungs, suggesting pathogenic re-activation of the Wnt pathway as a possible mechanism in IPF [9].

4.6.2 Lysyl Oxidase-Like 2 Pathway

LOXL2 is essential in the formation of connective tissue; it is an enzyme produced by fibroblasts that catalyzes the cross-linking of matrix proteins. Expression of LOXL2 is increased in IPF [2, 10], leading to increased cross-linking of matrix proteins, which may contribute to the increased matrix stiffness encountered in IPF.

4.6.3 Telomeres and Apoptosis

Telomeres are regions of repetitive, non-coding nucleoside sequences on the ends of chromosomes that serve to protect the chromosome from deterioration. Telomeres shorten with each cell division, and when a critical length is reached, apop-

tosis is initiated. The enzyme telomerase combats the successive shortening of chromosomes by creating new telomeres [11]. Telomere shortening is responsible for one-sixth of cases of familial IPF (Chap. 1), and appears to play a role in sporadic cases as well. In cross-sectional studies, patients with IPF have significantly shorter telomere lengths than age-matched controls [12]. Aging is the primary factor contributing to telomere shortening, which may explain the predilection of IPF for the elderly.

4.7 Pathology

Pathologic features that are important in the diagnosis of IPF include subpleural fibrosis, microscopic honeycombing, normal lung tissue, and fibroblastic foci [13]. Fibroblasts are typically seen clumped in groups and are recognized by their elongated spindle-like appearance. They are frequently noted adjacent to areas of fresh collagen deposition at the interface with normal lung. They are felt to represent the 'leading edge' of the injurious process.

Other pathologic features that may be seen, that are not diagnostic features but are permissible in the context of a lung biopsy that is otherwise diagnostic for IPF, include mild to moderate inflammation and a few very poorly formed granulomas. However, the presence of multiple granulomas always should be an alert to the possible diagnosis of chronic hypersensitivity pneumonitis (HP).

Typical histopathologic changes of IPF (usual interstitial pneumonia pattern) are shown in Fig. 4.2.

Pathologic features suggestive of a diagnosis other than IPF include [14]:

- multiple poorly formed granulomas — suggestive of chronic HP, especially if they are seen in a bronchiolocentric distribution;
- lymphoid aggregates — suggestive of an underlying connective tissue disease (CTD), especially rheumatoid arthritis or Sjögren's syndrome (especially if extensive);

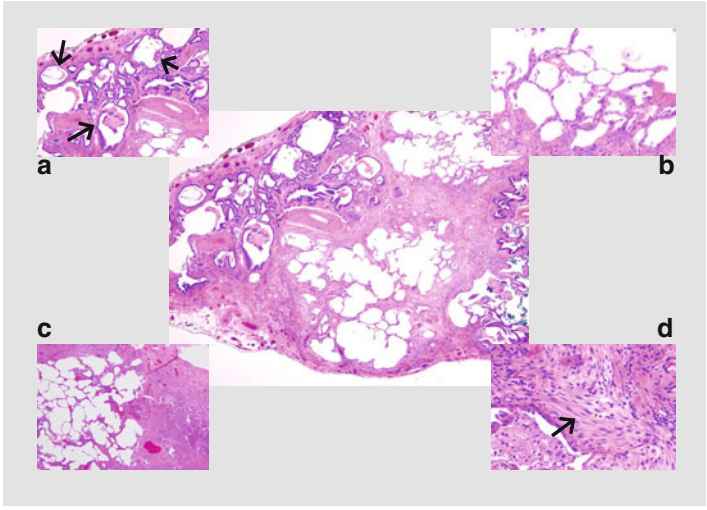

FIGURE 4.2 Typical histopathologic changes of idiopathic pulmonary fibrosis (usual interstitial pneumonia pattern). The central panel demonstrates the lung under low power microscopy with the various heterogeneous changes of a usual interstitial pneumonia-pattern demonstrated, including dense fibrosis, honeycombing, and normal lung. These changes are also shown under high power microscopy: (**a**) microscopic honeycombing (*arrows*), (**b**) areas of fibrosis (*lower*) transitioning to more normal aerated alveoli (*upper*), (**c**) areas of dense fibrosis (*right*) with well-demarcated transition to normal lung (*left*), and (**d**) cluster of elongated spindle-shaped cells that characterize a fibroblastic focus (*arrow*)

- moderate to severe inflammation — can be consistent with many other conditions including an underlying CTD or cellular non-specific interstitial pneumonia (NSIP);
- pleuritis — suggestive of an underlying CTD;
- peribronchiolar fibrosis — might be consistent with chronic HP, aspiration, or the idiopathic entity of bronchiolocentric fibrosis;
- elastosis — consistent with pleuroparenchymal fibroelastosis, especially in the upper lobes; and
- homogeneous changes in the lung tissue — characteristic and more typical of NSIP.

Key Points

- The pathogenesis of IPF is not well elucidated at present.
- IPF is thought to arise from initial repetitive injury to AECs and an abnormal wound healing process.
- Fibroblasts appear to be central to the propagation of disease when they fail to be 'turned off' and proliferate in a disinhibited manner.
- Persistently activated fibroblasts deposit an increased amount of collagen, which provides a scaffold for fibrosis.
- Cytokine imbalances have been found in patients with IPF, but the clinical relevance has yet to be proven.
- Telomere shortening, increased LOXL2 expression, and re-activation of the Wnt pathway are factors linked to IPF development.

References

1. Borensztajn K, Crestani B, Kolb M. Idiopathic pulmonary fibrosis: from epithelial injury to biomarkers–insights from the bench side. Respiration. 2013;86:441–52.
2. Ahluwalia N, Shea BS, Tager AM. New therapeutic targets in idiopathic pulmonary fibrosis. Aiming to rein in runaway wound-healing responses. Am J Respir Crit Care Med. 2014; 190:867–78.
3. Günther A, Korfei M, Mahavadi P, von der Beck D, Ruppert C, Markart P. Unravelling the progressive pathophysiology of idiopathic pulmonary fibrosis. Eur Respir Rev. 2012;21:152–60.
4. Phillips RJ, Burdick MD, Hong K, et al. Circulating fibrocytes traffic to the lungs in response to CXCL12 and mediate fibrosis. J Clin Invest. 2004;114:438–46.
5. Marmai C, Sutherland RE, Kim KK, et al. Alveolar epithelial cells express mesenchymal proteins in patients with idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2011;301:L71–8.

6. Batra H, Antony VB. Pleural mesothelial cells in pleural and lung diseases. J Thorac Dis. 2015;7:964–80.
7. Komiya Y, Habas R. Wnt signal transduction pathways. Organogenesis. 2008;4:68–75.
8. Sasaki T, Kahn M. Inhibition of β-catenin/p300 interaction proximalizes mouse embryonic lung epithelium. Transl Respir Med. 2011;2:8.
9. Chilosi M, Poletti V, Zamò A, et al. Aberrant Wnt/beta-catenin pathway activation in idiopathic pulmonary fibrosis. Am J Pathol. 2003;162:1495–502.
10. Barry-Hamilton V, Spangler R, Marshall D, et al. Allosteric inhibition of lysyl oxidase-like-2 impedes the development of a pathologic microenvironment. Nat Med. 2010;16:1009–17.
11. Armanios M. Syndromes of telomere shortening. Annu Rev Genomics Hum Genet. 2009;10:45–61.
12. Armanios M. Telomerase and idiopathic pulmonary fibrosis. Mutat Res. 2012;730:52–8.
13. 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;183:788–824.
14. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733–48.

Chapter 5
Prognosis, Clinical Course, and Monitoring of Patients with Idiopathic Pulmonary Fibrosis

5.1 Prognosis

The prognosis of idiopathic pulmonary fibrosis (IPF) is generally regarded as quite poor with a median survival from the time of diagnosis of anywhere from 2.5 to 4 years [1]. However, it is difficult a priori to predict the course of the disease in individual patients [2]. There are some patients who have a protracted course and survive 5 years or more, but this disease phenotype can only be recognized in retrospect. This represents about 20–25 % of all patients with IPF [3].

5.1.1 Patient Discussion About Prognosis

When talking to patients about the prognosis, it is imperative to place it in the appropriate context. It is important for the patient to appreciate the following:

- Their prognosis depends on when they present, ie, what is their time 'zero.' Patients who are diagnosed late in their disease course intuitively will have a worse prognosis. Patients who are elderly and sedentary with multiple

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comorbidities tend to be diagnosed late, while younger, more robust patients tend to be diagnosed earlier.

- Not all patients live 2.5–4 years; this is just the range of the average survival from different natural history studies. There are patients with IPF who live well beyond this. Paradoxically, there is data to suggest that the longer patients live with their IPF, the more likely it is that they will live longer. This is an important 'patient friendly' concept and underscores the importance of re-visiting prognosis over time as it can be dynamic in nature [1].
- It is very difficult to predict the course of the disease and therefore it is never too early to talk about medical therapy and transplant. Similarly, it is never too early to address end-of-life issues. This can be couched by the following introductory statement, *'Let's hope for the best, but prepare for the worst.'*

5.2 Clinical Course

The course of IPF may be characterized by a slow and steady deterioration, rapid progression, acute exacerbations, a 'stair-step' pattern of progression with periods of stability punctuated by episodes of progression, or a combination of patterns (see Fig. 1.1 in Chap. 1). Importantly, the past disease course does not predict the future trajectory [4].

5.3 Prognostic Indicators

5.3.1 Pulmonary Function Testing

Pulmonary function testing (PFT) is the primary tool by which IPF disease severity is assessed.

5.3.1.1 The Forced Vital Capacity

The forced vital capacity (FVC) (expressed as a percentage) predicted at baseline has prognostic implications, with those

patients who present with lower levels of lung function having worse outcomes [5]. Lower FVCs tend to imply more fibrosis and less compliant lungs and suggest that such patients are presenting later in their disease course. However, what is unknown in individual patients is the level of their lung function prior to disease onset since not all patients start with a baseline FVC of 100 % predicted. This also explains why some patients may present with 'normal' FVCs and yet still have significant disease if their baseline FVC was >100 %. Change in the FVC over time provides more precise and important prognostic information than the baseline FVC alone, since this demonstrates progression of disease [4]. In particular, a decline of 10 % in the FVC% predicted portends a poor outcome. This change can be either the absolute change (e.g., a decrease from 60 to 50 %) or the relative change (e.g., 60–54 %). Although the latter change is generally less in terms of absolute measures (milliliters), it is associated with almost equivalent prognostic significance. A decrease in the FVC of as little as 5 % also portends worse outcomes, albeit less striking than larger changes [6]. Change in the FVC has been used as the primary endpoint in many of the clinical drug trials [7].

5.3.1.2 The Single Breath Diffusing Capacity for Carbon Monoxide

The baseline single breath diffusing capacity for carbon monoxide (D_{Lco}) may impart more significant prognostic implications than FVC% [2]. However, there tends to be more variability around this measurement, which limits the value and prognostic significance of any change. With that being said, a decrease of 15 % is generally regarded as significant [6].

5.3.1.3 The Total Lung Capacity

The total lung capacity (TLC) % predicted, while commonly measured at baseline and sometimes in follow-up, has not gained traction as the primary measure of pulmonary function in patients with IPF (which remains the FVC). TLC is

generally regarded as the gold standard for lung volume measurement since it incorporates the residual volume that remains unmeasured following the FVC maneuver. However, there may be more variability around this measurement and it is more cumbersome to measure. In general, there should be good correlation between the TLC and FVC in patients with interstitial lung disease (ILD), except perhaps in those patients with combined pulmonary fibrosis/emphysema (CPFE), in whom there might be more air trapping and hence a higher residual volume.

5.3.2 The Six Minute Walk Test

The 6 min walking test (6MWT) is a simple test performed on a long (at least 30 m) uninterrupted corridor where patients are instructed to walk as far as they can in 6 min while being monitored. They are allowed to rest if they get tired or short of breath, but this will affect the primary outcomes measure — the distance achieved. In addition to distance, it is also now recommended that the arterial oxygen saturation (SpO_2), measured by pulse oximetry and pulse rate, be monitored and the amount of supplemental oxygen administered be recorded. Patients may walk with supplemental oxygen and it is recommended that they be halted if their SpO_2 declines below 80 % during the course of the test [8].

5.3.2.1 Distance

The distance attained during the 6MWT has been shown to correlate with subsequent outcomes [9]. Both the baseline distance and the change in distance over time have been shown to provide important prognostic information that is independent of the prognostic information provided by PFT measurements [10, 11]. Therefore, the 6MWT compliments PFTs in terms of the baseline assessment and the serial monitoring of patients.

The minimally important difference in the 6MWT distance is generally regarded as approximately 20–45 m [9, 11]. The bottom end of this range is useful to discern differences in

large population-based studies, while the top end of the range is generally regarded as the better threshold to denote true change in individual patients.

5.3.2.2 Desaturation

Some studies suggest the degree of desaturation during the course of the 6MWT imparts more important prognostic information than distance achieved [10].

5.3.2.3 Pulse Rate Recovery

Pulse rate recovery (PRR) is calculated by the difference in the pulse rate at the end of the 6MWT and after 1 min of recovery. For example, if the pulse rate is 120 beats per minute (bpm) at the end of the 6MWT and then is 110 bpm after 1 min of rest, this equates to a PRR of 10 bpm. The lower the PRR the worse the prognosis. The proposed cut-off point defining an abnormal PRR is less than 13 bpm [12].

5.3.3 Computed Tomography Scan of the Chest

A limited number of studies have attempted to correlate objective scoring of fibrosis on high resolution computed tomography (HRCT) to PFT and outcomes [13, 14], however, further study of the clinical utility of this technique is required. Currently, no well-validated fibrosis scoring system is available in the clinical setting.

Recent data suggests that measurement of the pulmonary artery diameter on computed tomography (CT), expressed as a ratio of the aortic diameter at the same level (pulmonary artery to aorta [PA/A] ratio), might impart important independent prognostic information. A PA/A ratio >1 is associated with higher risk of mortality (Fig. 5.1). An enlarged PA segment could be indicative of underlying pulmonary hypertension (PH), although enlargement could also be due to traction on the vessel from surrounding fibrosis.

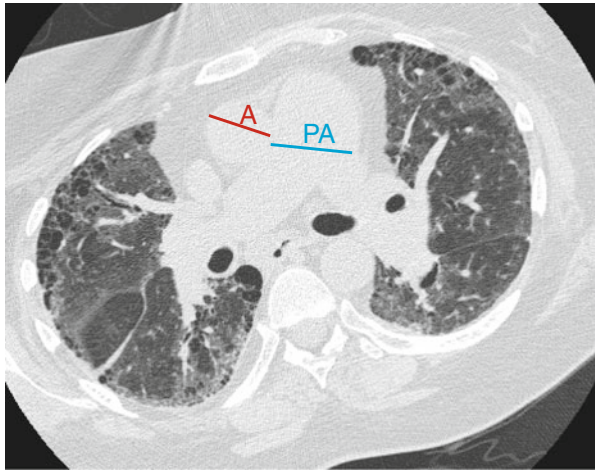

FIGURE 5.1 Enlarged pulmonary artery segment on computed tomography scan. The ratio of the pulmonary artery (*blue line*) to the aorta (*red line*) (PA/A >1) is predictive of survival in IPF

5.3.4 Composite Scores

The gender, age, physiology (GAP) index is the composite index that is gaining the most recognition and acceptance. It is easy to calculate from readily available variables, including demographics. The physiology component is constituted by the FVC% predicted and D_{Lco}% predicted [15].

The composite physiologic score (CPI) is the oldest of the composite scoring systems. It has been used in some clinical trials, but it has not garnered favor in the clinical setting largely due to the difficulty calculating the score [16].

A risk stratification score (ROSE) index scoring system [17] has a nice acronym, but is exceedingly difficult to calculate and therefore is not frequently used in clinical practice.

The distance-saturation product is a score constituted by the product of the distance walked in meters and lowest oxygen saturation achieved on 6MWT, expressed as a fraction. It has only been studied in patients walking only using room air and still requires further validation [18].

5.3.5 Pulmonary Hypertension

The development of PH is associated with a significantly worse prognosis and functional status in IPF [19]. Even mild elevations in pulmonary pressure are associated with worse outcomes in IPF, as demonstrated by Hamada et al. [20], who showed that a mean pulmonary artery pressure (mPAP) >17 mmHg was associated with significantly worse 5-year survival. Right heart catheterization remains the gold standard to diagnose PH. In approximately half of IPF cases the mPAP is in the range of 25–30 mmHg, while more severe PH (mPAP >40 mmHg) has been described in ~9 % of patients with advanced IPF [21]. Although echocardiography is a good screen for the presence of PH, it is not used to make the diagnosis since it only provides an estimate of the systolic pulmonary artery pressure (sPAP), whereas it is the mPAP that defines the presence of PH. Nonetheless, the presence of PH inferred from echocardiographic estimates of the sPAP has also been associated with a significantly worse prognosis. Two echocardiographic studies found that those patients with sPAP >60 mmHg and >50 mmHg had median survivals of only 6.7 and 8.4 months, respectively [22, 23]. Table 5.1 provides clues that may be important in risk stratifying patients for the presence of underlying PH.

5.3.6 Hospitalization

Any hospitalization after the diagnosis of IPF, even non-respiratory, but especially those that are respiratory in nature are associated with worse outcomes. Patients who are hospitalized for a respiratory reason have been shown to have a subsequent risk of in-hospital mortality of 22.4 % [24]. If end-of-life issues have not previously been discussed, it is prudent to do so as soon as possible, since intubation and mechanical ventilation generally carry a very poor prognosis with meaningful recovery a very unlikely outcome. Hospitalization is gaining increasing acceptance as an endpoint (alone or part of a composite of clinical worsening) in IPF clinical trials [7].

Table 5.1 Features that suggest the presence of pulmonary hypertension in patients with idiopathic pulmonary fibrosis

	Signs/symptoms of pulmonary hypertension
History	Shortness of breath on exertion out of proportion to the extent of interstitial lung disease Presyncope/syncope with exertion
Physical examination	Loud P2 heart sound Signs of right heart failure Elevated jugular venous pressure Lower extremity edema
PFT	DLco <40 % FVC%/DLco% ratio >1.5
6MWT	Distance <200 m SpO_2 <88 % on room air during walk Limited (<13 beats per minute) pulse rate recovery
Imaging	Ratio of PA to aorta diameter >1 on computed tomography of the chest
Labwork	Elevated NT-proBNP or BNP
Echocardiogram	Elevated RVSP Dilated right atrium and/or right ventricle Right ventricle dysfunction

6MWT 6 min walking test, *BNP* brain natriuretic peptide, *DLco* diffusing capacity of the lungs for carbon monoxide, *FVC* forced vital capacity, *NT-proBNP* N-terminal pro brain natriuretic peptide, *PA* pulmonary artery, *PFT* pulmonary function testing, *PRR* = *Δ* max pulse – pulse 1 min after cessation of walk, *RVSP* right ventricular systolic pressure

5.3.7 Biomarkers

Biomarkers are objectively quantifiable measurements that serve as a surrogate marker to clinical variables [25]. In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as '*a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic*

responses to a therapeutic intervention' [25]. Therefore, any of the prognostic indicators in the previous section could be regarded as biomarkers, including PFT. Ideally, a biomarker would be acquired non-invasively and have high validity and reliability. The general inference of a 'biomarker' is that of a blood test(s), which will be the remaining focus of this section. Biomarkers could serve multiple purposes in IPF, including identification of patients at risk for IPF, screening for patients with subclinical disease, predicting disease progression, and identifying patients likely to respond to therapy [26]. Unfortunately, there are no well-established, reliable, and commercially available blood biomarkers specific to IPF. Given the complexity of the pathogenesis of IPF, it is unlikely a single biomarker will prove to be 'the holy grail' in IPF diagnosis. It seems more likely that multimarker panels designed to assess the multiple biologic processes at play will be required to improve patient care. Some of the biomarkers assessed in IPF to date are detailed in the following sections.

5.3.7.1 Brain Natriuretic Peptide or N-Terminal Pro Brain Natriuretic Peptide

Levels of brain natriuretic peptide (BNP) or N-terminal pro brain natriuretic peptide (NT-proBNP) have been shown to correlate with outcomes. Whether these reflect the presence of underlying PH and or occult heart failure remains uncertain [23].

5.3.7.2 Red Cell Width Distribution

Red cell distribution width (RDW) is a readily available parameter that can be found on complete blood count reports. High levels (>15) have been shown to correlate with poor outcomes [27].

5.3.7.3 Krebs Von DerLungen-6

Krebs von derLungen-6 (KL-6) is a glycoprotein expressed on the surface of type II alveolar epithelial cells that has been

associated with poor outcomes in IPF. However, RCTs have failed to demonstrate a correlation between changes in KL-6 and treatment response [28].

5.3.7.4 Surfactant Protein A and D

Surfactant proteins A and D are both elevated in patients with IPF when compared to healthy controls and elevated levels are independent predictors of mortality or need for lung transplantation [26].

5.3.7.5 Vascular Endothelial Growth Factor (VEGF)

Pathologic angiogenesis has been implicated as a possible contributor to the development of fibrotic lung disease. Vascular endothelial growth factor (VEGF) is a major regulator of angiogenesis. Elevated serum concentrations of VEGF are associated with decreased survival in IPF [29].

5.4 Monitoring the Clinical Course

The course of IPF is highly variable and largely unpredictable. Patients therefore should be followed closely. It is recommended that patients be seen at least every 3–6 months and on an as needed basis. There are no specific guidelines or data to suggest serial monitoring alters the course of patients with IPF. In the absence of such, the following provides a suggested guideline for consideration:

- PFT every 3 months;
- 6MWT every 3 months; and
- annual CT chest scan.

Comorbidities should also be monitored and treatment implemented where possible, the following comorbidities are particularly important to monitor:

- gastroesophageal reflux disease;
- PH;
- obstructive sleep apnea;
- congestive heart failure;
- coronary artery disease;
- venous thromboembolism;
- lung cancer;
- depression and anxiety; and
- deconditioning.

5.5 Clinical Scenario of Increasing Shortness of Breath

The increasing shortness of breath experienced by a patient with IPF may be acute, subacute, or chronic. Differential diagnosis should be considered, including:

- pulmonary embolism;
- congestive heart failure;
- pneumonia;
- acute exacerbation of IPF;
- cardiac ischemia;
- disease progression; and
- pneumothorax.

Testing should be carried out to investigate and rule out differential diagnosis. Recommended testing includes:

- routine laboratory tests (e.g., complete blood count and chemistry panel);
- BNP or NT-proBNP;
- evaluation for myocardial infarction with electrocardiogram (ECG) and cardiac enzymes;
- appropriate evaluation for pulmonary embolism (determine pre-test probability, D-dimer, imaging);
- echocardiogram; and
- chest imaging (chest radiograph at a minimum with strong consideration of chest CT, perform CT angiogram to rule pulmonary embolism if appropriate).

Key Points

- The disease progression of IPF is highly variable.
- Lower FVC, D_{LCO}, 6MWT distance, and nadir SpO_2 during 6MWT portend decreased survival rates.
- Disease progression is monitored through evaluation of PFT and 6MWT.
- At this time there are no widely available blood biomarkers for IPF.
- Presence of PH and need for hospitalization increase the risk of mortality or lung transplantation.
- Common causes of acute worsening in IPF include pulmonary embolism, systolic or diastolic heart failure, cardiac ischemia, or infection.

References

1. Brown AW, Shlobin OA, Weir N, et al. Dynamic patient counseling: a novel concept in idiopathic pulmonary fibrosis. Chest. 2012;142:1005–10.
2. Nathan SD, Shlobin OA, Weir N, et al. Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. Chest. 2011;140:221–9.
3. Brown AW, Shlobin OA, Weir N, Albano MC, Ahmad S, Smith M, Leslie K, Nathan SD. Dynamic patient counseling: a novel concept in idiopathic pulmonary fibrosis. Chest. 2012;142:1005–10.
4. Ley B, Collard HR, King Jr TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;183:431–40.
5. Erbes R, Schaberg T, Loddenkemper R. Lung function tests in patients with idiopathic pulmonary fibrosis. Are they helpful for predicting outcome? Chest. 1997;111:51–7.
6. Zappala CJ, Latsi PI, Nicholson AG, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35:830–6.
7. Nathan SD, Meyer KC. IPF clinical trial design and endpoints. Curr Opin Pulm Med. 2014;20:463–71.

8. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44:1428–46.
9. Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. Eur Respir J. 2014;44:1447–78.
10. Flaherty KR, Andrei AC, Murray S, et al. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med. 2006;174:803–9.
11. du Bois RM, Weycker D, Albera C, et al. Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. Am J Respir Crit Care Med. 2011;183:1231–7.
12. Swigris JJ, Olson AL, Shlobin OA, Ahmad S, Brown KK, Nathan SD. Heart rate recovery after six-minute walk test predicts pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Respirology. 2011;16:439–45.
13. Battista G, Zompatori M, Fasano L, Pacilli A, Basile B. Progressive worsening of idiopathic pulmonary fibrosis. High resolution computed tomography (HRCT) study with functional correlations. Radiol Med. 2003;105:2–11.
14. Oda K, Ishimoto H, Yatera K, et al. High-resolution CT scoring system-based grading scale predicts the clinical outcomes in patients with idiopathic pulmonary fibrosis. Respir Res. 2014;15:10.
15. Ley B, Ryerson CJ, Vittinghoff E, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med. 2012;156:684–91.
16. Watters LC, King TE, Schwarz MI, Waldron JA, Stanford RE, Cherniack RM. A clinical, radiographic, and physiologic scoring system for the longitudinal assessment of patients with idiopathic pulmonary fibrosis. Am Rev Respir Dis. 1986;133:97–103.
17. Mura M, Porretta MA, Bargagli E, et al. Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. Eur Respir J. 2012;40:101–9.
18. Lettieri CJ, Nathan SD, Browning RF, Barnett SD, Ahmad S, Shorr AF. The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. Respir Med. 2006;100:1734–41.
19. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest. 2006;129:746–52.

20. Hamada K, Nagai S, Tanaka S, et al. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. Chest. 2007;131:650–6.
21. Shorr AF, Wainright JL, Cors CS, Lettieri CJ, Nathan SD. Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. Eur Respir J. 2007;30:715–21.
22. Nadrous HF, Pellikka PA, Krowka MJ, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest. 2005;128:2393–9.
23. Song JW, Song JK, Kim DS. Echocardiography and brain natriuretic peptide as prognostic indicators in idiopathic pulmonary fibrosis. Respir Med. 2009;103:180–6.
24. Brown AW, Fischer CP, Shlobin OA, et al. Outcomes after hospitalization in idiopathic pulmonary fibrosis: a cohort study. Chest. 2015;147:173–9.
25. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69:89–95.
26. Hambly N, Shimbori C, Kolb M. Molecular classification of idiopathic pulmonary fibrosis: personalized medicine, genetics and biomarkers. Respirology. 2015;20:1010–22.
27. Nathan SD, Reffett T, Brown AW, et al. The red cell distribution width as a prognostic indicator in idiopathic pulmonary fibrosis. Chest. 2013;143:1692–8.
28. 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;171:1040–7.
29. Ando M, Miyazaki E, Ito T, et al. Significance of serum vascular endothelial growth factor level in patients with idiopathic pulmonary fibrosis. Lung. 2010;188:247–52.

Chapter 6
Comorbidities and Complications of Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) tends to be a disease of the elderly and therefore patients are apt to present with or develop various comorbidities during the course of their disease (Table 6.1). Independent of age, patients with IPF have been shown to have a higher propensity for certain comorbidities that can impact their quality of life and outcomes.

6.1 Gastroesophageal Reflux Disease

There is a very strong association between gastroesophageal reflux disease (GERD) and IPF. Specifically, GERD has been described in more than 80 % of patients with IPF [1, 2]. In less than half of cases it can be silent and therefore the lack of any symptoms does not rule out GERD [2]. Whether GERD is involved in the pathogenesis or perpetuation of the disease is uncertain. Nonetheless, GERD therapy in the form of proton pump inhibitors and H2 blockers have an association with improved survival, in one retrospective study, and with greater preservation of lung function in another study [3, 4]. There is also at least one case series documenting improvement in lung function with Nissen fundoplication [5].

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Table 6.1 Common comorbidities of idiopathic pulmonary fibrosis

Pulmonary	Non-pulmonary
Chronic obstructive pulmonary disease	Anxiety
Lung cancer	Congestive heart failure
Pulmonary hypertension	Coronary artery disease
Sleep disordered breathing	Deconditioning
Venous thromboembolism	Depression
	Gastroesophageal reflux disease
	Hypogonadism

Conversely, there is also emerging data that GERD therapy might not have any effect on outcomes. Treatment for GERD has been endorsed by the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association 2015 Clinical Practice guidelines with a 'conditional recommendation for use' [6]. At present it is not clearly defined which patients require testing for GERD and whether or not all patients with IPF should be placed on anti-reflux therapy is uncertain and will require further studies.

6.2 Cardiovascular

6.2.1 Coronary Artery Disease

Patients with IPF have been shown to have a higher prevalence of coronary artery disease (CAD) and acute coronary syndrome (ACS) [7]. The presence of CAD should be considered in all patients with IPF, especially the elderly and those with additional risk factors including hypertension, hyperlipidemia, history of tobacco use, diabetes mellitus, and a family history of premature coronary artery disease. The presence of coronary calcification on computed tomography (CT) mediastinal images may be a crude, yet readily available screening tool [8]. Patients with IPF and associated significant CAD have been shown to have worse outcomes [9].

6.2.2 Heart Failure

Patients with IPF have a predisposition for heart failure, both systolic and diastolic. The estimated prevalence of heart failure with preserved ejection fraction is 9–16 % [10–12]. Whether IPF heightens this risk or if it is a reflection of IPF being a disease of the elderly is uncertain.

6.2.3 Thromboembolic Disease

Patients with IPF have a heightened propensity for thromboembolic events that can manifest as deep vein thrombosis or pulmonary embolism. One study documented a fourfold increased likelihood of a prothrombotic state in patients with IPF compared to healthy controls [13]. A pulmonary embolus should be suspected and ruled out in any patient with IPF who presents with acute on chronic shortness of breath or chest pain [7].

6.3 Pulmonary

6.3.1 Pulmonary Hypertension

Pulmonary hypertension (PH) can be regarded as a complication of IPF and a comorbidity. Reported prevalence ranges between 3 and 86 %, although most estimates are between 30 and 50 % [14]. The presence of PH is associated with significantly worse outcomes and is an important independent prognostic indicator [15, 16]. Clues to the presence of PH include:

- dyspnea out of proportion to pulmonary function test abnormalities;
- reduced distance on 6 min walking test and/or excessive desaturation and oxygen requirements;
- disproportionately low D_{Lco};
- enlarged pulmonary artery segment on CT scan (see Chap. 5, Fig. 5.2);

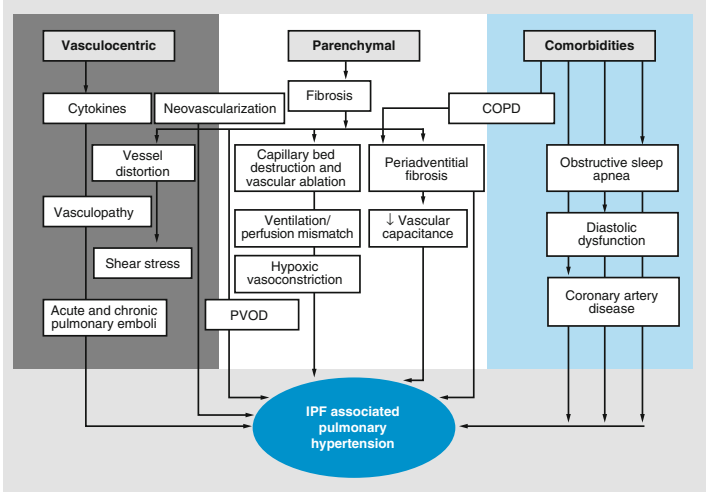

FIGURE 6.1 Pathophysiology of pulmonary hypertension in idiopathic pulmonary fibrosis. Depicted in this figure under three broad categories are the various factors that may interact in the genesis of pulmonary hypertension complicating idiopathic pulmonary fibrosis. *COPD* chronic obstructive pulmonary disease, *IPF* idiopathic pulmonary fibrosis, *PVOD* pulmonary veno-occlusive disease

- elevated brain natriuretic peptide (BNP) or N-terminal proBNP; and
- echocardiographic evidence of PH from estimate of systolic pulmonary artery pressure sPAP or evidence of right ventricular dysfunction or enlargement.

PH is defined by a pulmonary capillary wedge pressure of 25 mmHg or greater [17] and is diagnosed and categorized with mandatory right heart catheterization. The pathophysiology of PH is likely multifactorial and not due to progressive fibrosis and vascular obliteration alone (Fig. 6.1).

Other factors and comorbidities that could be contributing to PH should be ruled out before management can be implemented, including:

- heart failure (especially heart failure with preserved ejection fraction);
- untreated or inadequately treated hypoxemia;
- obstructive sleep apnea (OSA); and
- chronic thromboembolic PH (CTEPH).

At present, there are no medications approved for treating PH in patients with IPF. There is data to suggest treating more severe PH in this population might be helpful [18], however, the type of patient in terms of PH severity and interstitial lung disease (ILD) severity that is most likely to respond to pulmonary vasoactive therapy remains unknown and is an area of ongoing active research [18]. There is a potential downside to empirically treating patients with IPF with PH medications, including worsening of the ventilation-perfusion ratio by dilating blood vessels to poorly ventilated areas. If there is consideration of treating PH in a patient with IPF, then the patient is best served by referral to an expert center [18, 19].

6.3.2 Lung Cancer

Patients with IPF are at higher risk for the development of lung cancer compared to the general population. Multivariate analyses have demonstrated that the increased risk of lung cancer is not attributable to smoking alone and that other elements of fibrotic lung disease heighten the risk for lung cancer [7]. In contrast to lung cancers in those without fibrotic lung disease, tumors in patients with IPF are most commonly located peripherally and in the lower lobes [7]. It has been estimated that approximately 10 % of patients with IPF will succumb to lung cancer [20]. Annual chest CT imaging should be considered, since lung nodules are exceedingly difficult to recognize on plain chest X-rays in the context of background fibrosis. Early diagnosis is essential so that patients who are appropriate surgical candidates can be identified.

6.3.3 Combined Pulmonary Fibrosis Emphysema

Emphysema in the context of pulmonary fibrosis (see Chap. 2, Fig. 2.1) may be seen in approximately one third of patients. Whether this is a comorbidity or a distinct clinical phenotype is uncertain. These patients are very commonly male and invariably have a significant history of smoking. The effects on prognosis is uncertain as patients with combined pulmonary fibrosis emphysema (CPFE) have been described to have worse, equivalent, or better prognosis than those with IPF alone [7]. It is clear that such patients have a higher propensity for PH [7]. Marked symptoms and exertional hypoxemia in the context of normal spirometry can provide clues to the presence of CPFE. The opposing mechanical forces from the restrictive and obstructive process result in 'pseudonormalization' of the lung volumes. Another clue to the presence of CPFE is a disproportionately reduced D_{Lco} in comparison to lung volumes, since both disease processes cause vascular obliteration.

6.3.4 Obstructive Sleep Apnea

The prevalence of OSA has been demonstrated to be as high as 88 % in patients with IPF, with as many as 65 % having moderate to severe OSA (apnea/hypopnea index >15 events/h) [21]. This high prevalence may be attributable to the effect of reduced lung volumes on the geometry of the upper airways. Another contributing factor may be reduced lung compliance and associated increased work of breathing with greater negative intrathoracic pressure resulting in collapse of the upper airways. In any event, this comorbidity is essential to screen for as treatment can improve quality of life through reduction in daytime somnolence and improvement in energy level and general wellbeing. In this setting, the use of continuous positive airway pressure (CPAP) (± supplemental O_2, depending on sleep study results) reduces nocturnal hypoxemia and may prevent the development or

worsening of PH [7]. There is no documented correlation between the severity of IPF and the prevalence or severity of OSA.

6.4 Anxiety and Depression

The psychological consequences of IPF are underappreciated and frequently go undetected and unaddressed. They are quite common, affecting approximately 20 % of patients [7]. If depression is diagnosed traditional treatment measures, including antidepressant medications and cognitive behavioral therapy should be instituted. In addition, referral to pulmonary rehabilitation should be considered as studies have demonstrated a reduction in fatigue and symptoms of depression and anxiety [22]. Patient support groups may be helpful too; local availability of support groups can be searched for on the Pulmonary Fibrosis Foundation website at www.pulmonaryfibrosis.org.

6.5 Complications

6.5.1 Acute Exacerbations of Idiopathic Pulmonary Fibrosis

The annual incidence of acute exacerbations of IPF (AE-IPF) ranges from 1 to 20 % of patients with IPF, depending on the population studied and the definition used [23]. AE-IPF accounts for more than 50 % of hospital admissions and up to 40 % of all deaths [23]. The classic definition of an acute exacerbation includes [25]:

- the subacute onset of shortness of breath; accompanied by
- new alveolar infiltrates on the background of radiographic usual interstitial pneumonia; with
- other potential etiologies such as heart failure, pneumonia, or pulmonary embolism excluded.

The classic definition of AE-IPF has been called into question given the frequent inability to perform invasive procedures, such as bronchoscopy, to rule out infection. In addition, outcomes appear similar between AE-IPF and suspected AE-IPF and exacerbations of IPF due to identifiable causes such as infection or aspiration. The optimal definition of AE-IPF remains an ongoing area of debate [23].

Evaluation of patients with potential AEs should be based on excluding other entities [25]. Respiratory cultures should be obtained, preferably by bronchoscopic lavage if feasible. In patients who have a tenuous respiratory situation this may not be feasible or only becomes feasible once they are placed on mechanical ventilation. Although performance of a bronchoscopy should not be the primary reason to intubate patients, many of these patients will require mechanical ventilation for progressive respiratory failure. Patients may not fulfill all the criteria for an AE, in which case they can be regarded as having a 'suspected' AE. While such cases may represent true AE-IPF, it is also possible that the event could be due to other entities that can cause alveolar infiltrates, such as infection or heart failure.

The prognosis for AE-IPF is poor, with a short-term mortality of approximately 50 % in most patients and approximately 80 % in those requiring intensive care unit admission [24]. Those who survive the initial hospitalization continue to have a high mortality rate over the next year [23]. It is therefore very important to have early end-of-life discussions with patients and their families, and to present a realistic prognostic outlook. The likelihood of liberation from mechanical ventilation is extremely low, especially in elderly patients with IPF or those with multiple comorbidities for whom lung transplantation is not an option. With this information, patients and families may wish to avoid mechanical ventilation and opt for palliative care measures.

There are no proven therapies for AE-IPF. Patients are generally managed with high-dose intravenous steroids at doses of anywhere from methylprednisolone 40 mg every 6 h to bolus dose methylprednisolone 500–1000 mg daily for 3 days with subsequent tapering. However, this is not proven and

there are no firm guidelines or data to support this approach. The utility of anti-fibrotic therapies in AEs is unknown. It is recommended to continue anti-fibrotic therapy in patients already on it, but de novo initiation of therapy in the setting of an AE has not been demonstrated to be helpful [24]. Most patients are also invariably managed with broad-spectrum antibiotics in the event of an occult infection. The most effective treatment is lung transplantation, but this is only feasible in a small minority of patients and usually in those who were already evaluated and listed prior to acute worsening. In some patients the institution of extracorporeal membrane oxygenation may be warranted as a bridge to transplantation. There is recent single center data suggesting that the use of plasmapheresis and rituximab may have a role in the treatment of AEs, however this requires further study [26].

6.5.2 Pneumothorax

Pneumothorax is an unusual complication of IPF and is more likely to be seen in patients with more advanced disease, particularly in the context of CPFE and as a complication of mechanical ventilation. The possibility of pneumothorax should be considered in patients who present with acute or chronic shortness of breath of abrupt worsening in oxygenation. A CT scan of the chest might be needed to make the diagnosis since the pneumothorax may be loculated in a plane that escapes detection on chest X-ray. These should be managed with tube thoracostomy. In patients with 'stiff' or poorly compliant lungs, these might prove difficult to re-expand.

6.5.3 Aspergilloma

Aspergilloma is a contained area of aspergillus infection and, although rare, can be seen in large areas of honeycombing or in bullae that accompany CPFE (Fig. 6.2). This is usually an incidental radiographic finding, but in rare cases may present with hemoptysis.

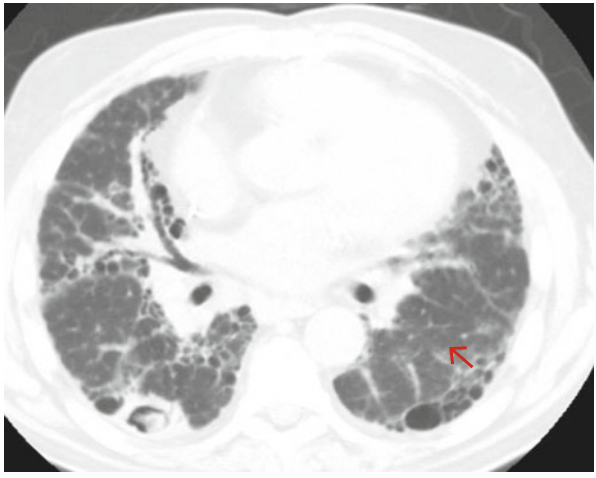

FIGURE 6.2 Computed tomography scan showing aspergilloma. The *red arrow* highlights an aspergilloma (fungal ball within a cyst) in a patient with idiopathic pulmonary fibrosis

Key Points

- Comorbidities are common and contribute to the morbidity and mortality of IPF.
- GERD may be occult and has an association with IPF, perhaps as a cause of lung injury.
- Patients with IPF have a higher incidence of pulmonary embolism and lung cancer than age-matched controls.
- CAD and heart failure are common in this aging population.
- Pulmonary hypertension may develop and is associated with worse outcomes.
- Depression and anxiety are prevalent and likely related to impaired quality of life and poor prognosis.
- AEs generally do not respond well to treatment and result in high mortality (50–90 %).

References

1. Raghu G, Freudenberger TD, Yang S, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J. 2006;27:136–42.
2. Tobin RW, Pope 2nd CE, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1998;158:1804–8.
3. 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; 184:1390–4.
4. Hoppo T, Jarido V, Pennathur A, et al. Antireflux surgery preserves lung function in patients with gastroesophageal reflux disease and end-stage lung disease before and after lung transplantation. Arch Surg. 2011;146:1041–7.
5. Raghu G, Yang ST, Spada C, Hayes J, Pellegrini CA. Sole treatment of acid gastroesophageal reflux in idiopathic pulmonary fibrosis: a case series. Chest. 2006;129:794–800.
6. Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. 2015;192:e3–19.
7. King C, Nathan SD. Identification and treatment of comorbidities in idiopathic pulmonary fibrosis and other fibrotic lung diseases. Curr Opin Pulm Med. 2013;19:466–73.
8. Nathan SD, Weir N, Shlobin OA, et al. The value of computed tomography scanning for the detection of coronary artery disease in patients with idiopathic pulmonary fibrosis. Respirology. 2011;16:481–6.
9. Nathan SD, Basavaraj A, Reichner C, et al. Prevalence and impact of coronary artery disease in idiopathic pulmonary fibrosis. Respir Med. 2010;104:1035–41.
10. Panos RJ, Mortenson RL, Niccoli SA, King Jr TE. Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. Am J Med. 1990;88:396–404.
11. Nathan SD, Shlobin OA, Ahmad S, Urbanek S, Barnett SD. Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis. Chest. 2007;131:657–63.

12. Raghu G, Nathan SD, Behr J, et al. Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. Eur Respir J. 2015;46:1370–7.
13. Navaratnam V, Fogarty AW, McKeever T, et al. Presence of a prothrombotic state in people with idiopathic pulmonary fibrosis: a population-based case–control study. Thorax. 2014;69: 207–15.
14. Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. Eur Respir J. 2015;46:1113–30.
15. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest. 2006;129: 746–52.
16. Shorr AF, Wainright JL, Cors CS, Lettieri CJ, Nathan SD. Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. Eur Respir J. 2007;30:715–21.
17. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34–41.
18. Hoeper MM, Behr J, Held M, et al. Pulmonary hypertension in patients with chronic fibrosing idiopathic interstitial pneumonias. PLoS One. 2015;10, e0141911.
19. Saggar R, Khanna D, Vaidya A, et al. Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis. Thorax. 2014;69:123–9.
20. Tomassetti S, Gurioli C, Ryu JH, et al. The impact of lung cancer on survival of idiopathic pulmonary fibrosis. Chest. 2015;147: 157–64.
21. Mermigkis C, Bouloukaki I, Antoniou K, et al. Obstructive sleep apnea should be treated in patients with idiopathic pulmonary fibrosis. Sleep Breath. 2015;19:385–91.
22. Swigris JJ, Fairclough DL, Morrison M, et al. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. Respir Care. 2011;56:783–9.
23. Ryerson CJ, Cottin V, Brown KK, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis: shifting the paradigm. Eur Respir J. 2015;46:512–20.
24. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J. 2011;37:356–63.

25. Maher TM, Whyte MK, Hoyles RK, et al. Development of a consensus statement for the definition, diagnosis, and treatment of acute exacerbations of idiopathic pulmonary fibrosis using the Delphi technique. Adv Ther. 2015;32:929–43.
26. Donahoe M, Valentine VG, Chien N, et al. Autoantibody-targeted treatments for acute exacerbations of idiopathic pulmonary fibrosis. PLoS One. 2015;10:e0127771.

Chapter 7
Treatment of Idiopathic Pulmonary Fibrosis

The treatment of idiopathic pulmonary fibrosis (IPF) can be broadly divided into pharmacologic therapies and non-pharmacologic interventions (Chap. 8). There are two agents that have been shown to slow the rate of deterioration in lung function in IPF. These two drugs, pirfenidone and nintedanib, have been variably approved in countries around the world.

7.1 Pirfenidone

Pirfenidone is an orally bioavailable synthetic compound that has anti-fibrotic, anti-inflammatory, and antioxidant effects.

7.1.1 History

Pirfenidone has been studied in IPF since the 1990s. Early studies in Japan resulted in its approval by the Japanese Ministry of Health, Labor, and Welfare in 2008 [1, 2]. Two pivotal Phase III randomized placebo-controlled trials, CAPACITY I (NCT00287729) and CAPACITY II (NCT00287716), were undertaken in North America and Europe [3]. The primary endpoint for both studies was the change in forced vital capacity (FVC) at 72 weeks.

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While the first study was positive, the other failed to show a difference in FVC between the treatment and placebo groups. Although the combined data was positive, the US Food and Drug Administration (FDA) initially elected not to approve the drug, while the European Medicines Agency (EMA) did issue an approval. A third 'tiebreaker' randomized controlled trial (RCT), the ASCEND study (NCT01366209), was therefore undertaken in the US. The 52-week trial again studied change in the FVC as the primary endpoint [4]. ASCEND was a positive study and resulted in the approval of pirfenidone in October of 2014. The data from the three pirfenidone Phase III RCTs are shown in Table 7.1.

7.1.2 Mechanism of Action

The exact mechanism through which pirfenidone exerts its effects in IPF are unknown. However, it is a pleiotropic molecule with effects at multiple domains that could be important in the pathogenesis of IPF. Possible mechanisms of action include [5]:

- Anti-inflammatory effects through suppression of tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), IL-12, and IL-8.
- Anti-fibrotic properties likely from inhibition of expression of transforming growth factor β (TGF-β), a profibrotic cytokine. A number of other anti-fibrotic pathways might be targeted as well.
- Antioxidant properties.

7.1.3 Dose

Pirfenidone is administered as three capsules three times a day. Each capsule contains 267 mg of active drug for a total daily dose of 2403 mg.

Table 7.1 Data from the phase III randomized controlled trials of pirfenidone

Study	Year	Number of patients	Study design	Inclusion criteria	Primary outcome	Secondary outcomes
Taniguchi et al. [2]	2010	275	Phase III double-blind, placebo-controlled	IPF per ATS/ERS guideline Age 20–75 years O_2 desaturation ≥5 % on 6MET SpO_2 ≥85 % during 6MET	**Vital capacity decline at week 52:** Placebo (–0.16 L) High dose (–0.09 L) p=0.042	**Progression free survival** (p=0.028)
CAPACITY study 004 [3]	2011	435	Phase III double-blind, placebo-controlled	Definite IPF by CT or biopsy proven Age 40–80 years FVC ≥50 % D_{Lco} ≥35 % Either FVC or D_{Lco} ≤90 % 6MWT ≥150 m	**Change in % predicted FVC at week 72:** Placebo (–12.4 %) High dose (–8.0 %) p=0.001	**Progression free survival** (p=0.023)

(continued)

Table 7.1 (continued)

Study	Year	Number of patients	Study design	Inclusion criteria	Primary outcome	Secondary outcomes
CAPACITY study 006 [3]	2011	344	Phase III double-blind, placebo-controlled	Definite IPF by CT or biopsy proven Age 40–80 years FVC ≥50 % DLco ≥35 % Either FVC or DLco ≤90 % 6MWT ≥150 m	**Change in % predicted FVC at week 72:** Placebo (−9.6 %) Pirfenidone (−9.0 %) p = 0.501	**Mean change in 6MWT distance:** Placebo (−76.9 m) Pirfenidone (−45.1 m) p = 0.0009
ASCEND [4]	2014	555	Phase III double-blind, placebo-controlled	Definite IPF by CT or biopsy proven Age 40–80 years FVC 50–90 % D_{Lco} 30–90 % FEV1/FVC ratio ≥0.8 6MWT distance ≥150 m	**Change in % predicted FVC at week 52:** p < 0.001	**6MWT change at week 52:** p = 0.04 **Progression free survival:** p < 0.001

6MET 6 min steady-state exercise test, *6MWT* 6 min walking test, *ATS* American Thoracic Society, *CT* computed tomography, D_{Lco} diffusing capacity of the lungs for carbon monoxide, *ERS* European Respiratory Society, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *IPF* idiopathic pulmonary fibrosis, *L* liters

7.1.4 Pharmacokinetics

Metabolism is primarily in the liver through the cytochrome P450 1A2 (CYP1A2). The use of CYP1A2 inhibitors therefore increase pirfenidone levels and the following guidance should be taken into account before initiating treatment:

- strong CYP1A2 inhibitors should be avoided, e.g., fluvoxamine;
- moderate CYP1A2 inhibitors (including ciprofloxacin and amiodarone) should warrant the consideration of reduction in the dose of pirfenidone [5]; and
- inducers of CYPA12, including cigarette smoking and omeprazole, may reduce levels of pirfenidone and should be avoided [6].

Patients with mild or moderate hepatic dysfunction may be treated with pirfenidone but require careful monitoring. Use of pirfenidone is contraindicated in severe hepatic dysfunction. Pirfenidone can be used to treat patients with comorbid renal dysfunction, but is contraindicated in end-stage renal disease. No dose adjustments are required for age, gender, race, or body size. Although, dose adjustments can be made on a case-by-case basis to reduce side-effects, especially if the side-effects are adversely impacting quality of life.

7.1.5 Side-Effects

The most common side-effects are gastrointestinal (GI) and dermatologic. Indigestion is common and improves when medication is taken with food. Specifically, rash and photosensitivity may be seen and appropriate patient counseling about sun exposure avoidance is prudent. Common side-effects are shown in Table 7.2.

Table 7.2 Common side-effects of pirfenidone and nintedanib

	Pirfenidone	Nintedanib
Gastrointestinal	Anorexia (8 %), nausea (20 %), dyspepsia (12 %), vomiting (7 %), diarrhea (6 %), loss of weight (5 %)	Diarrhea (44 %), nausea (17 %), vomiting (9 %), GI perforation (0.3 %)
Dermatologic	Rash (20 %) Photosensitivity (8 %)	N/A
Cardiovascular	N/A	Myocardial infarction (1.1 %)
Hematologic	N/A	Bleeding events (3 %)
Hepatic	Transaminitis (2.5 %)	Transaminitis
Embryo fetal toxicity	N/A	Yes

The incidences of these side-effects are all placebo-corrected based on data from the respective Phase III clinical trials [2–4, 7]
GI gastrointestinal, *N/A* not applicable

7.1.6 Administration

Prior to prescription of pirfenidone it is important to fully inform patients about the details of medication administration and monitoring that will occur throughout the course of treatment:

- Baseline liver function tests should be done, then repeated monthly for the first 6 months and every 3 months thereafter.
- Pirfenidone capsules should be taken with meals. This is important to abrogate GI side-effects since co-administration with food results in reduced peak exposure (related to some of the side-effects).
- The importance of sun exposure precautions should be discussed.
  - avoid direct sunlight exposure for extended periods; and
  - use appropriate sunscreen, at least SPF 30.
- Manage patient expectations about treatment results and goals.

7.2 Nintedanib

7.2.1 History

Nintedanib was initially developed as an anti-cancer drug. It is a pleiotropic molecule and is a triple kinase inhibitor. There have been three RCTs of this drug, the Phase II TOMORROW study (NCT00514683) [8] and the two pivotal Phase III clinical trials, INPULSIS I (NCT01335464) and INPULSIS II (NCT01335477) [7]. All three studies were positive based on the primary endpoint of change in the FVC over 52 weeks. In addition, the TOMORROW study and one of the INPULSIS trials showed reduction in the rate of acute exacerbations of IPF. Table 7.3 summarizes the results of RCTs of nintedanib.

7.2.2 Mechanism of Action

Nintedanib is multiple-receptor tyrosine kinase inhibitor that inhibits three receptor families implicated in angiogenesis that also serve as important pro-fibrotic mediators [5]:

- anti-vascular endothelial growth factor (VEGF);
- anti-fibroblast growth factor (FGF); and
- anti-platelet derived growth factor (PDGF).

7.2.3 Dose

Nintedanib is available in 100 and 150 mg tablets, and the standard dose is 150 mg twice a day. Dose adjustments and drug holidays are permissible for intractable or intolerable side-effects.

7.2.4 Pharmacokinetics

Nintedanib is metabolized in the liver via cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp). Drugs that affect these enzymes can alter drug levels and exposure; the following drug interactions should be taken into account:

- P-gp and CYP3A4 inhibitors (e.g., ketoconazole, erythromycin) may result in increased exposure to nintedanib. Dose adjustments or discontinuation of these drugs may be necessary [5].
- CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, and St. John's Wort) should be avoided as they decrease exposure to nintedanib [5].
- Patients with mild hepatic impairment can be treated with nintedanib with close monitoring. Nintedanib is not recommended in moderate or severe liver disease.
- No dose adjustment is required in mild or moderate renal insufficiency. The safety and efficacy of nintedanib in severe renal insufficiency has not been established.

7.2.5 Side-Effects

The most common side-effect is diarrhea, which occurs in over 60 % of patients [5]. This is usually manageable with anti-motility agents and/or dose reduction. A small percentage of patients have to discontinue medication for this side-effect. A full list of side-effects is shown in Table 7.2.

7.2.6 Administration

Prior to prescription of the drug it is important to:

- Carry out baseline liver function testing, then follow up monthly for the first 6 months and every 3 months thereafter.
- Manage patient expectations in terms of diarrhea and management strategies.
- Counsel patient that the medication will not improve lung function and therefore does not make patients feel better.
- It is important for patients to understand that the medication only slows the rate of loss of lung function. The goal is clinical stability, but clinical decline does not necessarily mean that the drug is not working.

Table 7.3 Randomized, controlled trials of nintedanib [7, 8]

Study	Year	Number of patients	Study design	Inclusion criteria	Primary outcomes	Secondary outcomes
TOMORROW [8]	2011	432	Phase II double-blind, placebo-controlled	IPF by ATS/ERS criteria FVC ≥50 % predicted D_{Lco} 30–79 % predicted PaO_2 ≥55 mmHg up to 1500 m altitude PaO_2 >50 mmHg >1500 m altitude	**Annual rate of decline in FVC:** Placebo (0.19 L/year) 150 mg twice daily (0.06 L/year) p = 0.06	**Acute exacerbations:** Placebo (15.7 per 100 patient years) 150 mg twice daily (2.4 per 100 patient years) p = 0.02
INPULSIS-1 [7]	2014	513	Phase III double-blind, placebo-controlled	IPF adjudicated prior to enrollment FVC ≥50 % predicted D_{Lco} 30–79 % predicted	**Annual rate of decline in FVC:** Placebo (−239.9 mL/year) Nintedanib (−114.7 mL/year) p < 0.001	**Time to acute exacerbation:** No difference (p = 0.67)

(continued)

Table 7.3 (continued)

Study	Year	Number of patients	Study design	Inclusion criteria	Primary outcomes	Secondary outcomes
INPULSIS-2 [7]	2014	548	Phase III double-blind, placebo-controlled	IPF adjudicated prior to enrollment FVC ≥50 % predicted D_{Lco} 30–79 % predicted	**Annual rate of decline in FVC:** Placebo (−207.3 mL/year) Nintedanib (−113.6 mL/year) p < 0.001	**Time to acute exacerbation:** HR = 0.38 (p = 0.005)

ATS American Thoracic Society, D_{Lco} diffusing capacity of the lungs for carbon monoxide, *ERS* European Respiratory Society, *FVC* forced vital capacity, *HR* hazard ratio, *IPF* idiopathic pulmonary fibrosis, *L* liters, PaO_2 partial pressure arterial oxygen

7.3 Common Questions for Anti-fibrotic Drug Administration

7.3.1 How Do We Know the Medication Is Working?

Anti-fibrotics slow down the loss of lung function rather than improving it, therefore, it can be difficult for the patient and physician to determine how effectively the drug is working.

The medication will not improve lung function and therefore does not necessarily make patients feel better.

At present there is no test or biomarker to inform if the medication is working in individual patients.

The medication only slows the rate of loss of lung function. Patients should not expect improvement in pulmonary function tests and their disease will likely progress even with therapy.

7.3.2 To Whom Do I Prescribe an Anti-fibrotic Agent?

All patients with IPF are potential candidates for therapy, and initiation of therapy is a discussion to be had with all patients once an accurate diagnosis of IPF has been made. Of note, patients with 'possible' IPF were also included in the INPULSIS trials and therefore there is data to support the use of this agent in such cases as well.

7.3.3 When Do I Start the Drug?

Since both agents only slow the rate of loss of lung function, a cogent argument can be made for starting the drug as soon as possible after the diagnosis, even in the context of patients who are asymptomatic and/or who have normal lung function.

In the clinical trials of both agents, patients with FVC 50–90 % with DLco >30 % were studied [2–4, 7, 8]*, although therapy may be beneficial outside of that lung function range.*

Initiation of an anti-fibrotic drug needs to be considered in the context of the patient's functional status, comorbidities, concomitant medications, risk of side-effects, cost of medication, as well as the patient's wishes and desires.

7.3.4 When Should I Stop the Anti-fibrotic Medication, If Ever?

Although the studies that resulted in their approval were only of intermediate duration (52–72 weeks), there is data attesting to the long-term safety of both agents [9, 10]. *It makes intuitive sense that therapy should be a life-long commitment in the absence of intolerable side-effects.*

7.3.5 What Constitutes a Treatment Failure?

Even if there is apparent progression of disease based on serial reduction in the FVC, it does not mean that the medication is not beneficial and is not a reason to discontinue the drug. There is no proven way to gauge treatment success or failure in individual patients. Even those patients who have a 10 % decrement in their FVCs while on therapy have been shown to do significantly better if they continue on drug [11].

7.3.6 What is the Role of Combination Therapy?

While it likely that combination therapy will be more efficacious than monotherapy, this remains to be proven in the context of appropriate RCTs. Issues to consider with the implementation of combination therapy include:

- *drug-drug interactions;*
- *increased risk of side-effects; and*
- *proof of efficacy.*

7.4 Drugs to Be Avoided

7.4.1 Azathioprine and Steroids

Antimetabolite agents, such as azathioprine, in conjunction with prednisone were formerly regarded as the standard of care for patients with IPF from 2000 up until 2014 [12]. However, the results of the National Institute of Health (NIH) sponsored PANTHER-IPF study (NCT00650091) showed that azathioprine in conjunction with prednisone not only did not help patients, but that it was harmful, leading to increased hospitalizations and mortality in the treatment group [13]. Whether the azathioprine component, the steroid component, or the dose of the combination caused harm is uncertain. This form of combination therapy is still used in other idiopathic interstitial pneumonias (IIPs) including non-specific interstitial pneumonia (NSIP), although the data to support its use in other IIPs is lacking. Whether the deleterious effects of azathioprine can be extrapolated to other similar agents, such as cyclophosphamide is also uncertain. Regardless, immunosuppressive agents should not be used in IPF.

7.4.2 Warfarin

There are theoretical reasons to believe that anti-thrombotic therapy might benefit patients with IPF. This is predicated on the notion of alveolar fibrin-like deposition in the early stages of the disease. However, the ACE-IPF study (NCT00957242) of warfarin versus placebo undertaken by the NIH IPF network showed that warfarin as a treatment for IPF is associated with increased risk of hospitalization and mortality [14]. If patients with IPF require anticoagulation for other indications, such as atrial fibrillation, then these study results should not preclude the implementation of warfarin.

7.4.3 Ambrisentan

This endothelium receptor antagonist was studied for its anti-fibrotic properties in patients with IPF in the ARTEMIS-IPF trial (NCT00768300). This study was stopped early at the suggestion of the Data Safety Monitoring Board for a trend towards increased hospitalization amongst the patients who received the active drug [15].

7.4.4 Other Agents

Other agents shown not to work in the context of completed but negative Phase III clinical trials include [16]:

- imatinib;
- etanercept;
- bosentan;
- macitentan;
- N-acetylcysteine;
- interferon-γ 1b; and
- interferon-α.

7.5 Pulmonary Hypertension

Pulmonary hypertension (PH) is not uncommon in patients with IPF, however, there are no drugs approved at present to treat PH associated with IPF. The current best practice for managing patients with comorbid disease include:

- Look for and treat predisposing factors:
  - obstructive sleep apnea;
  - occult heart failure; and
  - uncorrected/partially corrected hypoxemia.
- Treatment with pulmonary vasodilators is not routinely recommended. If there is any consideration for the off-label treatment of PH in the context of IPF, then patients should be referred to an expert center for further evaluation.

- Beware that more harm than good could result from treatment with pulmonary vasodilator therapy.
  - Worsening ventilation perfusion mismatching with worsening oxygenation.
  - Pulmonary veno-occlusive-like lesions have been described in IPF [17]. Pulmonary veno-occlusive disease is a contraindication for PH therapies as they may precipitate pulmonary edema.
  - Occult heart failure, specifically heart failure with preserved ejection fraction is a common comorbidity (9–16 %) in IPF [18, 19]. This may be worsened by PH therapies.
- Further prospective randomized, placebo-controlled studies of pulmonary vasodilator therapy in IPF are warranted and ongoing.

Key Points

- Two anti-fibrotic agents are currently approved to treat IPF; nintedanib and pirfenidone.
- These drugs slow down rate of loss of lung function, but do not reverse or cure disease.
- The older treatment paradigm of treating inflammation with the combination of azathioprine, corticosteroids, and N-acetylcysteine has been shown to be harmful.
- Several drugs are in development and future therapies are likely to be combination in nature.
- There are no approved agents to treat PH associated with IPF, but this is a target of current clinical trials.

References

1. 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;171:1040–7.

2. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35:821–9.
3. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377:1760–9.
4. King Jr TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2083–92.
5. King CS, Nathan SD. Practical considerations in the pharmacologic treatment of idiopathic pulmonary fibrosis. Curr Opin Pulm Med. 2015;21:479–89.
6. Potts J, Yogaratnam D. Pirfenidone: a novel agent for the treatment of idiopathic pulmonary fibrosis. Ann Pharmacother. 2013;47:361–7.
7. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82.
8. Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011;365:1079–87.
9. Cottin V, Maher T. Long-term clinical and real-world experience with pirfenidone in the treatment of idiopathic pulmonary fibrosis. Eur Respir Rev. 2015;24:58–64.
10. Richeldi L, Costabel U, Selman M, et al. Efficacy and safety of nintedanib in patients with IPF beyond week 52: data from the Phase II TOMORROW trial. Am J Respir Crit Care Med. 2015;191:A1019.
11. Nathan SD, Albera C, Bradford WZ, et al. Effect of continued treatment with pirfenidone following a clinically meaningful decline in percent predicted forced vital capacity in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2015;191:A1016.
12. 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;183:788–824.
13. Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King Jr TE, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366:1968–77.
14. 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;186:88–95.

15. Raghu G, Behr J, Brown KK, Egan JJ, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med. 2013;158:641–9.
16. Tzouvelekis A, Bonella F, Spagnolo P. Update on therapeutic management of idiopathic pulmonary fibrosis. Ther Clin Risk Manag. 2015;11:359–70.
17. Sherner J, Collen J, King CS, Nathan SD. Pulmonary hypertension in idiopathic pulmonary fibrosis: epidemiology, diagnosis, and therapeutic implications. Curr Respir Care Rep. 2012;1:233–42.
18. Nathan SD, Shlobin OA, Ahmad S, Urbanek S, Barnett SD. Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis. Chest. 2007;131:657–63.
19. Raghu G, Nathan SD, Behr J, et al. Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. Eur Respir J. 2015;46:1370–7.

Chapter 8
Non-pharmacologic Management of Idiopathic Pulmonary Fibrosis

8.1 Oxygen Therapy

Supplemental oxygen for patients with idiopathic pulmonary fibrosis (IPF) who experience rest, nocturnal, or exertional desaturation can improve symptoms and quality of life. However, there is no data to show that supplemental oxygen improves survival, although it can improve exercise capacity [1, 2]. Towards the late stages of IPF, high-flow oxygen devices such as an oxymizer or high humidity high-flow nasal cannula may be needed to maintain adequate oxygen saturations and ameliorate symptoms. Oxymizers provide a reservoir of oxygen to draw from on inhalation, which increases the net oxygen concentration delivered to the patient for a given liter flow. High-flow nasal cannulas allow the clinician to control the liter flow (typically 30–50 L/min) and percentage FiO_2, allowing for very high concentrations of oxygen to be delivered by a comfortable interface. Figure 8.1 shows a variety of available devices to provide higher level flow oxygen for patients with high oxygen requirements.

S. Nathan et al., *Guide to Clinical Management of Idiopathic Pulmonary Fibrosis*,
DOI 10.1007/978-3-319-32794-5_8,

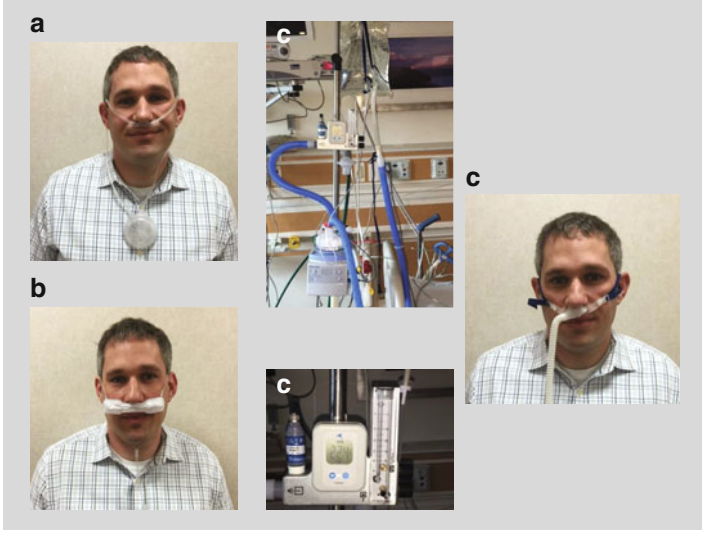

FIGURE 8.1 Higher flow oxygen devices. (**a**) The oxymizer pendant, (**b**) the oxymizer 'moustache', (**c**) high humidity high flow nasal cannula system with capacity to control liter flow and FiO_2 of oxygen

8.2 Pulmonary Rehabilitation

Patients become more symptomatic as IPF progresses and are prone to a vicious cycle of deconditioning. The more breathless they are, the less they can do, which results in the perpetuation of deconditioning. This phenomenon has downstream consequences of increased dyspnea on exertion, easy fatigue, and psychological consequences in the form of anxiety and depression. Clinically significant depression has been described in 23 % of patients with IPF [3]. As disease progresses, these symptoms are exacerbated to the point of interference in the simplest of activities of daily living. Further ramifications include skeletal muscle deconditioning, social isolation, and reduced emotional well-being [4].

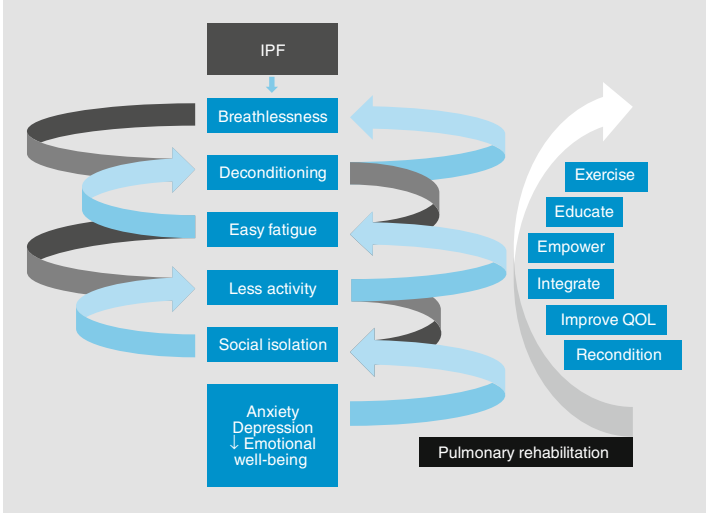

FIGURE 8.2 The impact of idiopathic pulmonary fibrosis on quality of life, with pulmonary rehabilitation as a mitigating intervention. *IPF* idiopathic pulmonary fibrosis, *QOL* quality of life

Pulmonary rehabilitation is a supervised exercise program designed to reverse this vicious cycle of events. In addition to exercise training it also includes disease-specific education and psychosocial support. The goal is to reduce symptoms, optimize functional status, increase participation in daily life activities, and improve psychological well-being (Fig. 8.2).

Pulmonary rehabilitation programs were originally designed for patients with chronic obstructive pulmonary disease (COPD), although there is growing use and emerging data in patients with IPF that attests its utility [5–16] (Table 8.1).

A course of pulmonary rehabilitation is recommended for patients once they become significantly symptomatic or limited. The nature of the course instituted is generally similar to that of patients with COPD. The effects of pulmonary rehabilitation may not be sustained over time and hence the importance of follow-up maintenance pulmonary rehabilitation and ongoing exercise.

Table 8.1 Trials of pulmonary rehabilitation in interstitial lung disease [5–16]

First author, year	Number of patients	Design	Population	Duration	6MWT change (meters)	Notes
Jastrzebski et al. (2006) [5]	31	Prospective	ILD (67.7 % IPF)	6 weeks	NR	Improved QOL and dyspnea
Nishiyama et al. (2008) [6]	28	RCT	IPF	10 weeks	46.3[a]	Improved QOL
Holland et al. (2008) [7]	57	RCT	ILD (59.6 % IPF)	8 weeks	35[a]	Improved exercise capacity and symptoms
Ferreira et al. (2009) [8]	99	Retrospective	ILD (~50 % IPF)	6–8 weeks	56[a]	Improved dyspnea
Ovalevli et al. (2010) [9]	17	Prospective	IPF	12 weeks	45[a]	Improved QOL Home-based study
Rammaert et al. (2011) [10]	17	Prospective	IPF	8 weeks	No change	Improved dyspnea and endurance Home-based study
Kozu et al. (2011) [11]	90	Prospective	IPF (50 %) vs. COPD (50 %)	8 weeks	16.2[a]	Improved dyspnea Benefits not maintained at 6 months

Kozu et al. (2011) [12]	65	Prospective	IPF	8 weeks	Variable	Improved 6MWT and decreased hospitalization if MRC dyspnea 2 or 3
Swigris et al. (2011) [13]	21	Prospective	IPF	6 weeks	61.6[a]	Improved fatigue
Huppman et al. (2013) [14]	402	Observational	ILD (50 % IPF)	4 weeks	46[a]	Improved QOL
Jackson et al. (2014) [15]	21	RCT	IPF	3 month	No change	Increase in exercise time
Vainshelboim et al. (2014) [16]	32	RCT	IPF	12 weeks	81[a]	Improved dyspnea and QOL

6MWT 6 min walk test, *COPD* chronic obstructive pulmonary disease, *ILD* interstitial lung disease, *IPF* idiopathic pulmonary fibrosis, *MRC* medical research council, *NR* not reported, *QOL* quality of life, *RCT* randomized controlled trial
[a]Denotes statistically significant results

8.3 Palliative Care

Palliative care is a valuable adjunctive service that is generally under-utilized or considered late in the patients' disease course. Palliation of symptoms (such as shortness of breath and cough) should be considered early and according to the following guidance:

- Palliation of shortness of breath
  - consider institution of oral morphine in patients with advanced disease;
  - supplemental oxygen may be beneficial (consider high-flow oxygen devices and non-invasive positive pressure ventilation on a case-by-case basis).
- Palliation of cough (this can be the most bothersome symptom to some patients and can be recalcitrant to most forms of therapy)
  - consider treating common causes of cough, like post-nasal drip and gastroesophageal reflux disease;
  - over-the-counter antitussive medications;
  - morphine derivatives such as codeine can be helpful;
  - other agents to consider include gabapentin, baclofen, and thalidomide (only at an expert center).
- Fatigue, evaluate for and treat the following conditions:
  - obstructive sleep apnea;
  - hypothyroidism;
  - anemia; and
  - hypogonadism (low testosterone)
- Asthenia (abnormal weakness or lack of energy)
  - can be a medication-related side effect (eg, pirfenidone) or may be seen in advanced stages of disease;
  - possibly related to an increased work of breathing and a catabolic state due to this;
  - medication changes and supplemental nutrition may be helpful in this regard.

8.4 Hospice Care

Hospices offer a comprehensive program of care to patients and families facing a serious illness, such as IPF, that may result in death in 6 months or less. Its focus is on palliative rather than curative treatment, and its implementation can be at home or in an inpatient setting.

The institution of hospice care may facilitate services that are otherwise unavailable to patients, such as more holistic care including social work and chaplaincy services as well as access to symptom management around the clock. End of life discussions and patient wishes should be made clear early on in the disease course (no matter how uncomfortable or seemingly early/unnecessary) owing to the very unpredictable nature of the disease course in many patients. Futile attempts at mechanical ventilation should be averted in patients with progressive disease as their cause of respiratory failure. Short term attempts at mechanical ventilation are reasonable in those patients who may have a reversible cause of their decompensation or who are listed for lung transplantation.

8.5 Lung Transplantation

IPF is now the most common indication for lung transplantation [17]. Patients who may be candidates for transplant should be referred to a lung transplant center as soon as possible, even if they do not appear to need a lung transplant. This enables them to undergo a comprehensive evaluation and have the appropriate education provided in a timely fashion. This is especially important in the context of a disease that has an unpredictable course. Unfortunately, lung transplantation is an option for only a minority of patients with IPF. Guidelines of who to refer and when to list are shown in Table 8.2; the overarching belief is that referral soon after diagnosis is advisable, given the variable rate of disease progression.

Absolute contraindications to lung transplantation are shown in Table 8.3 [18], although there are certainly a myriad

Table 8.2 Guidelines for referral and listing of patients with idiopathic pulmonary fibrosis for lung transplantation

Guidelines for referral of patients with idiopathic pulmonary fibrosis for lung transplant evaluation
• Histopathologic or radiographic evidence of usual interstitial pneumonitis irrespective of lung function
• Abnormal lung function:
◦ FVC <80 % predicted or D_{Lco} <40 % predicted
• Any dyspnea or functional limitation attributable to lung disease
• Any oxygen requirement, even if only during exertion
Guidelines for listing of patients with idiopathic pulmonary fibrosis for lung transplantation
• 10 % or greater drop in FVC during 6 months of follow-up
• 15 % or greater drop in D_{Lco} during 6 months of follow-up
• Desaturation to SpO_2 < 88 % **or** distance <250 m on 6MWT **or** >50 m decline in 6 min walk distance over a 6 month period
• Pulmonary hypertension on right heart catheterization or echocardiogram
• Hospitalization due to respiratory decline, pneumothorax, or acute exacerbation

Adapted from Weill et al. [18]
6MWT 6 min walking test, D_{LCO} diffusing capacity of the lungs for carbon monoxide, *FVC* forced vital capacity, SpO_2 arterial oxygen saturation

of relative contraindications that must be considered as well. Early referral to a lung transplant center can facilitate early identification of contraindications, some of which may be modifiable with interventions (eg, weight loss), to help improve lung transplant candidacy. Historically, patients with IPF have received more single lung transplants than any other disease group, although, the most recent International Society for Heart and Lung Transplantation registry report indicates that over the last 10 years more bilateral than single

Table 8.3 Contradictions to lung transplantation

- Recent malignancy (other than non-melanoma skin cancer)
- Significant dysfunction of another major organ system (unless combined organ transplantation can be performed)
- Coronary artery disease without re-vascularization
- Acute medical instability (sepsis, myocardial infarction, etc)
- Uncorrectable bleeding diathesis
- Highly virulent or resistant infection (varies by institution):
  - Active tuberculosis;
  - Human immunodeficiency virus;
  - Hepatitis B and C;
  - *Burkholderia cenocepacia* or *Burkholderia gladioli* infection;
  - Multi-drug resistant or smear positive *Mycobacterial abscessus* infection
- Significant chest wall or spinal deformity expected to cause restriction post-transplant
- Body mass index ≥35 (absolute contraindication), 30–34.9 (relative contraindication)
- Non-adherence to medical therapy
- Psychiatric issues that may interfere with ability to follow complex treatment regimen
- Lack of adequate social support system
- Severely limited functional status with poor rehabilitation potential
- Age >70–75 years (varies by institution)

Adapted from Weill et al. [18]

lung transplants have been performed for IPF, with the most recent statistics of 60.2 % versus 39.8 %, respectively [19].

Both types of lung transplant have positives and negatives and which procedure is optimal for patients with IPF remains controversial in the context of individual demographics,

outcomes, and scarce organ availability. The 1-year survival post-transplant is approximately 85 % and the 5-year survival post-transplant is approximately 50 % [19]. There is data to suggest that survival is better with the bilateral procedure [19]; however, there is also data demonstrating that once other factors are accounted for, survival is very similar between the two procedures [17].

Key Points

- Oxygen therapy can improve symptoms and quality of life for patients with IPF who experience rest, nocturnal, or exertional desaturation, especially towards later stages of disease.
- As disease progresses, symptoms can lead to a vicious cycle of deconditioning that has downstream consequences of increased dyspnea, easy fatigue, psychological imbalances (eg, anxiety and depression), skeletal muscle deconditioning, social isolation, and reduced emotional well-being.
- Pulmonary rehabilitation is a supervised exercise program designed to reverse this cycle of events and improve symptoms, whilst providing education and psychological support.
- Palliative care is often ignored or considered late in disease progression, ideally palliation of symptoms should be considered early on.
- Palliative care or hospice consultation should be considered longitudinally as quality of life and prognosis are discussed and re-visited over time.
- Lung transplantation may improve quality and quantity of life in selected patients with little to no comorbidities.
- Early referral for lung transplantation (even at time of diagnosis) is advisable given the unpredictable nature of disease.

References

1. Hallstrand TS, Boitano LJ, Johnson WC, Spada CA, Hayes JG, Raghu G. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. Eur Respir J. 2005;25:96–103.
2. Morrison DA, Stovall JR. Increased exercise capacity in hypoxemic patients after long-term oxygen therapy. Chest. 1992;102:542–50.
3. Ryerson CJ, Berkeley J, Carrieri-Kohlman VL, Pantilat SZ, Landefeld CS, Collard HR. Depression and functional status are strongly associated with dyspnea in interstitial lung disease. Chest. 2011;139:609–16.
4. Swigris JJ, Brown KK, Make BJ, Wamboldt FS. Pulmonary rehabilitation in idiopathic pulmonary fibrosis: a call for continued investigation. Respir Med. 2008;102:1675–80.
5. Jastrzebski D, Gumola A, Gawlik R, Kozielski J. Dyspnea and quality of life in patients with pulmonary fibrosis after six weeks of respiratory rehabilitation. J Physiol Pharmacol. 2006;57 Suppl 4:139–48.
6. Nishiyama O, Kondoh Y, Kimura T, et al. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2008;13:394–9.
7. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax. 2008;63:549–54.
8. Ferreira A, Garvey C, Connors GL, et al. Pulmonary rehabilitation in interstitial lung disease: benefits and predictors of response. Chest. 2009;135:442–7.
9. Ozalevli S, Karaali HK, Ilgin D, Ucan ES. Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Multidiscip Respir Med. 2010;5:31–7.
10. Rammaert B, Leroy S, Cavestri B, Wallaert B, Grosbois JM. Home-based pulmonary rehabilitation in idiopathic pulmonary fibrosis. Rev Mal Respir. 2011;28:e52–7.
11. Kozu R, Senjyu H, Jenkins SC, Mukae H, Sakamoto N, Kohno S. Differences in response to pulmonary rehabilitation in idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. Respiration. 2011;81:196–205.
12. Kozu R, Jenkins S, Senjyu H. Effect of disability level on response to pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2011;16:1196–202.

13. Swigris JJ, Fairclough DL, Morrison M, et al. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. Respir Care. 2011;56:783–9.
14. Huppmann P, Sczepanski B, Boensch M, et al. Effects of inpatient pulmonary rehabilitation in patients with interstitial lung disease. Eur Respir J. 2013;42:444–53.
15. Jackson RM, Gómez-Marín OW, Ramos CF, et al. Exercise limitation in IPF patients: a randomized trial of pulmonary rehabilitation. Lung. 2014;192:367–76.
16. Vainshelboim B, Oliveira J, Yehoshua L, et al. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. Respiration. 2014;88:378–88.
17. Brown AW, Kaya H, Nathan SD. Lung transplantation in IIP: a review. Respirology. 2015:1–12 [Epub ahead of print].
18. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014 – an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015;34:1–15.
19. Yusen RD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-second official adult lung and heart-lung transplantation report – 2015; focus theme: early graft failure. J Heart Lung Transplant. 2015;34:1264–77.

Chapter 9
The Future for Idiopathic Pulmonary Fibrosis

The future of idiopathic pulmonary fibrosis (IPF) is bright and dynamic with innovation and discovery occurring at a rapid pace. In fact, at the time of writing, there were 107 open and enrolling studies involving IPF diagnosis and treatment listed on www.clinicaltrials.gov. Future discoveries are bound to occur at the genomic level, providing a clearer understanding of single nucleotide polymorphisms (SNPs) that predispose to the disease or predetermine the course in individual patients. As this knowledge evolves, it is conceivable that the classification of IPF and perhaps the broad group of idiopathic interstitial pneumonias (IIPs) will be driven by the genomic profile of patients rather than their radiographic or pathologic phenotype. Genomic signature recognition and patterns may enable biomarker development, in turn allowing for more accurate non-invasive diagnosis of IPF, other IIPs, and chronic hypersensitivity pneumonitis (HP). It is also conceivable that the role of pharmacogenomics will evolve such that individualized or tailored therapies can be matched to patients' genomic profile, thereby improving the efficacy of prescribed medications and reducing the likelihood of associated toxicities.

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9.1 Medical Therapies

Typically, any drug that meets the bar for regulatory approval has to go through three phases of testing:

- Phase I trials in healthy volunteers (primarily for safety and pharmacokinetics);
- Phase II trials in patients with the disease for further safety, efficacy, and dosing evaluation; and
- Phase III trials that are the pivotal studies to demonstrate efficacy prior to approval.

Currently, there are no novel IPF drugs that are in Phase III clinical trials. Therefore, it is likely that it will be a few years before any additional novel agents are approved for IPF. However, there are some agents that are available and approved for other conditions that are of interest as potential therapies for IPF. Ultimately, it is likely that management of this complex disorder will include multimodality therapy targeting different pathways and consequences of the disease. The sections below outline some of the therapies being studied as possible treatments for IPF.

9.1.1 Drugs Currently Approved for Other Indications

9.1.1.1 Cotrimoxazole

Cotrimoxazole is an antibiotic that combines trimethoprim and sulfamethoxazole and is commonly available for the treatment of a variety of bacterial infections. Patients with IPF are susceptible to occult infection and there is evidence of alterations in the microbiome in such individuals [1]. In 1996, the clinical improvement of a patient with advanced fibrotic lung disease who was treated with cotrimoxazole was

observed, and subsequently 14 patients also demonstrated improvement [2]. These findings led Varney et al. [2] to conduct a pilot trial of 20 patients with fibrotic IIPs, whereby treatment with cotrimoxazole demonstrated improvements in functional status and forced vital capacity (FVC). This trial was followed by a larger randomized controlled trial (RCT) of 181 patients that demonstrated improvements in mortality and decreased infections in those who were adherent to therapy [3]. At time of writing, an additional Phase III RCT assessing the efficacy of cotrimoxazole is enrolling participants (NCT01777737) [4].

9.1.2.2 Azithromycin

Azithromycin is a commonly used antibiotic that has been demonstrated to attenuate development of bleomycin-induced pulmonary fibrosis in a mouse model [5] and is postulated to reduce cough. At time of writing, a small Phase III double-blind study is enrolling patients with IPF to assess the effects of azithromycin on cough (NCT02173145) [6].

9.1.3.3 Omeprazole

Omeprazole is a proton pump inhibitor that is approved for the treatment of gastroesophageal reflux disease (GERD). Patients with IPF commonly have comorbid GERD, and GERD is considered a risk factor for IPF development (Chap. 5) [7, 8]. Anti-reflux therapies are therefore associated with a reduction in mortality in patients with IPF [7]. Additionally, there is data to suggest that anti-reflux therapy slows the rate of decline in the FVC [8]. At time of writing, a Phase II pilot RCT to assess the efficacy of omeprazole for treatment of IPF-associated cough is enrolling participants [9].

9.1.4.4 Riociguat

Riociguat is approved for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. The efficacy and safety of riociguat is currently being studied in a Phase II trial, RISE-IIP, of patients with any of the IIPs and associated pulmonary hypertension (NCT02138825) [10]. This is the first trial to include all of the IIPs together and, by virtue of its higher prevalence, the majority of enrolled patients are likely to have IPF.

9.1.5.5 Sirolimus

Sirolimus is a macrolide antibiotic that is approved for immunosuppression in transplant patients. This drug exhibits immunosuppressive activity by inhibiting the activation of mammalian Target of Rapamycin (mTOR) and thus the activation and proliferation of B and T cells and the activation of non-immune cells. At time of writing, a Phase II pilot study to determine if sirolimus decreases the number of circulating fibroblasts in patients with IPF is ongoing [11]. Sirolimus has been associated, however, with the development of pneumonitis in rare cases [12].

9.1.6.6 Rituximab

Rituximab is an anti-CD20 monoclonal antibody that destroys B cells. It is approved for autoimmune diseases such as rheumatoid arthritis. Currently, a phase II study (NCT01969409) is ongoing evaluating the effects of rituximab on production of autoantibodies in patients with IPF [13]. As noted in Chap. 6, there is some data to suggest that this drug may have a role in the treatment of acute exacerbation of IPF (AE-IPF) [14].

9.1.2 Novel Therapies

9.1.1.1 FG-3019

FG-3019 is a human monoclonal antibody that targets connective tissue growth factor (CTGF) and is under early investigation for a number of indications, including IPF. Phase II trials to evaluate the safety and tolerability of FG-3019 in patients with IPF are currently underway (NCT01262001), with the primary end-point being change in FVC [15]. Based on encouraging initial results from preliminary data, a second higher-dose group has been added (NCT01890265) [16]. To date, over 200 patients have been enrolled in the various trials of this drug.

9.1.2.2 Tipelukast (MN-001)

Tipelukast is an orally available, small, novel molecule that has been demonstrated to have anti-fibrotic and-anti-inflammatory properties in preclinical models. Tipelukast exerts such effects through inhibition of 5-lipoxygenase (5-LO) and phosphodiestereases, and is a leukotriene (LT) receptor antagonist. The novel aspect of this drug is its inhibitory effect on the 5-LO/LT pathway (a factor thought to be pathogenic in the development of fibrosis) [17]. In 2015, the US Food and Drug Administration issued Fast Track designation for the development of tipelukast for IPF, which is now entering Phase II clinical trials to assess safety and tolerability (NCT02503657) [18].

9.1.3.3 BMS-986020

BMS-986020 is a lysophosphatidic acid receptor antagonist that has shown promising results in preclinical trials and has entered Phase II trials (NCT01766817). The primary endpoint is to reduce the rate of decline in FVC and to be well tolerated by patients [19].

9.1.4.4 SAR156597

SAR156597 is a bispecific monoclonal antibody directed against interleukin (IL)-4 and IL-13, two cytokines implicated in the pathogenesis of IPF. In 2015, the Phase II ESTAIR trial was initiated to evaluate safety and efficacy of SAR156597 at two dose levels for 52 weeks (NCT02345070) [20].

9.1.5.5 PRM-151

PRM-151 is a recombinant form of the endogenous protein, pentraxin-2, which acts as a monocyte and macrophage differentiation factor and is believed to have anti-fibrotic properties [21]. At time of writing, a Phase II pilot study to assess the efficacy and safety of PRM-151 in patients with IPF is underway (NCT02550873).

9.1.6.6 BG00011

BG00011 (alternatively known as STX 100) is a humanized monoclonal antibody that is administered subcutaneously and targets alpha v beta 6 (αvβ6) integrin. In 2015 a Phase II dose escalation study assessing the immunogenicity of BG00011 in patients with IPF was initiated and is currently ongoing (NCT01371305) [22].

9.1.7.7 Lebrikizumab

Lebrikizumab is a humanized monoclonal antibody that targets IL-13, and is being investigated for the treatment of IPF, asthma, chronic obstructive pulmonary disease, and atopic dermatitis. At time of writing, a Phase II trial investigating the safety and efficacy of lebrikizumab as a monotherapy or in combination with pirfenidone is ongoing (NCT01872689) [23].

9.2 Other Areas of Investigation

9.2.1 Laparoscopic Reflux Surgery

Given the known association between IPF and GERD, there has been speculation that anti-reflux surgery may halt the progression of IPF. WRAP-IPF is a Phase II study investigating the effects of anti-reflux surgery on decline in FVC [24].

9.2.2 Pulmonary Rehabilitation

Studies to determine the effect of pulmonary rehabilitation on fibrotic lung disease have been carried out [25]; several are completed, and a couple of trials are currently open and recruiting (Table 9.1).

9.2.3 Cryobiopsy

Cryobiopsy as a means of diagnosis of IPF is being studied in patients with interstitial lung disease who were due to undergo videothoracoscopy-assisted surgical lung biopsy [26].

9.2.4 Stem Cells

Stem cell therapy is an area currently under investigation as a treatment for IPF; Phase I and II studies designed to assess the effectiveness of stem cells on pulmonary fibrosis are ongoing [27, 28]. Patients frequently pose questions about stem cell therapy. Unfortunately, there is a lot of false hope generated by unregulated websites with unproven claims of successful treatment of IPF. It is important for patients to be aware that stem cell therapy needs to be subjected to the appropriate clinical trials before it can be recommended as a therapy for IPF.

Table 9.1 Summary of open clinical studies assessing pulmonary rehabilitation for patients with pulmonary fibrosis

Study title (clinical trial identifier)	Study design	Comments
Long term effects of an inpatient pulmonary rehabilitation program in patients with pulmonary fibrosis (NCT01772667)	Randomized, open label	Effects at 3 months of 3 weeks inpatient rehabilitation
The NIH exercise therapy for advanced lung disease trials: response and adaptation to aerobic exercise in patients with interstitial lung disease (NCT02019641)	Randomized, open label	10 weeks of outpatient rehabilitation

9.2.5 *Treatment of Acute Exacerbation of Idiopathic Pulmonary Fibrosis*

There are currently no proven therapies for the treatment of AE-IPF, although, two studies are underway to determine if they can decrease the mortality of this deadly complication of IPF:

- Plasmapheresis, rituximab, and steroids — Phase I/II study (NCT01266317) to assess feasibility, safety, and efficacy in 10 patients with AE-IPF [29].
- Cyclophosphamide — Phase III study (NCT02460588) to assess safety and efficacy in approximately 120 patients with IPF [30].

9.2.6 *Biomarkers*

Biomarkers to diagnose IPF, identify patients at risk for IPF, screen patients with subclinical disease, predict disease

progression, and predict response to therapy are being explored (see Chap. 5).

9.3 Conclusion

Considerable advancements have been made in recent years in the treatment of IPF. Improved understanding of the pathogenesis of the disease has led to the development of two pharmacologic treatments for IPF with demonstrated efficacy in RCTs. Despite this huge leap forward, IPF remains a deadly disease and there is much work to be done. It is hoped that continued research into the genetic basis and pathophysiologic mechanisms of IPF will lead to improved techniques for earlier diagnosis and more effective treatment. Until that time, therapy will rely on the use of currently approved medications in combination with supportive care including oxygen, pulmonary rehabilitation, symptom and comorbidity management, and lung transplantation when appropriate.

Key Points

- Agents that are approved for other conditions are currently being explored as potential therapies for IPF.
- There are several novel treatments in the early drug development stages for IPF.
- The future therapeutic paradigm is likely one of combination drug therapy.
- There are no drugs approved for PH in any IIP, however, riociguat is currently in Phase II studies for comorbid PH and IPF.
- Future developments in pharmacogenomics might enable the course of disease in individual patients to be determined, biomarker development (therefore non-invasive diagnosis of IPF), and tailored therapies for IPF and other forms of IIP.

References

1. Han MK, Zhou Y, Murray S, et al. Lung microbiome and disease progression in idiopathic pulmonary fibrosis: an analysis of the COMET study. Lancet Respir Med. 2014;2:548–56.
2. Varney VA, Parnell HM, Salisbury DT, Ratnatheepan S, Tayar RB. A double blind randomised placebo controlled pilot study of oral co-trimoxazole in advanced fibrotic lung disease. Pulm Pharmacol Ther. 2008;21:178–87.
3. Shulgina L, Cahn AP, Chilvers ER, et al. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: a randomised controlled trial. Thorax. 2013;68:155–62.
4. Fundación Pública Andaluza para la gestión de la Investigación en Sevilla; Junta de Andalucia. Pilot study Phase III to evaluate the efficacy and safety of trimethoprim-sulfamethoxazole in the treatment of idiopathic pulmonary fibrosis. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://www.clinicaltrials.gov/show/NCT01777737.
5. Wuyts WA, Willems S, Vos R, Vanaudenaerde BM, et al. Azithromycin reduces pulmonary fibrosis in a bleomycin mouse model. Exp Lung Res. 2010;36:602–14.
6. University Hospital Inselspital Berne. Azithromycin for the treatment of cough in idiopathic pulmonary fibrosis- a clinical trial. In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT02173145.
7. 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;184:1390–4.
8. Lee JS, Collard HR, Anstrom KJ, et al. Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. Lancet Respir Med. 2013;1:369–76.
9. Newcastle-upon-Tyne Hospitals NHS Trust. A randomised, placebo-controlled trial of omeprazole in idiopathic pulmonary fibrosis (IPF). In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT02085018.

10. Bayer. A randomized, double-blind, placebo-controlled Phase II study to investigate the efficacy and safety of riociguat (0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg TID) in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonias (IIP). In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT02138825.
11. University of Virginia; National Heart, Lung, and Blood Institute (NHLBI). Double-blind placebo-controlled pilot study of sirolimus in IPF. In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT01462006.
12. Singh U, Gupta A, Jasuja S. Sirolimus-induced pneumonitis. Indian J Nephrol. 2009;19:80–1.
13. University of Alabama at Birmingham; National Institutes of Health (NIH). Autoantibody reduction therapy in patients with idiopathic pulmonary fibrosis (ART-IPF). In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT01969409.
14. Donahoe M, Valentine VG, Chien N, et al. Autoantibody-targeted treatments for acute exacerbations of idiopathic pulmonary fibrosis. PLoS One. 2015;10:e0127771.
15. Raghu G, Scholand MB, de Andrade J, et al. Phase 2 trial of FG-3019, anti-CTGF monoclonal antibody, in idiopathic pulmonary fibrosis (IPF): preliminary safety and efficacy results. Eur Respir J. 2012;40 (Suppl 56):511s.
16. FibroGen press release: FibroGen announces one-year data supporting the safety and efficacy profilr of FG-3019 in patients with idiopathic pulmonary fibrosis. 2014. http://investor.fibrogen.com/phoenix.zhtml?c=253783&p=irol-newsArticle&ID=1982805 Accessed 29 Mar 2016.
17. MediciNova: MN-001 Dibrotic diseases. (2016). http://medicinova.com/clinical-development/core/mn-001-nash/. Accessed 18 Feb 2016.
18. MediciNova. A randomized, placebo-controlled, double-blind six month study followed by an open-label extension Phase to evaluate the efficacy, safety and tolerability of MN-001 in subjects with idiopathic pulmonary fibrosis (IPF). In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US).

2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT02503657.
19. Bristol-Myers Squibb. Safety and efficacy of a lysophosphatidic acid receptor antagonist in idiopathic pulmonary fibrosis. In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT01766817.
20. Sanofi. Efficacy and safety of SAR156597 in the treatment of idiopathic pulmonary fibrosis (IPF): A randomized, double-blind, placebo-controlled, 52-week dose-ranging study. In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT02345070.
21. Promedior press release: Promedior announces initiation of a Phase 2 clinical study of PRM-151 in idiopathic pulmonary fibrosis (IPF). 2015. http://www.promedior.com/news/releases/2015%200907%20Promedior%20Announces%20Initiation%20of%20Phase%202%20Study%20of%20PRM-151%20in%20IPF.html. Accessed 18 Feb 2016.
22. Biogen. Randomized, double-blind, placebo-controlled, multiple dose, dose-escalation study of STX-100 in patients with idiopathic pulmonary fibrosis (IPF). In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT01371305.
23. Hoffmann-La Roche. A Phase II, randomized, double-blind, placebo-controlled, study to assess the efficacy and safety of lebrikizumab in patients with idiopathic pulmonary finbrosis. In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT01872689.
24. University of California; National Heart, Lung, and Blood Institute (NHLBI). Weighing risks and benefits of laparoscopic anti-reflux surgery in patients with idiopathic pulmonary fibrosis. In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT01982968.
25. ClinicalTrials.gov. Results using the search term 'pulmonary rehabiliation and ipf'. 2016. https://clinicaltrials.gov/ct2/results?term=pulmonary+rehabilitation+and+ipf&Search=Search. Accessed 29 Mar 2016.

26. Laval University. Diagnostic yield of transbronchial cryobiopsies in subjects with interstitial lung disease. In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT02235779.
27. Clinica Universidad de Navarra, Universidad de Navarra. Treatment of idiopathic pulmonary fibrosis with bone marrow derived mesenchymal stem cells. In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT01919827.
28. Kasiak Research Pvt. Ltd. A prospective, multicentric, Phase I/II, open label, randomized, interventional study to evaluate the safety and efficacy of intravenous autologous adipose derived adult stem cells for treatment of idiopathic pulmonary fibrosis (IPF). In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT02135380.
29. University of Pittsburgh. Open-label, feasibility study of combined plasma exchange (PEX), rituximab, and corticosteroids in patients with acute idiopathic pulmonary fibrosis exacerbations. In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016. Available from: https://clinicaltrials.gov/show/NCT01266317.
30. Assistance Publique – Hôpitaux de Paris. Cyclophosphamide added to corticosteroid in the treatment of acute exacerbation of idiopathic pulmonary fibrosis: a placebo-controlled randomized trial. In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2000- [cited 18 Feb 2016]. Available from: https://clinicaltrials.gov/show/NCT02460588.