Idiopathic Pulmonary Fibrosis

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Joseph P. Lynch III and John A. Belperio

Abstract

Idiopathic pulmonary fibrosis (IPF) is a specific clinicopathologic syndrome presenting in older adults with the predominant features: dyspnea, dry cough, restrictive defect on pulmonary function tests (PFTs), hypoxemia, characteristic abnormalities on high-resolution thin section computed tomographic (HRCT) scans, usual interstitial pneumonitis (UIP) pattern on lung biopsy. Surgical lung biopsy is the gold standard of diagnosis, but the diagnosis can be established in some cases by HRCT, provided the clinical features are consistent. The cause of IPF is unknown. However, IPF is more common in adults >60 years old, smokers (current or ex), and patients with specific occupational or noxious exposures. Familial IPF, associated with several distinct genetic mutations, accounts for 1.5–3% of cases. Unfortunately, the prognosis is poor, and most patients die of respiratory failure within 3–6 years of diagnosis. However, the course is highly variable. In some patients, the disease is fulminant, progressing to lethal respiratory failure within months, whereas the course may be indolent, spanning >5 years in some patients. Therapy has not been proven to alter the course of the disease or influence mortality, but recent studies with pirfenidone and tyrosine kinase inhibitors are promising. Lung transplantation is the best therapeutic option, but is limited to selected patients with severe, life-threatening disease and no contraindications to transplant.

Keywords

Idiopathic pulmonary fibrosis • Cryptogenic fibrosing alveolitis • Usual interstitial pneumonia • Idiopathic interstitial pneumonia • Honeycombing

J.P. Lynch III, MD (✉) • J.A. Belperio, MD
Division of Pulmonary and Critical Care Medicine,
David Geffen School of Medicine at UCLA,
Los Angeles, CA, USA
e-mail: jplynch@mednet.ucla.edu

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Idiopathic pulmonary fibrosis (IPF) is a specific clinicopathologic syndrome presenting in older adults and associated with the following features: dyspnea, dry cough, restrictive defect on pulmonary function tests (PFTs), hypoxemia (at rest or with exercise), characteristic abnormalities on thin section high-resolution computed tomographic (HRCT) scans, the presence of usual interstitial pneumonitis (UIP) pattern on lung biopsy or CT, a progressive course [1, 2]. The terms IPF and cryptogenic fibrosing alveolitis (CFA) are synonymous [1]. IPF is associated with the *histopathological pattern* of UIP [1–4], but UIP pattern can also be found in other diseases (e.g., connective tissue disease (CTD), asbestosis, diverse occupational, environmental, or drug exposures) [1, 5]. Thus, the diagnosis of IPF can be established only when these and other alternative etiologies have been excluded [1]. IPF is the most common of the idiopathic interstitial pneumonias (IIPs), constituting 47–71% of cases [2, 6]. Other IIPs (e.g., respiratory bronchiolitis interstitial lung disease (RBILD), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), lymphoid interstitial pneumonia (LIP), nonspecific interstitial pneumonia (NSIP), and cryptogenic organizing pneumonia (COP)) are distinct entities, with marked differences in prognosis and responsiveness to therapy [1, 3, 4]. These entities are discussed elsewhere in this book. In this review, we restrict our discussion to idiopathic UIP.

A *definitive* diagnosis of IPF requires the demonstration of UIP by surgical lung biopsy (SLB) unless the HRCT features are classified as "definite" according to the recently published ATS/ERS/JRS/ALAT guidelines on IPF [1a, 3]. Because of small sample size and disease heterogeneity, transbronchial lung biopsies or percutaneous needle biopsies are *not* adequate to diagnose UIP [1, 3]. However, SLB is expensive and has potential morbidity, and many clinicians are reluctant to recommend SLB for patients with suspected IPF. In clinical practice, SLB is performed in <30% of patients with IPF [2, 7]. Currently, many clinicians rely upon HRCT to corroborate the diagnosis of UIP [1, 8, 9]. SLBs are performed primarily in patients manifesting atypical or indeterminate patterns on CT [8, 10, 11].

Table 10.1 Histopathology of usual interstitial pneumonia

Cardinal features
Geographic and temporal heterogeneity
Alternating zones of normal and abnormal lung
Predilection for peripheral (subpleural) and basilar regions
Fibroblastic foci
Excessive collagen and extracellular matrix
Honeycomb change
Additional features
Smooth muscle hypertrophy
Metaplasia and hyperplasia of type II pneumocytes
Destroyed and disrupted alveolar architecture
Traction bronchiectasis and bronchioloectasis
Secondary pulmonary hypertension

What Are the Characteristic Histopathological Features of UIP?

The cardinal histopathological findings of UIP include: geographic and temporal heterogeneity, alternating zones of normal and abnormal lung, predilection for peripheral (subpleural) and basilar regions, fibroblastic foci (aggregates of proliferating fibroblasts and myofibroblasts), excessive collagen and extracellular matrix (ECM), honeycomb change (HC) [3] (Table 10.1). Additional features include: smooth muscle hypertrophy, metaplasia and hyperplasia of type II pneumocytes, destroyed and disrupted alveolar architecture, traction bronchiectasis and bronchioloectasis, secondary pulmonary hypertensive changes [3]. Histopathological features of UIP are discussed by Drs. Colby and Leslie elsewhere in this book and will not be further addressed here.

Clinical Features of UIP

Cardinal features of UIP include dry cough, exertional dyspnea, end-inspiratory velcro rales, diffuse parenchymal infiltrates on chest radiographs, honeycomb cysts on HRCT scans, a restrictive defect on PFTs, and impaired oxygenation [1, 2] (Table 10.2). Physical examination reveals crackles in >80% of patients with UIP, and clubbing in 20–50% [1, 2, 6]. IPF/UIP

Table 10.2 Clinical features of idiopathic pulmonary fibrosis

Shortness of breath, exercise limitation
Cough
Age > 50 years
Crackles on physical examination (>80%)
Clubbing on physical examination (>20–50%)
Restrictive defect (reduced lung volumes) on pulmonary function tests
Hypoxemia (at rest or with exercise)
Characteristic HRCT scan

progresses inexorably over months to years [1, 2, 6]. Extrapulmonary involvement does not occur [6] and should suggest other disorders (particularly CTD-associated pulmonary fibrosis) [12]. However, certain diseases such as ischemic cardiac disease [13, 14], deep venous thrombosis [13], diabetes mellitus [15], and gastroesophageal reflux (GER) [16] are more common in patients with IPF.

Laboratory studies are nonspecific. Elevations in the erythrocyte sedimentation rate occur in 60–90% of patients with IPF; circulating antinuclear antibodies (ANAs) or rheumatoid factor is detected in 10–26% [1, 6, 17]. Two recent retrospective studies cited circulating antineutrophil cytoplasmic antibodies (ANCAs) in a distinct minority of patients with IPF [18, 19]. None of these serological findings correlate with extent or severity of disease or predict prognosis [2, 6]. However, for new cases of *suspected* IPF, we obtain serologies for CTD [e.g., ANA and antibodies to SSA, SSB, Scl-70 (scleroderma), Sm, RNP, Jo-1, double stranded DNA] [5, 12, 20] and hypersensitivity pneumonitis (HP) to rule out those disorders as treatment and prognosis may differ from IPF.

Elevations of the glycoprotein KL-6 [21] and lung surfactant proteins (SP)-A and -D [22] have been noted in serum and bronchoalveolar lavage fluid (BALF) in patients with IPF, and may have prognostic value. These assays are available in only a few research laboratories, and additional studies are required to assess their specificity and clinical role.

Clinical Course and Prognosis

The clinical course of IPF is heterogeneous, but most patients worsen gradually (over months to years) [2]. Mean survival from the onset of symptoms is 3–5 years [2, 6, 8, 23–25]. However, the course is highly variable, and some patients remain stable for years [2, 6, 26]. In others, the course is rapid, with fatal respiratory failure evolving over a few months [27]. Additionally, some patients have gradual progression over years, followed by acute exacerbations, associated with abrupt and often fatal hypoxemic respiratory failure [26, 28]. Spontaneous remissions do not occur [2, 6]. Ten-year survival is less than 15% [2, 6, 23, 24, 29, 30].

The major cause of death is respiratory failure [31, 32]. Surveys of IPF patients in the UK and USA noted that progression of lung disease accounted for 72% [32] and 60% [33] of deaths, respectively. Other causes include pulmonary embolism [31], cardiac failure, cerebrovascular accidents (primarily in the elderly), and lung cancer [31, 34]. Lung cancer occurs in 4–13% of patients with IPF [2, 34]. The risk is higher in smokers, but the heightened risk of lung cancer is not solely due to the effects of cigarette smoking [34].

Acute Exacerbations of IPF

A subset of patients with IPF develop an accelerated course often as a terminal event, with features of diffuse alveolar damage (DAD) or organizing pneumonia on lung biopsy or autopsy [28, 35]. This syndrome, termed "acute exacerbation of IPF," is indistinguishable from idiopathic AIP [36], and is similar to acute respiratory distress syndrome (ARDS). The factors responsible for this accelerated phase of IPF are unknown, but viral infections, high concentrations of oxygen, or drug reactions are plausible etiologic factors [28, 36]. Although this syndrome is usually fatal, some patients respond dramatically to high dose corticosteroids (e.g., pulse methylprednisolone) [28, 35].

Incidence and Epidemiology of IPF

IPF is rare; depending upon criteria used to define IPF, overall rates (per 100,000) range from 14.0 to 42.7 (prevalence) and from 6.8 to 16.3 (incidence) [1, 33, 37, 38]. The incidence of IPF increased progressively in the UK between 1991 and 2003 [38]. Similarly, in the USA, deaths attributed to pulmonary fibrosis increased significantly from 1992 to 2003 (>28% increase) [33]. IPF typically affects older adults, with peak onset after the sixth decade of life; there is a slight male predominance [1, 33, 37, 38]. IPF is more common in current or former smokers [11, 39–41]. The incidence of IPF and mortality rates is markedly higher in the elderly. A retrospective study in the USA cited a prevalence (per 100,000) of 4.0 among persons aged 18–34 years and 227 among those 75 years or older [37]. In the USA, projected deaths due to IPF (per million) in 2008 were as follows: 18 (ages 45–54), 71 (age 55–64), 306 (age 65–74), 827 (age 75–84), 1,380 (age > 85) [33]. Despite its rarity, IPF accounts for more than 16,000 deaths annually in the USA [33]. Interestingly, mortality rates from IPF exhibit a seasonal variation, with the highest rates in the winter months [42]. In the USA, mortality rates from IPF are climbing more rapidly in women than men [33], possibly reflecting the impact of cigarette smoking. IPF is rare in children [except in kindreds with surfactant protein C (SFPC) mutations] [43].

Epidemiology

Environmental factors likely play a contributory role [39]. Exposure to or inhalation of minerals, dusts, organic solvents, urban pollution, or cigarette smoke has been associated with an increased risk for IPF in some studies [44]. A meta-analysis of six case–control studies found six exposures associated with IPF: ever smoking, agriculture farming, livestock, wood dust, metal dust, stone/sand [39]. Interstitial lung disease (ILD) is an occupational disease in coal miners, sandblasters, and workers exposed to asbestos, tungsten carbide, beryllium, and other metals [44], suggesting that at least some cases of "idiopathic" UIP represent pneumoconioses. The considerable variability that exists in the development of pulmonary fibrosis among workers exposed to similar concentrations of fibrogenic/organic dusts implies that genetic factors likely modulate the lung injury [39].

Infections may trigger exacerbations of IPF [44]. Epstein–Barr virus (EBV), cytomegalovirus (CMV), human herpes virus (HHV-8), or hepatitis C have been considered as *possible* agents in the pathogenesis of IPF, but the role of these (or other infectious agents) remains conjectural [44].

Chronic aspiration secondary to GER has been suggested as a risk factor for IPF [16], but a causal relationship between acid aspiration and IPF remains controversial. Esophageal reflux has been noted in more than two-thirds of patients with IPF awaiting lung transplant (LT) [16, 45]. Aspiration of stomach contents may cause lung injury and fibrosis [44]. Among LT recipients (with or without IPF), GER can cause allograft injury [46] and appears to be a risk factor for bronchiolitis obliterans syndrome (BOS) [46, 47]. In a small series of patients with early IPF, aggressive treatment of GER was associated with stabilization or improvement of lung function [45]. Additional studies are required to assess the role of GER or aspiration in the pathogenesis or progression of IPF and therapeutic strategies to prevent or reduce GER.

Genetics

Familial IPF, which accounts for 0.5–3% of cases of IPF, is indistinguishable from nonfamilial forms, except patients tend to be younger with the familial variant [40, 41, 48, 49]. Progression of early asymptomatic ILD to symptomatic IPF may occur over a span of decades [40]. An autosomal dominant trait with variable penetrance is suspected in most, but not all, cases [41, 48, 49]. In some patients, genetic polymorphisms for interleukin-1 receptor antagonist (IL-1ra) and tumor necrosis factor-α (TNF-α) may be important in determining risk [48]. Mutations in SFPC genes have been associated

with familial interstitial pneumonitis (FIP) that includes UIP, NSIP, and other histological variants [43]. Further, germ line mutations in the genes encoding telomerase reverse transcriptase (hTERT) and telomerase RNA (hTR) were implicated in dyskeratosis congenita, a rare hereditary disorder associated with pulmonary fibrosis and aplastic anemia [50]. These mutations result in telomere shortening, which has been implicated in age-related disease. Interestingly, older age and smoking also cause telomere shortening [50]. Further, short telomeres were more common in FIP and sporadic IPF compared to controls, even when mutations in hTERT and hTR were lacking [51, 52]. Pulmonary fibrosis may also complicate diverse genetic disorders such as Hermansky–Pudlak syndrome [48], familial hypocalciuric hypercalcemia [49], neurofibromatosis [49], etc. IPF occurs in Caucasians and in nonwhites; prevalence among different ethnic groups has not been studied [1]. A retrospective study of IPF in New Zealand cited a lower incidence in those of Maori or Polynesian descent than in those of European descent [53].

Differences in susceptibility to fibrogenic agents may reflect genetic polymorphisms [49]. Animal models involving different inbred strains of rodents demonstrate dramatic variability in the lung inflammatory/fibrotic response to injurious agents. We believe that IPF is a heterogeneous disorder caused by a number of environmental/occupational exposures *in combination with* genetic predispositions.

Radiographic Manifestations of IPF

Conventional Chest Radiographs

Chest radiographs in IPF typically reveal diffuse, bilateral interstitial or reticulonodular infiltrates, with a predilection for basilar and peripheral (subpleural) regions [2, 54]. The proclivity for peripheral lung zones is best demonstrated by HRCT [9] (Figs. 10.1–10.5). As the disease progresses, lung volumes shrink. Intrathoracic lymphadenopathy or pleural thickening is not evident on chest radiographs, but may be noted on CT scans [9]. Similar radiographic features are observed in asbestosis and CTD-associated pulmonary fibrosis [5, 9]. Chest radiographs have limited prognostic value, but serial radiographs (including old films) may gauge the pace and evolution of the disease.

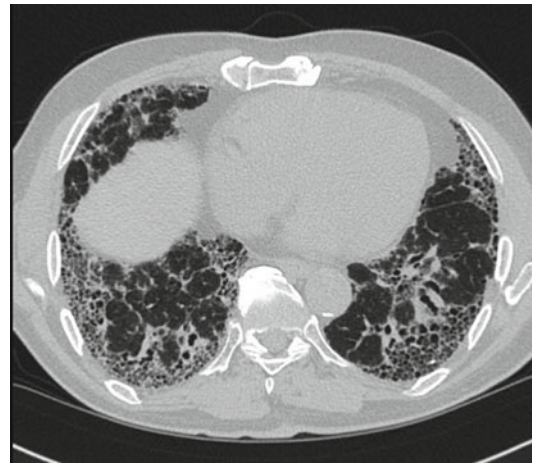

Fig. 10.1 Usual interstitial pneumonia. HRCT scan shows extensive peripheral (subpleural) honeycomb change. No significant ground-glass opacities

High Resolution Thin Section CT Scan

Thin section high-resolution computed tomographic (CT) scans are invaluable to diagnose and stage IPF [8, 9, 54]. HRCT can assess the nature and extent of parenchymal abnormalities, narrow the differential diagnosis, and in some patients, substantiate a specific diagnosis, obviating the need for SLB.

How Reliable Is CT to Establish the Diagnosis of UIP?

Cardinal features of UIP on HRCT scan include: heterogeneous, "patchy" involvement; predilection for peripheral (subpleural) and basilar regions; HC; coarse reticular opacities (interlobular and intralobular septal lines); traction bronchiectasis or bronchioloectasis; minimal or no ground-glass opacities (GGOs) [8, 9, 54] (Table 10.3). The 2011 guidelines suggest that the presence of four features:

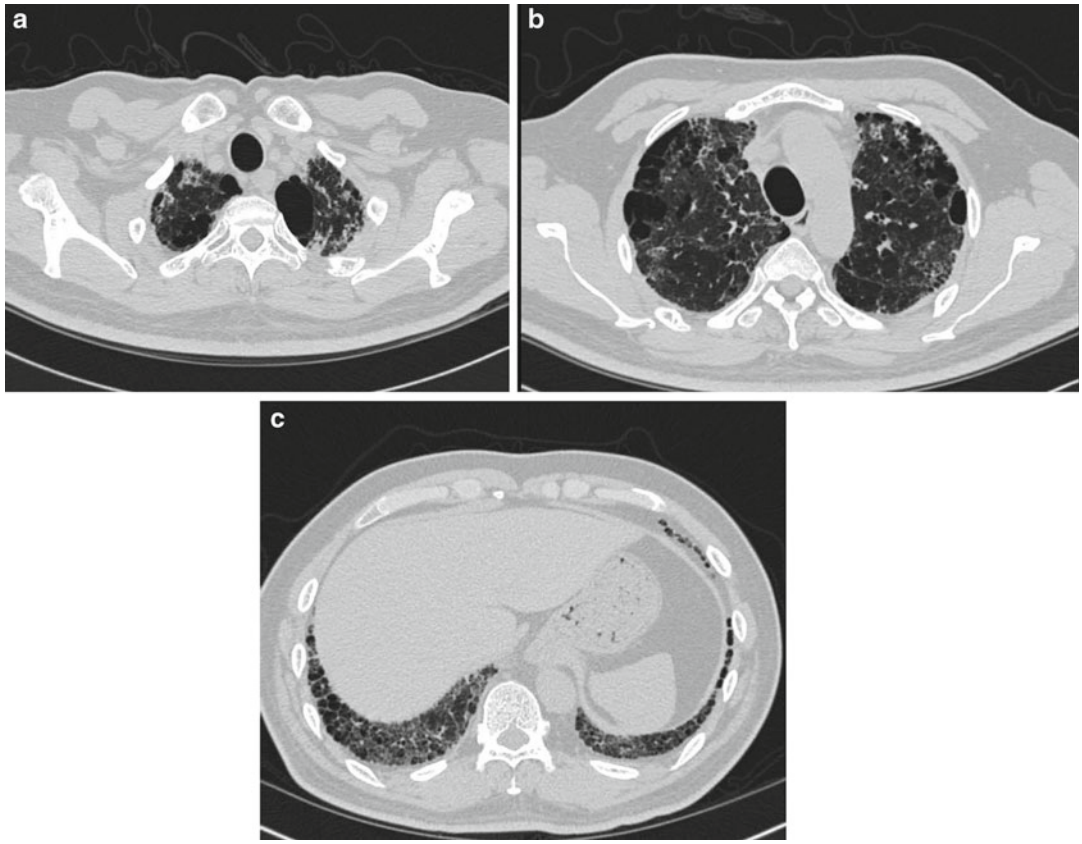

Fig. 10.2 Usual interstitial pneumonia. (**a**) HRCT scan at the level of the apices shows some focal emphysematous changes as well as a few honeycomb cysts. (**b**) HRCT from the same patient at the level of the aortic arch shows well-defined subpleural honeycomb change. Note the dilated bronchi, consistent with traction bronchiectasis. (**c**) HRCT scan from the same patient. Note classical subpleural location of the honeycomb change

subpleural, basally predominant disease; reticular abnormality; honeycombing with or without traction bronchiectasis and the absence of features listed as inconsistent with a UIP pattern allow a definitive diagnosis of a UIP pattern to be made without the need for surgical biopsy [1a]. With advanced disease, distortion, small lung volumes, and pulmonary hypertensive changes may be observed [9]. Zones of emphysema may be found in smokers [9]. Pleural involvement is not found. HC is a key feature discriminating UIP from other interstitial pneumonias [8, 9, 54]. However, CT features of UIP and NSIP overlap, and distinguishing these entities may be difficult [8, 10]. Further, classical CT features of UIP are present in only 37–67% of patients with histologically confirmed UIP [8–10]. CT scans that are "atypical" or "indeterminate" may represent UIP, NSIP, or other histological variants [8, 10].

Differential Diagnosis

Extensive GGO is *not* a feature of IPF, and suggests an alternative diagnosis such as DIP, NSIP, LIP, COP, HP, pulmonary alveolar proteinosis, etc.) [3, 4, 54]. In contrast, HC is a cardinal feature of UIP and is rare in other IIPs [8, 9]. Cystic radiolucencies may be observed in other disorders (e.g., Langerhans cell granulomatosis, sarcoidosis, lymphangioleiomyomatosis (LAM), pneumoconiosis, etc.), but the distribution of lesions and presence of concomitant abnormalities can differentiate these disorders from UIP [9, 54].

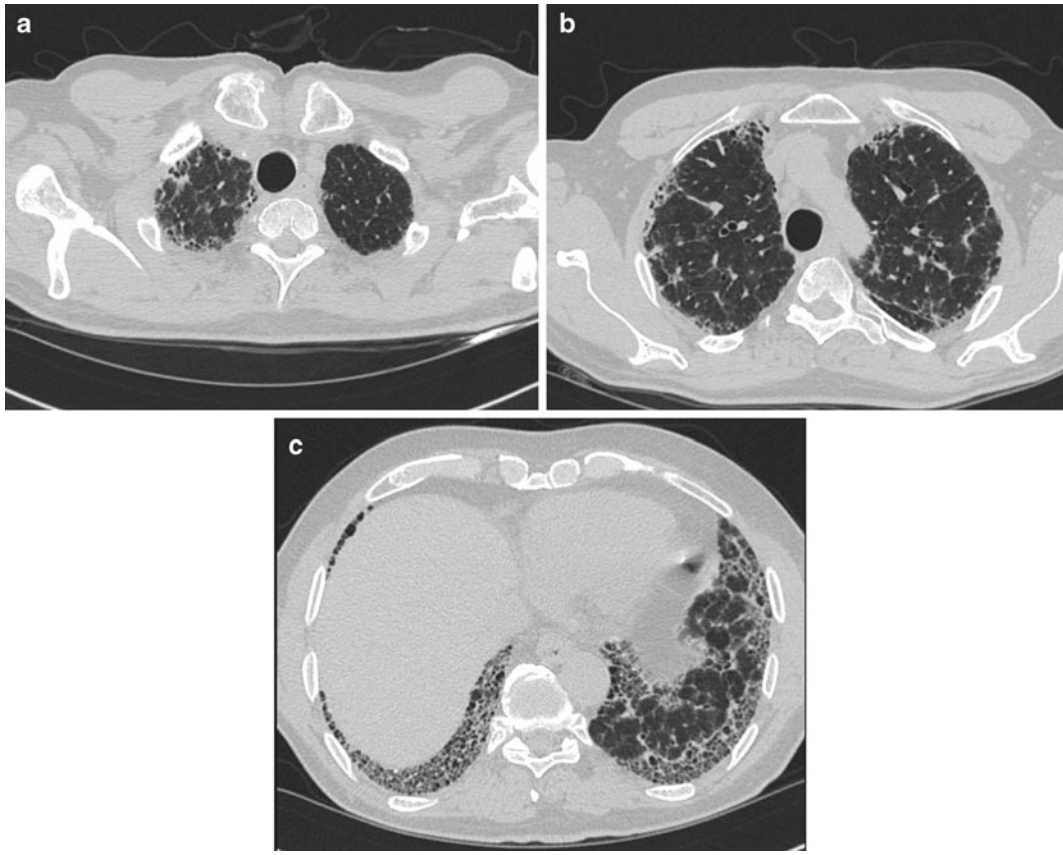

Fig. 10.3 Usual interstitial pneumonia. (**a**) HRCT at the level of the apices shows a few honeycomb cysts and thickened interlobular septa. (**b**) HRCT scan from the same patient at the level of the upper lobes. Note peripheral (subpleural) distribution of honeycomb change. (**c**) HRCT from the same patient at the level of the *lower lobes*. Subpleural (peripheral) distribution of the disease process is evident

PFTs (Including Exercise Tests) in IPF

Characteristic physiologic aberrations in UIP include: reduced lung volumes, normal or increased expiratory flow rates, increased forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio, reduced diffusing capacity for carbon monoxide (DL_{CO}), hypoxemia or widened alveolar-arterial paO_2 gradient [$D(A\text{-}aO_2)$] which is accentuated by exercise, reduced lung compliance, downward and rightward shift of the static expiratory pressure–volume curve, abnormalities on cardiopulmonary exercise tests (CPETs) [2] (Table 10.4). Impairments in gas exchange (i.e., DL_{CO}) and oxygenation may be evident early in the course of the disease, even when spirometry and lung volumes are normal [2]. A restrictive ventilatory defect, with reduced total lung capacity (TLC), is characteristic of IPF, but lung volumes may be normal if emphysema coexists [2]. Lung volumes (e.g., TLC, FVC) are typically higher in smokers (current or former) with IPF compared to nonsmokers [2]. When emphysema coexists, DL_{CO} and oxygenation are disproportionately reduced [2, 55]. CPET demonstrates hypoxemia, widened $A\text{-}aO_2$ gradient, submaximal exercise endurance, reduced oxygen consumption (VO_2), high respiratory frequency, low tidal volume (V_T) breathing pattern, increased dead space (V_D/V_T), increased minute ventilation for the level of VO_2, and a low O_2 pulse [56]. Arterial desaturation and abnormal widening of $A\text{-}aO_2$ gradient with exercise may be elicited with relatively simple tests, such as the 6-min

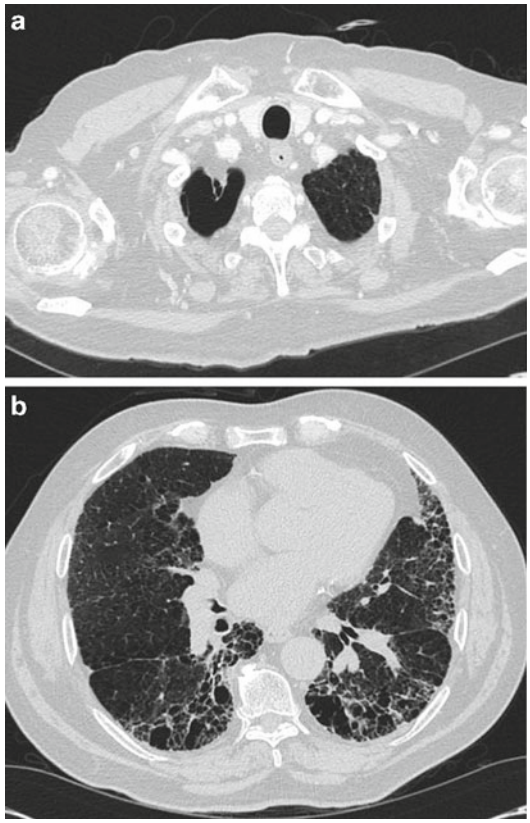

Fig. 10.4 Usual interstitial pneumonia and superimposed emphysema. (**a**) HRCT at the level of the apices shows subpleural cystic changes in the anterior segment of the *right upper lobe*, which reflects primarily paraseptal emphysema. The *upper lobes* are relatively free of interstitial changes. (**b**) HRCT from the same patient at the *lower lobes*. Extensive bilateral honeycomb change is evident. Geographic heterogeneity is present. Areas of honeycomb change are interspersed with areas of relatively normal lung. Note the peripheral (subpleural) distribution

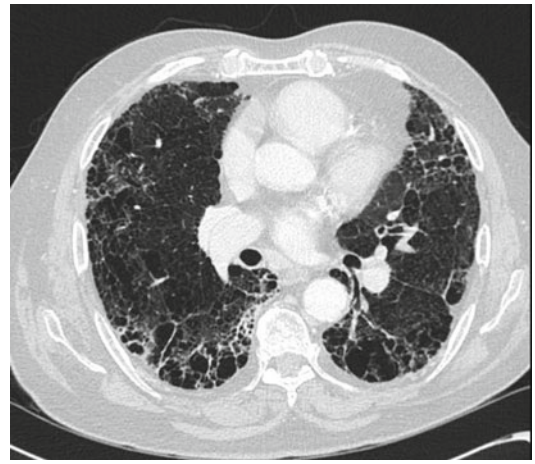

Fig. 10.5 Usual interstitial pneumonia and some areas of superimposed emphysema. HRCT scan demonstrates several emphysematous cysts as well as scattered, subpleural honeycomb cysts

Table 10.3 Usual interstitial pneumonia: HRCT features

Heterogeneous, "patchy" involvement
Proclivity for peripheral (subpleural) and basilar regions
Reticular (linear) opacities
Honeycomb change
Minimal or no ground-glass opacities
Traction bronchiectasis or bronchioloectasis
Distortion, small lung volumes, pulmonary hypertension (advanced disease)

Table 10.4 Physiologic aberrations in IPF/UIP

Reduced lung volumes (vital capacity, total lung capacity)
Normal or increased expiratory flow rates
Increased FEV_1/FVC ratio
Reduced DL_{CO}
Widened alveolar-arterial O_2 gradient (accentuated with exercise)
Reduced lung compliance
Downward and rightward shift of the static expiratory pressure–volume curve
Abnormalities on cardiopulmonary exercise tests (CPET)

walk test (6MWT) [57]. Several mechanisms are responsible for exercise-induced desaturation including: ventilation–perfusion (V/Q) mismatching, O_2 diffusing limitation, and low mixed venous pO_2 [56]. Supplemental O_2 during exercise may improve exercise performance and reduce strain to the myocardium. Dyspnea is a cardinal symptom of IPF and profoundly limits exercise performance. Other nonpulmonary factors which limit exercise performance include: deconditioning, peripheral muscle dysfunction, and nutritional status [56].

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) has been reported in 28–84% of patients with advanced IPF [58–61]. Correlations of physiological parameters with PAH are imprecise [58–60].

However, PAH is more often present when DL_{CO} is severely reduced or hypoxemia is present [59, 60]. PAH worsens as IPF progresses [62]. Transthoracic echocardiography (TTE) is a surrogate marker of PAH. Estimates of systolic pulmonary arterial pressure (sPAP) and size and functional status of the right ventricle (RV) by TTE are useful to predict PAH. In one study of 88 IPF patients, sPAP (estimated by TTE) correlated inversely with DL_{CO} and paO_2 and was an independent predictor of mortality [58]. Median survival rates according to sPAP were as follows: sPAP < 35 mmHg, 4.8 years; sPAP ≥ 36 < 50 mmHg, 4.1 years; sPAP ≥ 50 mmHg, 0.7 years [58]. In a cohort of 110 patients with IPF in Mexico, estimated sPAP ≥ 75 mmHg was an independent predictor of mortality [hazard ratio (HR) 2.25] [55]. In another study of 79 patients with IPF, PAH [defined as mean PAP (mPAP) > 25 mm by right heart catheterization (RHC)] was associated with increased 1-year mortality (28%) compared to 5.5% mortality without PAH [63]. Given the prognostic importance of PAH, we perform TTE in patients with moderate to severe IPF or those requiring supplemental oxygen. However, TTE may be unreliable in some patients, either by inability to estimate sPAP or adequately image the RV [61, 64]. In addition, specificities and negative predictive values of TTE are suboptimal [61, 64]. Given the limitations of TTE, RHC may be considered for selected IPF patients exhibiting O_2 desaturation or severe derangements in DL_{CO} (<35% predicted). However, data regarding therapy of PAH complicating IPF are limited. Anecdotal responses to prostanoids or sildenafil were cited in small nonrandomized studies [65] but survival benefit has not been examined [61].

Predictors of Survival in IPF/UIP

Median survival from the diagnosis of UIP ranges from 2 to 4 years in various studies. Advanced age [1, 17, 23, 30, 66] and male gender [1, 23, 29] were associated with a worse prognosis (higher mortality) in most studies. Interestingly, three studies cited improved survival among current or former smokers with UIP compared to never smokers [29, 30, 67]. However, others found no such effect [68, 69]. The apparent "protective effect" of cigarette smoking may relate to inhibitory effects of cigarette smoke on lung fibroblast proliferation and chemotaxis [2]. A recent study of 249 patients with IPF noted that survival was improved in nonsmokers compared to former or current smokers after adjustment for composite physiologic index (CPI) levels [11]. In that study, current smokers had less severe disease at presentation and represented a "healthy smoker" effect. Interestingly, the concomitant presence of emphysema had no influence on survival. A recent retrospective study from Mexico cited a lower median survival time among patients with IPF and coexistent emphysema compared to IPF without emphysema (25 vs. 34 months, respectively) [55].

Prognostic Value of Histological Features

Early studies of IPF or CFA suggested that prognosis and responsiveness to therapy were improved when SLB displayed "cellularity" (as opposed to severe fibrosis) [1, 70]. In retrospect, these early studies almost certainly included IIPs other than UIP [3]. Among patients with IIPs, the finding of UIP on SLB is a robust and single most important factor influencing mortality [10, 29].

Predictive Value of PFTs (Including Exercise Tests)

Not surprisingly, severe derangements in PFTs or oxygenation predict a worse prognosis (lower survival) in patients with IPF [2, 6]. Numerous studies cited higher mortality rates when DL_{CO} or lung volumes were severely impaired [2, 24, 71]. The "cut-off" points predicting higher mortality vary considerably. Mortality increases when FVC falls below 60% of predicted values or when DL_{CO} is <30–40% predicted [2, 6, 24, 55]. Changes in TLC are less predictive of prognosis or survival [2, 6].

The relationship between any single physiologic variable and prognosis is complex and no

single parameter can reliably predict prognosis in individual patients. Further, disparate results have been reported from different centers. In four studies, the following parameters correlated with mortality: % predicted FVC and widened A-aO_2 gradient [72], FVC < 50% predicted [55], reduced lung volumes and abnormal oxygenation during maximal exercise [30], multistage paO_2 on CPET (p = 0.006) [67]. British investigators examined 2-year survival among a cohort of 115 IPF patients awaiting LT [24]. The best predictors of survival (assessed at 2 years) were: DL_{CO} < 39% predicted and increased fibrosis on HRCT scan [24]. In a separate study by these investigators [66], 106 nonsmokers with IPF were prospectively followed. By univariate analysis, the following parameters predicted survival: age; FEV_1; FVC, DL_{CO}, paO_2; O_2 saturation; HRCT fibrosis score; clearance of inhaled technetium ^{99}m-diethylenetriamine penta-acetic acid (^{99}mTc-DTPA) from the lungs ($t_{0.5}$) [66]. By multivariate analysis, the following parameters were independent predictors of survival: ($t_{0.5}$), percent predicted TLC, percent predicted DL_{CO}, age. Inclusion of other PFT or CT scores did not improve the model. Although it is intuitively obvious that severe impairment in PFTs or oxygenation predicts higher mortality, *statistical correlations* in large patient cohorts are not readily applicable to *individual* patients.

Change in pulmonary functional parameters over time may be prognostically useful. However, variability among PFTs confounds interpretation. Measurement of FVC is less variable than TLC or DL_{CO} [2] and is best suited for serial measurements. Improvement or stability in VC or DL_{CO} with therapy is associated with improved prognosis in patients with IPF [2, 73]. Conversely, deterioration in VC or DL_{CO} at 3 or 6 months, 1 year, or later time points predicts a worse survival [2, 73–75]. In a retrospective study, serial PFTs were performed in 80 patients with IPF [73]. By multivariate analysis, >10% decrease in FVC at 6 months was an independent risk factor for mortality (HR, 2.47, $p = 0.006$) [73]. Collard et al. evaluated the prognostic value of serial clinical (dyspnea score) and physiologic parameters in 81 patients with IPF [75]. Not surprisingly, survival was worse among patients with deteriorating dyspnea scores or PFTs [FVC% predicted, P(A-aO_2)] at 6 or 12 months [75]. British investigators retrospectively reviewed the prognostic significance of histopathologic diagnosis, baseline PFTs, and serial trends in pulmonary functional indices (e.g., FVC, FEV_1, DL_{CO}) at 6 and 12 months in 104 patients with IIP (UIP, $n = 63$; fibrotic NSIP, $n = 37$) [74]. Survival was better in fibrotic NSIP compared with UIP ($p = 0.001$) but not in patients with severe functional impairment. Mortality during the first 2 years was linked solely to the severity of functional impairment at presentation (i.e., lower DL_{CO} and FVC levels). The *CPI* score [72] was the strongest determinant of outcome ($p < 0.001$) [74]. At 6 months, serial PFTs and histopathologic diagnosis were prognostically equivalent [74]. However, at 12 months, serial PFT trends (DL_{CO}, FVC, FEV_1, CPI) predicted mortality better than any other covariates including histological pattern (all $p < 0.0005$). In this context, ΔDL_{CO} provided the best prognostic information (2-year survival); histological pattern provided no additional prognostic value.

6-Min Walk Test

Hypoxemia at rest or with exertion is associated with heighted mortality in IPF [56, 76]. Further, 6-min walk distance (6MWD) correlates with DL_{CO}% predicted [24, 57] and has prognostic value. In one study of IPF patients awaiting LT, survival time was shorter among patients with 6MWD < 350 m [77]. In a subsequent study of 454 IPF patients awaiting LT, lower 6MWD was associated with increased mortality (assessed at 6 months) and was superior to FVC% predicted as a predictor of mortality [57]. Patients with 6MWD < 207 m had a more than fourfold greater mortality than those with 6MWD ≥ 207 m, even after adjustment for demographics, FVC% predicted, pulmonary hypertension, and medical comorbidities [57]. Flaherty et al. assessed the prognostic value of 6MWT in a cohort of 197 patients with IPF [76]. By multivariate analysis, 6MWD was not a reliable predictor of mortality, but the degree of desaturation during 6MWT had

greater prognostic value. Patients with O_2 saturation ≤ 88% during their initial 6MWT had a median survival of 3.2 years compared to 6.8 years for those with baseline SaO_2 > 88% ($p = 0.006$). Recently, a 6-min step test was advocated as another way of assessing exercise capacity and prognosis in patients with IPF or other ILDs [78]. Formal CPET provides additional data including measurement of maximal oxygen uptake (VO_2), an integrated measure of respiratory, cardiovascular, and neuromuscular function [56]. Fell et al. evaluated VO_2 as a predictor of survival in a cohort of 117 patients with IPF [79]. Patients with baseline VO_2 < 8.3 ml/kg/min had an increased risk of death after adjusting for age, smoking status, FVC, and DL_{CO}. Further, VO_2 was a stronger predictor than desaturation < 88% on 6MWT. However VO_2 did not predict survival when examined as a continuous variable. However, CPET with arterial cannulation is invasive, logistically difficult, difficult to perform for some patients, and lacks practical value.

Prognostic Value of HRCT

The extent and "pattern" of aberrations on CT have prognostic significance [8, 9, 80]. The *global extent of disease* on CT correlates roughly with severity of functional impairment in IPF [9, 72]. More importantly, the *pattern* on CT has prognostic value. Three major patterns include: GGOs, reticular or linear pattern, HC [9, 54]. GGO may reflect intra-alveolar or interstitial inflammation, fibrosis, or a combination. Reticular lines reflect fibrosis within alveolar ducts, septa, or spaces, but an inflammatory component may coexist. HC reflects irreversible destruction of alveolar walls and fibrosis [9, 54]. Reticular or "honeycomb" patterns predict a low rate of response to therapy [9, 54]. Early studies in patients with IPF (not all of whom had SLB) noted that a pattern of "predominant GGO" on CT predicted an improved prognosis and responsiveness to therapy when compared to reticular or mixed patterns [9, 54]. However, those sentinel studies may be misleading. Extensive or predominant GGO is rarely found in IPF. Patients exhibiting "predominant GGO" on CT are more likely to have NSIP than UIP [9, 54], which likely explains the more favorable prognosis in this context.

Extent of fibrosis on CT (CT-fib) correlates with functional impairment and the extent of histologic fibrosis by SLB and is an independent predictor of mortality [9, 10, 24, 29]. British investigators assessed risk factors for 2-year survival in a cohort of 115 patients with IPF awaiting LT [24]. By multivariate analysis, only CT-fib scores and DL_{CO} percent predicted were independent predictors of mortality. The risk of death increased by 106% for each unit increase in CT-fib score and 4% for every 1% decrease in DL_{CO} percent predicted [24]. Receiving operating curve (ROC) analysis gave the best fit (predictive value) using a combination of DL_{CO} and CT-fib scores. The optimal points on the ROC curves for discriminating between survivors and nonsurvivors corresponded to 39% predicted DL_{CO} and to a CT-fib score of 2.25. The curve resulting from the model yielded a sensitivity and specificity of 82% and 84%, respectively, for discriminating survivors from nonsurvivors at 2 years.

Flaherty et al. assessed the impact of CT fibrotic scores in a cohort of 168 with IIPs (UIP = 106; NSIP = 33; RBILD/DIB = 22; other = 7) [29]. A CT-fib score ≥ 2 in any lobe was highly predictive of UIP (sensitivity, 90%; specificity, 86%). The presence of an interstitial score ≥ 2 in any lobe was associated with increased mortality [relative risk (RR) of 3.35, $p = 0.02$]. The degree of fibrosis of CT is a surrogate marker for the histological pattern of UIP. CT scans that are "typical of CFA/IPF" were associated with more fibrosis and a higher mortality than "atypical" CT scans [9, 54]. In a study of 96 patients with IIP (73 had UIP and 23 had NSIP by SLB), CT scans "characteristic of UIP" (i.e., deemed as "definite" or "probable" UIP by experienced radiologists) predicted a worse survival [10]. Among patients with histologically confirmed UIP, mortality was higher when CT features were typical ("definite" or "probable") UIP compared to those with a nondiagnostic CT ($p = 0.04$) [10]. Median survival rates were 2.08 years among patients with *both* histologic *and* CT diagnosis of UIP compared to 5.76 years among patients with

histologic UIP but atypical CT [10]. CT features of UIP (particularly honeycombing) likely reflect more advanced disease. A recent study retrospectively reviewed CT scans from 98 patients with a histologic diagnosis of UIP [8]. Patterns of CT scans were categorized as: (1) definite UIP, (2) probable UIP, (3) suggestive of alternative diagnosis. Mean survival rates were 45.7, 57.9, and 76.9 months, respectively, median survival rates were 34.8, 43.4, and 112 months, respectively. While these differences between groups did not achieve statistical significance, these data suggest that CT scans interpreted as definite UIP have a worse prognosis. By multivariate analysis, extent of traction bronchiectasis and fibrosis scores influenced prognosis.

Are Serial HRCT Scans Valuable?

Serial CT scans have been used to assess evolution of the disease or response to treatment in patients with IPF [2, 9, 54]. Reticular patterns or HC never regressed whereas GGO improved in 33–44% of patients [2, 9, 54]. When global extent of disease lessened on CT, it was due to reduction in the extent of GGO. Importantly, despite early regression of GGO in some patients, GGO usually progresses inexorably to a reticular pattern or HC [2, 9, 54]. Given the potential for fibrosis to evolve over months to years, the value of CT in predicting *long-term* prognosis is modest. Serial PFTs are more useful than CT scans to document the initial extent of impairment and monitor the course of the disease. Changes in CT are usually concordant with changes in FVC and DL_{CO} [2, 9, 54].

Clinical–Radiographic–Physiologic Scores

Watters et al. developed a composite score incorporating clinical (dyspnea), radiographic (chest X-rays), and physiological parameters (i.e., the clinical–radiographic–physiologic (CRP) score) as a means to more objectively monitor the course of IPF [81]. Subsequently, a modified CRP score (arbitrary total of 100 points) was developed in a cohort of 238 patients with UIP [30]. This modified score incorporated the following variables: age (maximum 25.6 points), smoking history (maximum 13.6 points), clubbing (maximum 10.7 points), percent predicted TLC (maximum 11 points), paO_2 at maximal exercise (maximum 10.5 points), changes on chest X-rays (profusion of interstitial opacities or pulmonary hypertension) (maximum 28.6 points) [30]. In addition, an abbreviated CRP score was developed, which excluded paO_2 at maximal exercise. Importantly, the modified CRP scores predicted 5-year survival with remarkable accuracy [30]. Five-year survival rates at CRP scores of 20, 40, 60, and 80 points were 89%, 53%, 4%, and <1%, respectively. The abbreviated CRP was less accurate, but more adaptable to clinical practice. These quantitative CRP scoring systems are invaluable for research investigations, but are cumbersome for use in clinical settings.

British investigators developed a CPI incorporating CT and physiologic parameters [72]. The CPI score evaluated disease extent observed by HRCT and selected functional variables (e.g.,% predicted FVC, DL_{CO}, and FEV_1). Exercise components were not included in this index. The CPI accounts for coexisting emphysema, which may confound pulmonary functional indexes. In the CPI, both DL_{CO} and FVC were weighted positively [i.e., higher DL_{CO} or FVC resulted in lower (better) CPI scores] whereas the FEV_1 is weighted negatively [i.e., a higher FEV_1 results in a higher (i.e., worse) CPI score]. Specifically, the formula for CPI was as follows: [extent of disease on CT = 91.0 − (0.65 × percent predicted DL_{CO}) − (0.53 × percent predicted FVC) + (0.34 × percent predicted FEV_1)]. CPI correlated more strongly with disease extent on CT than the individual pulmonary functional parameters. More importantly, CPI predicted mortality better than PFTs in all subgroups including 36 patients with UIP on SLB. On univariate analysis, several variables correlated with mortality including: greater extent of disease on CT ($p < 0.0005$), greater functional impairment (DL_{CO}, FVC, TLC, FEV_1, alveolar volume (VA), paO_2, A-aO_2 gradient), higher CPI scores (all had $p < 0.0005$). When compared with

individual pulmonary functional components, CT disease extent was a more powerful predictor of mortality. However, the CPI index was the most powerful index and predicted survival better than the extent of disease on CT or any of the individual PFT components. Further, the CPI was compared to the original [81] or modified [30] CRP scoring systems in 30 patients with UIP who underwent CPET. The CPI was a superior predictor of outcome than the physiologic component of the original CRP score ($p = 0.02$) and the physiologic component of the modified CRP score ($p = 0.009$). Additional studies using these or similar CRP scoring systems would be of interest.

Magnetic Resonance Imaging

Dynamic magnetic resonance imaging (MRI) may discriminate inflammatory from fibrotic lesions in IIPs [82], but data are limited. The role of MRI in the diagnosis/staging of IPF needs to be further studied.

Ancillary Staging Techniques

Radionuclide scans have been used to assess prognosis in diverse ILDs. Increased intrapulmonary uptake of gallium^{67} citrate (Ga^{67}) may be a marker of alveolitis [83]. However, Ga^{67} scans are expensive, difficult to quantitate, inconvenient (scans are performed 48 h after injection with the radioisotope), require exposure to radiation, and are nonspecific [83]. Importantly, Ga^{67} scans do not predict prognosis or responsiveness to therapy and lack *practical* value in the staging or follow-up of IPF [83]. Clearance of ^{99}Tc-diethylenetriamine penta-acetate (DTPA) aerosol is accelerated in IPF and is a marker of increased lung permeability [66, 83]. Increased clearance occurs in smokers and other inflammatory lung disorders; its prognostic value is debatable [83]. Some investigators cited changes in pulmonary vascular permeability on positron emission tomographic (PET) scans in patients with IPF [83], but sensitivity, specificity, and clinical value have not been clarified. We do not employ radionuclide techniques for either the staging or follow-up of IPF.

Bronchoalveolar Lavage

Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) contributed significant insights into the pathogenesis of IPF and other ILDs but practical value is limited [1, 84]. Increases in polymorphonuclear leukocytes, eosinophils, mast cells, alveolar macrophages, and myriad cytokines are noted in BAL fluid from patients with IPF; lymphocyte numbers are usually normal [1, 84, 85]. BAL neutrophilia is present in 67–90% of patients with IPF [1, 84, 85] but does not predict prognosis or therapeutic responsiveness. By contrast, BAL lymphocytosis is rarely found in IPF and suggests an alternative diagnosis (e.g., cellular NSIP or HP) [85].

Pathogenesis of UIP

Although the etiological agent(s) in IPF has not been elucidated; two key features, that is, alveolar epithelial cell (EC) injury and dysregulation of fibroblasts (FBs) appear to be pivotal in the pathogenesis [86, 87]. Lung FBs isolated from patients with IPF demonstrate greatly enhanced proliferation and production of collagen and ECM [87]. Injury to alveolar ECs and destruction of the subepithelial basement membranes are likely early events in the pathogenesis of IPF [87]. Alveolar ECs exhibit hypertrophy/hyperplasia and ultrastructural alterations in IPF and have the potential to secrete a vast array of cytokines and growth factors [87]. Soluble mediators secreted by cells in the surrounding milieu lead to local recruitment, differentiation, and proliferation of FBs. In this context, for example, transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), tumor necrosis factor-α (TNF-α), connective tissue growth factor (CTGF), and interleukin-8 (IL-8) likely play key roles [87]. These secreted peptides induce leukocyte influx and promote fibrosis. Historically, it was believed that inflammatory leukocytes were the source of these pro-fibrotic cytokines. However, alveolar ECs appear to be the most important source of these cytokines. Stimulation of cytokine production by injured ECs may play a critical role in initiating fibrosis in IPF; the

influx of inflammatory leukocytes may be a sequela of EC activation rather than a primary event in the pathogenesis of IPF. The varying degrees of inflammation and fibrosis in the IIPs are likely dependent on, and determined by, local tissue microenvironments that are pathologically altered by a combination of host and environmental factors.

A distinctive feature of IPF/UIP is the so-called fibroblastic foci (FF), often found at the leading edge of normal and fibrotic lung [3]. It has been proposed that FF are a manifestation of ongoing lung injury [3]. Epithelial cell death is most prominent immediately adjacent to FF [3]. Further, FBs and myofibroblasts isolated from patients with IPF induce apoptosis of alveolar ECs in vitro, demonstrate increased production of collagens, increased expression of tissue inhibitors of metalloproteinases (TIMPs), and a relative decrease in collagenases [86, 87]. The combination of excessive production and deposition of ECM proteins and reduced proteolysis of ECM contributes to the fibrotic process in IPF [87]. It has been suggested that FF represent "wound healing" responses to repetitive EC injury, resulting in dysfunctional epithelial–mesenchymal cross-talk [87]. A critical aspect of this dysregulated process is the inability for alveolar ECs to regenerate, re-epithelialize, and form a normal barrier across the alveolar wall [87]. This results in a persistent "on-signal," in part mediated by chemokines, cytokines, and growth factors that activate the underlying mesenchyme. Mesenchymal cells that form FF in IPF are activated and display a contractile phenotype, commonly referred to as myofibroblasts [87]. Myofibroblast differentiation and fate is controlled by soluble growth factors such as TGF-β and matrix-derived signals [86, 87]. Under the influence of TGF-β, myofibroblasts display increased production of collagen, vimentin, β-actin, and TIMPs [86, 87]. This combination of features leads to a bias towards excessive matrix deposition and wound contraction in IFP. Greater understanding of mechanisms that mediate apoptosis of these cells, a process that has been described in the resolution of cutaneous wound healing [87], may allow development of new therapeutic targets in IPF [86].

A pro-angiogenic environment may favor fibrosis in IPF [2]. Neovascularization is a prominent feature of fibrosis in both humans and animal models [2]. Interleukin-8 (IL-8) and IFN-γ-inducible protein-10 (IP-10), members of the CXC chemokine family, affect fibrosis via angiogenic mechanisms [2]. IL-8 and its murine functional homologue macrophage inflammatory protein-2 (MIP-2) induce neutrophil and endothelial cell chemotaxis in vitro and stimulate neovascularization [2]. In contrast, IP-10 inhibits angiogenesis and endothelial cell chemotaxis [2]. In humans with IPF, IL-8 is markedly elevated in BAL fluid and serum whereas IP-10 levels in IPF lung biopsies are reduced compared to controls [2]. These findings suggest that a pro-angiogenic environment exists in IFP and may propagate fibrosis.

Several other pathophysiological processes may be critical in the abnormal lung repair process in IPF. Plausible mediators of the fibrotic process include: integrin-mediated intercellular adhesion molecules (ICAM) [86], abnormal surfactant proteins [43], imbalances in the production and/or localization of matrix metalloproteinases (MMPs) and TIMPs [87], predominance of type II cytokine profiles (particularly IL-4 and IL-13), eicosanoids, oxidative stress responses [2].

Treatment of IPF

Treatment options for IPF are still limited. Until relatively recently, randomised, double-blind, placebo-controlled (RDBPC) studies have been lacking, and optimal therapy is controversial. Historically, corticosteroids (CS) or immunosuppressive or cytotoxic agents were used, in an attempt to ablate any inflammatory component. However, inflammatory cells are *relatively* inconspicuous in IPF [88], and the degree of inflammation does not correlate with disease severity [2]. In animal models, fibrosis can occur even in the absence of neutrophils or lymphocytes [2]. Thus, it is not surprising that anti-inflammatory therapies have limited or no benefit in IPF [2, 23]. Several retrospective studies found no survival advantage with *any* form of therapy [2, 23, 24, 30]. In 2000, the ATS/ERS Consensus Statement

on IPF concluded: "no data exist that adequately document any of the current treatment approaches improves survival or the quality of life for patients with IPF" [1]. More recently the 2011 ATS/ERS/JRS/ALAT guidelines stated that "the preponderance of evidence to date suggests that pharmacologic therapy for IPF is without definitive, proven benefit". Since this statement was published. three trials of therapy have been reported that suggest some treatment effect [1a, 88a, 88b, 88c]. Despite the lack of proven benefit, physicians have in the past offered treatment in an attempt to slow or prevent inexorable progression to fatal respiratory failure. In the sections that follow, we briefly discuss treatment options.

Corticosteroids

Corticosteroids were the mainstay of therapy for more than 4 decades, but are of unproven efficacy and are associated with significant toxicities [2, 23]. Early studies of patients with IPF cited response rates of 10–30% with CS (alone or combined with immunosuppressive agents), but complete or sustained remissions were rare [2, 70, 89, 90]. More importantly, many "responders" likely had IIPs other than UIP (e.g., NSIP, COP, or RBILD/DIP). In recent studies, response rates to CS among patients with histological evidence for UIP were low (0–17%) [2]. Large retrospective studies of patients with IPF showed no survival benefit with CS [2, 23, 30]. Given the potential severe toxicities associated with CS, high dose CS should *not* be used to treat IPF [1]. However, since anecdotal responses to CS are *occasionally* noted in patients with IPF, the ATS/ERS consensus statement acknowledged that *selected* patients with clinical or physiological impairment or worsening PFTs should be treated [1]. *Among patients requiring treatment*, recommended therapy was as follows: oral azathioprine (AZA) or cyclophosphamide (CP) *plus low-dose* prednisone or prednisolone [0.5 mg/kg (lean body weight per day) for 4 weeks, then 0.25 mg/kg for 8 weeks, then 0.125 mg/kg]. This represents a substantial departure from earlier regimens advocating *high-dose* prednisone (e.g., ≥1 mg/kg/day for ≥6–12 weeks) [70, 89]. Combined therapy should be continued for 6 months in the absence of adverse effects. Treatment should be continued *beyond* 6 months only if patients improve or remain stable. These recommendations [1] reflect expert opinion, but have *not* been validated in clinical trials. We believe CS should *not* be given to patients at high risk for adverse effects (e.g., age > 70 years, osteoporosis, diabetes mellitus, extreme obesity, etc.)

Azathioprine

AZA has been used to treat IPF for more than three decades but efficacy is debatable. Only two prospective studies evaluated AZA for IPF [70, 89]. In both studies, AZA was *combined* with prednisone. In the first study, 20 patients with progressive IPF were initially treated with prednisone *alone* for 3 months [70]. At that point, AZA (3 mg/kg/day) was *added* and both agents were continued for an additional 9 months or longer. Twelve patients (60%) responded. The *independent* effect of AZA was difficult to assess since all patients received prednisone concomitantly. In a second, double-blind trial by these investigators, 27 patients with newly diagnosed, *previously untreated* IPF were randomized to receive AZA (3 mg/kg/day) *plus* high dose prednisone ($n = 14$) or high dose prednisone plus placebo ($n = 13$) [89]. At 1 year, PFTs (FVC, DL_{CO}, A-aO_2 gradient) were similar between groups. Vital capacity improved (>10% above baseline) in five patients receiving AZA/prednisone and in two patients receiving prednisone/placebo. DL_{CO} improved (>20% above baseline) in three patients receiving AZA/prednisone, and in two receiving prednisone/placebo. Mortality was similar at 1 year (four patients died in each group). At late follow-up (mean 9 years), 43% of AZA-treated patients had died compared to 77% in the prednisone plus placebo cohort. This survival difference was not statistically significant.

AZA has potential bone marrow, gastrointestinal toxicities, and is associated with a heightened risk for infections [91]. In contrast to cyclophosphamide, AZA does not induce bladder injury and is less oncogenic [91]. AZA (2–3 mg/kg/day)

is our preferred agent for IPF patients with progressive disease. A 6-month trial is reasonable. However, in general toxicities associated with AZA outweigh benefit.

Cyclophosphamide

Cyclophosphamide (either oral or by intravenous pulse) has been used to treat IPF, but results are unimpressive [2, 30, 90]. Anecdotal responses to oral or pulse CP have been cited, but marked or sustained improvement is rarely achieved [2]. Toxicities associated with CP are substantial, and include bone marrow toxicity, opportunistic infections, infertility, bladder injury, and oncogenesis [91]. We believe that the toxicities associated with CP outweigh benefit.

Other Immunosuppressive/Cytotoxic Agents

Cyclosporin A and mycophenolate mofetil have been used to treat IPF, but data are limited to anecdotal case reports and retrospective series [2].

TNF Inhibitors

Infliximab, a chimeric anti-TNF-α antibody, has been used to treat pulmonary fibrosis complicating connective tissue disorders [92], but data affirming efficacy in IPF are lacking. Etanercept, a recombinant soluble human TNF-α receptor antagonist, has been used to treat IPF, but is of unproven benefit. A RDBPC trial in 88 patients with progressive IPF found no significant differences in predefined efficacy endpoints [i.e., Δ% predicted FVC and DL_{CO} and $\Delta p(A\text{-}aO_2)$ gradient at rest] at 48 weeks [93]. However, a *trend* in favor of etanercept-treated patients was noted in several secondary measures. Additional trials are required before TNF-α inhibitors can be endorsed as therapy for IPF.

Colchicine

Colchicine displays antifibrotic effects in vitro and in animal models but was ineffective in IPF in both retrospective and prospective, randomized trials [2].

N-Acetylcysteine

N-acetylcysteine (NAC) is an antioxidant that stimulates glutathione synthesis and attenuates fibrosis in animal models. A multicenter, RDBPC trial (IFIGENIA) in Europe evaluated the efficacy of oral NAC in IPF [94]. All patients received "conventional" therapy with AZA (2 mg/kg/day) plus prednisone (0.5 mg/kg/day, with taper). Patients were then randomized to oral NAC (1,800 mg/day) or placebo. At the end of 1 year, PFTs had deteriorated in both cohorts. However, the rates of decline in FVC and DL_{CO} were less in patients receiving NAC ($p<0.05$) [94]. These changes in PFTs were small (absolute difference in FVC of 4.8% and in DL_{CO} 5.1%) and of doubtful clinical significance. The benefit (if any) of NAC as therapy for IPF remains controversial. Nonetheless, NAC is inexpensive and has few side effects, making this an attractive option for IPF. A multicenter RDBPC trial sponsored by the IPFnet to address the impact of NAC in IPF is in progress.

Endothelin-1 Receptor Antagonists

Endothelin-1 (ET-1) receptor antagonists reduce collagen deposition in animal models and have a *theoretical* role to treat IPF. A multicenter RDBPC trial evaluating Bosentan Use in Interstitial Lung Disease (BUILD-1) randomized 158 IPF patients to bosentan or placebo [95]. Patients with severe pulmonary dysfunction (FVC < 50% predicted or DL_{CO} < 35% predicted) or concomitant PAH were excluded. At 12 months, 6MWD (the primary endpoint) worsened in both groups (no significant differences between groups). Mean changes from baseline in FVC at 12 months were −6.4 and −7.7% in the bosentan and placebo groups, respectively. Mean changes from baseline in DL_{CO} at 12 months were −4.3 and −5.8% in the bosentan and placebo groups, respectively. However, a *trend* in favor of bosentan was noted in the secondary endpoint [time to death or disease

progression, (HR 0.64, $p=0.12$)] [95]. In a larger study (BUILD-3), patients with mild to moderate IPF were randomized to bosentan (n=407) or placebo (n=209) for 12 months [95a]. No significant difference between groups were observed in the primary endpoint (time to IPF worsening or all-cause death).

Interferon-γ

Interferon-γ (IFN-γ) attenuates collagen synthesis by FBs in vitro and attenuates fibrosis in animal models [87]. Despite initial enthusiasm for recombinant IFN-γ-1b in humans, this agent conferred no survival benefit in two large, RDBPC trials [95b, 95c].

Indications for Therapy

Given the lack of proven efficacy of any therapeutic modality, and toxicities associated with CS or immunosuppressive agents, we reserve treatment for patients with a deteriorating course, severe or progressive symptoms, and no obvious contraindications to therapy. Empirical treatment is more attractive when surrogate markers of alveolitis are present (e.g., GGO on CT or BAL lymphocytosis). We offer treatment to *selected* patients, but only after an honest discussion with the patient and family of the low likelihood of success and the potential for significant adverse effects. For patients desiring treatment, we recommend oral AZA (2 mg/kg/day), either alone or combined with modest doses of prednisone (e.g., 0.5 mg/kg/day for 4 weeks, with gradual taper). We rarely employ CP. Prednisone is tapered to 10 mg daily (or equivalent) within 3 months. We do not recommend CS when specific contraindications or risk factors are present (e.g., obesity, diabetes mellitus, osteoporosis, age > 70 years, history of psychiatric illness, poorly controlled hypertension). Unless adverse effects necessitate early discontinuation of therapy, we treat for 6 months and reassess at that point. Treatment is continued only when improvement or stability has been demonstrated *by objective tests* (e.g., PFTs or CT). Single lung transplantation (SLT) is advised for patients with severe disease or failing medical therapy [96]. Additional novel therapies are being studied (discussed later), but therapeutic efficacy has not yet been shown.

Monitoring the Course of the Disease or Response to Therapy

The following functional measurements are essential for the initial assessment and monitoring of IPF: spirometry, DL_{CO}; 6MWT [2]. FVC is highly reproducible, and correlates better with prognosis than TLC; DL_{CO} is more variable [56]. Although authors differ regarding what constitutes "significance," the ATS/ERS defined the following changes as clinically significant: FVC or TLC ≥ 10–15%; DL_{CO} ≥ 20%; ≥4 mm increase in paO_2 saturation or >4 mm increase in paO_2 during exercise [1]. The 6MWT provides a non-invasive, simple method to assess exercise capacity and the need for supplemental O_2 [56]. We perform serial spirometry, DL_{CO}, and 6MWT at 3–4 month intervals to monitor the course of the disease. More frequent studies may be necessary in the event of clinical deterioration. More sophisticated studies (such as CPEP, measurement of compliance or elastic recoil) lack practical, clinical value [56].

Ancillary Therapies

Supplemental oxygen improves quality of life and exercise capacity in hypoxemic patients with IPF [1, 2]; impact on survival has not been studied. Pulmonary rehabilitation has been advocated to improve quality of life and exercise capacity [97], but data affirming benefit are lacking. Pulmonary hypertension may complicate advanced UIP, but the benefit of PAH-specific therapy is this context has not yet been elucidated [61]. Oral codeine or other antitussive agents may be used to control cough [1], but are of limited benefit. Opiates have

been used to reduce dyspnea in patients with severe chronic lung disease, but have not been shown to be effective [2].

Lung Transplantation

SLT may be considered for patients with severe IPF [96]. Two-year survival following LT ranges from 60 to 80%; 5 year survival is 40 to 60% [98, 99]. International Society for Heart and Lung Transplant (ISHLT) Registry data for recipients with IPF cited improved survival with bilateral sequential lung transplantation (BSLT) compared to SLT ($p=0.03$) [98]. Survival rates were similar up to 3 years, but diverged thereafter [98]. Recent data from the ISHLT cited lower survival rates at 3 months post-LT among patients with IPF (84%) or idiopathic PAH (74%) compared to cystic fibrosis (90%) and chronic obstructive pulmonary disease (COPD) (91%) [99]. Among patients surviving to 1 year, IPF and COPD had the worst long-term survival, most likely reflecting older age and comorbidities [99]. Most deaths following LT are due to chronic allograft rejection or complications of immunosuppressive therapy [99]. Due to a shortage of donor organs, waiting time for LT may be prolonged (up to 2–3 years) and many patients with IPF die while awaiting LT [96]. Unless contraindications exist, patients with severe functional impairment (e.g., FVC < 60% predicted, DL_{CO} < 40% predicted), oxygen dependency, and a deteriorating course should be listed promptly for transplantation [96].

Severe Acute Respiratory Failure Complicating IPF

Acute respiratory failure requiring mechanical ventilation (MV) may complicate IPF (either due to progression of IPF or an intercurrent illness) [100, 101]. In this context, mortality is high (>90%). Given the poor prognosis, MV is usually ill-advised in patients with severe IPF unless a potentially reversible process (e.g., pneumonia, pulmonary edema, pulmonary embolism, etc.) is diagnosed in a relatively young patient.

Novel Agents

Current therapies for IPF based upon altering the inflammatory component are only marginally effective. Major advances await the development of novel therapies that prevent fibroproliferation and/or enhance alveolar re-epithelialization [87]. Novel agents that have been tested include pirfenidone, for which there are now four reports of RDBPC, a tyrosine kinase inhibitor and anticoagulants (discussed below).

Pirfenidone

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) attenuates pulmonary fibrosis in animal models, inhibits collagen synthesis in vitro, and blocks the mitogenic effect of pro-fibrotic cytokines in adult human lung FBs from IPF patients [86]. A phase II RDBPC trial compared pirfenidone to placebo (2:1 ratio) in a cohort of 107 patients with IPF [102]. The study was stopped prematurely because acute exacerbations were noted in five patients receiving placebo (14%) compared to no cases in the pirfenidone group. The primary endpoint (change in lowest O_2 saturation on 6MWT over 6 or 9 months) was not met. There were no significant differences between groups in mortality, TLC, DL_{CO}, or resting paO_2. The rate of decline in FVC at 9 months was lower in the pirfenidone group ($p=0.037$), but differences between groups were small and of doubtful clinical significance. In a second Japanese study, 275 patients were randomised to receive either high dose (1800 mg./day), low dose (1200 mg/day) or placebo for 52 weeks. The high dose group had a lower rate of reduction in vital capacity and in the incidence of progression, defined as either death or a decrease of >10% vital capacity, compared with the placebo group [88a]. Pirfenidone has been approved for use in Japan and also in China and India. Two international placebo-controlled RDBPC evaluating pirfenidone as therapy for IPF were recently completed (InterMune, Brisbane, CA) and have been published recently. The primary end point of these

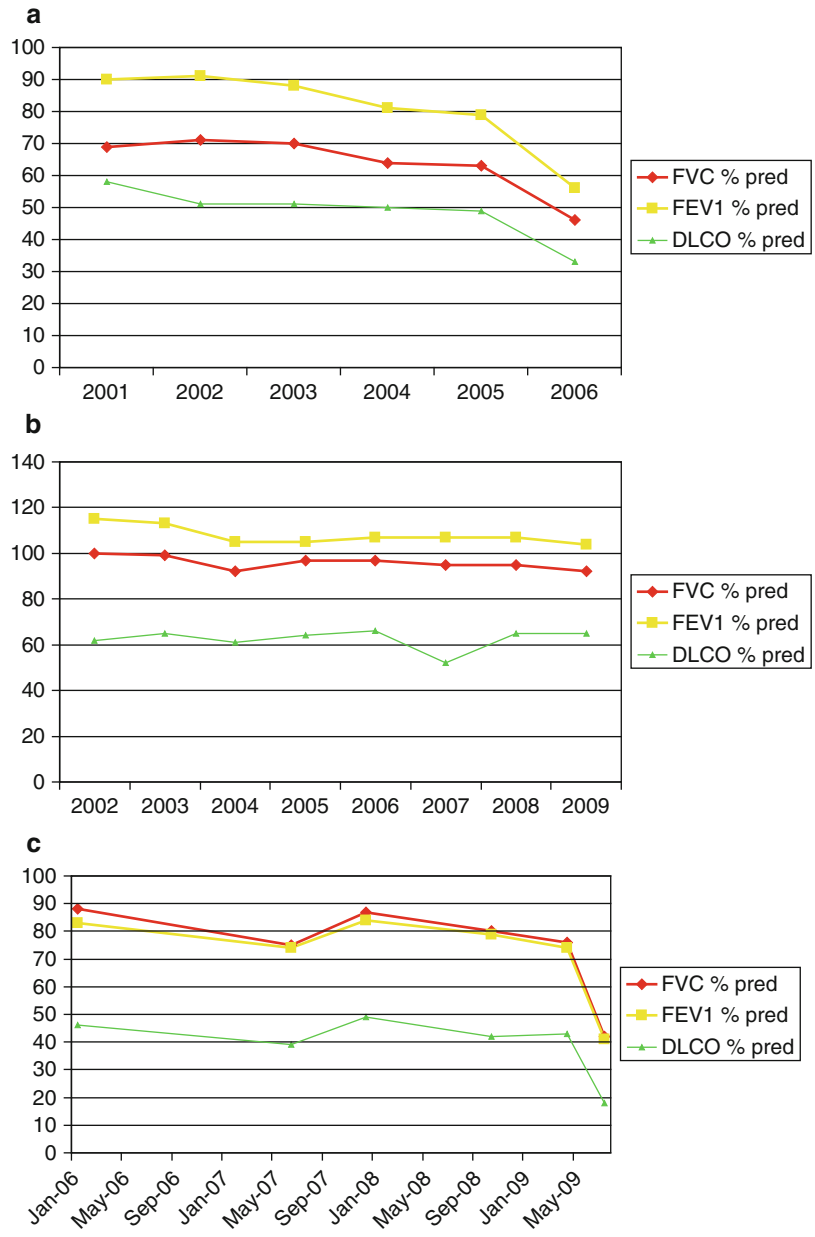

Fig. 10.6 Pulmonary function tests (PFTs) for (**a**) (case 1), (**b**) (case 2), and (**c**) (case 3). (**a**) Case 1 is a 66-year-old female who presented with cough and mild dyspnea on exertion (DOE) in March 2001. HRCT showed reticulation and honeycomb change (HC) in a peripheral and basilar distribution consistent with IPF. VATS biopsy showed temporally and spatially heterogenous pattern of interstitial fibrosis and chronic inflammation, fibroblastic foci, and focal areas of HC consistent with usual interstitial pneumonitis (UIP). Azathioprine was initiated. She developed marked hypoxemia and worsening PFTs and was listed for lung transplant (LT). Left single LT was performed in April 2007 and she has done well. (**b**) Case 2 is a 70-year-old male presented in July 2001with mild DOE and cough. HRCT showed reticulation with a subpleural and bibasilar predominance; no ground-glass opacities or HC. PFTs revealed a mild reduction in DL_{CO} but were otherwise normal. Surgical lung biopsy (SLB) in May 2003 demonstrated temporal and spatial heterogeneity, mild chronic inflammation, frequent fibroblastic foci, and HC consistent with UIP. The patient was enrolled in the interferon-γ (IFN-γ) (Actimune) trial and remained stable. IFN-γ was discontinued in March 2007. Despite no specific therapy, he remains stable. (**c**) Case 3 is a 70-year-old male in excellent health who developed moderate DOE in October 2006. HRCT scan showed typical features of UIP. SLB in June 2007 confirmed UIP pattern. Over the next 2 years, exercise capacity worsened despite relatively stable PFTs. In May 2009, he was hospitalized with an acute exacerbation of IPF that was treated with pulse methylprednisolone. Shortly following discharge, he developed another acute exacerbation for which he was rehospitalized. In hospital, he required high flow oxygen (12 l/min) and was dyspneic at rest. He underwent single LT in July 2009

two almost identical studies that included 779 patients and that evaluated 2403 mg/day pirfenidone with placebo was change in forced vital capacity over a 72 week period. One of the studies was positive with a magnitude of effect similar to that seen in the Japanese studies. The second study did not reach its primary end point but in this and the positive study, several secondary end point indices were positive, including progression-free survival and change in distance walked in six minutes [88b]. The European Commission has recently granted marketing authorisation for Esbriet (pirfenidone) for the treatment of mild to moderate IPF in the EU.

Anticoagulants

Inflammation and vascular injury in IPF may lead to a prothrombotic state that could exacerbate lung injury [103]. Japanese investigators randomized 56 IPF patients to anticoagulants (warfarin) or placebo [104]. Three-year survival and freedom from acute exacerbations were improved in the anticoagulated group. However, dropout rate was high, and selection bias may have influenced the study. Given the risk associated with anticoagulation, additional studies involving greater numbers of patients are required before endorsing this form of therapy. Recently, a placebo-controlled study evaluating warfarin therapy for IPF conducted under the auspices of the IPFnet has been discontinued for lack of efficacy.

Tyrosine Kinase Inhibitor

A phase II RDBPC study of the effect of a tyrosine kinase inhibitor BIBF 1120 on the rate of decline of forced vital capacity has just been published [88c]. The rate of reduction of forced vital capacity was reduced by 68% with the highest dose of active drug compared with placebo and there was efficacy in a number of secondary end points including progression-free survival. In addition there was some evidence for a dose-response effect. This efficacy of the drug is now being tested in two phase III RDBPC studies.

Clinical Vignettes (See Fig. 10.6)

IPF is a heterogeneous disease, with marked differences in prognosis and disease evolution. While most patients display a gradual decline in function over months to years (case 1), some patients remain stable for years even without therapeutic intervention (case 2). Finally, a precipitous decline in lung function and marked hypoxemia may signal an acute exacerbation of IPF (case 3).

Summary

Current therapies for IPF are of limited efficacy with the exception of pirfenidone and the promise of the tyrosine kinase inhibitor BIBF 1120. In the years ahead, it will be important to identify and develop new molecular agonists or antagonists designed to interrupt or reverse the fibrotic process. Novel agents that inhibit fibrosis in vitro or in animal models and are worthy of study in future clinical trials include: angiotensin-II antagonists, platelet-activating factor receptor antagonists, inhibitors of leukocyte integrins, cytokines or proteases; agents that block IL-4, IL-12, or TGFβ; imatinib mesylate, sirolimus, keratinocyte growth factor; relaxin; lovastatin; endothelin-1 antagonists; strategies which promote matrix resorption (e.g., by enhancing the activity of MMPs) [86]. Hopefully, development of effective antifibrotic therapies may improve the outcome of what currently is a frustrating and enigmatic disease.

References

1. American Thoracic Society and the European Respiratory Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International Consensus Statement. Am J Respir Crit Care Med 2000;161: 646–64.
1a. Raghu G, Collard HR, Egan JJ, et al. ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788–824.

2. Lynch III J, Mahidhara RSFM, Keane MP, Zisman DA, Belperio JA. Idiopathic pulmonary fibrosis. In: Lynch III JP, editor. Interstitial pulmonary and bronchiolar disorders. New York: InformaUSA; 2008. p. 333–64. 227.
3. Katzenstein AL, Mukhopadhyay S, Myers JL. Diagnosis of usual interstitial pneumonia and distinction from other fibrosing interstitial lung diseases. Hum Pathol. 2008;39(9):1275–94.
4. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med. 2002;165:277–304.
5. Hwang JH, Misumi S, Sahin H, Brown KK, Newell JD, Lynch DA. Computed tomographic features of idiopathic fibrosing interstitial pneumonia: comparison with pulmonary fibrosis related to collagen vascular disease. J Comput Assist Tomogr. 2009;33(3): 410–5.
6. Lynch 3rd JP, Saggar R, Weigt SS, Zisman DA, White ES. Usual interstitial pneumonia. Semin Respir Crit Care Med. 2006;27(6):634–51.
7. Peikert T, Daniels CE, Beebe TJ, Meyer KC, Ryu JH. Assessment of current practice in the diagnosis and therapy of idiopathic pulmonary fibrosis. Respir Med. 2008;102(9):1342–8.
8. Sumikawa H, Johkoh T, Colby TV, et al. Computed tomography findings in pathological usual interstitial pneumonia: relationship to survival. Am J Respir Crit Care Med. 2008;177(4):433–9.
9. Zisman DA, Flaherty K, Kazerooni E, Martinez F, Lynch III J. Idiopathic pulmonary fibrosis: role of high-resolution thin-section computed tomographic scanning. In: Lynch III JP, editor. Idiopathic pulmonary fibrosis. New York: Marcel Dekker; 2004. p. 237–52.
10. Flaherty KR, Thwaite E, Kazerooni EA, Gross B, et al. Radiologic vs histologic diagnosis in UIP and NSIP: survival implications. Thorax. 2003;58:143–8.
11. 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(2):190–4.
12. Nunes H, Uzunhan Y, Valeyre D, Brillet PY, Kambouchner M, Wells AU. Connective tissue disease-associated interstitial lung disease. In: Lynch III JP, editor. Interstitial pulmonary and bronchiolar disorders, vol. 227. New York: InformaUSA; 2008. p. 429–86.
13. Hubbard RB, Smith C, Le Jeune I, Gribbin J, Fogarty AW. The association between idiopathic pulmonary fibrosis and vascular disease: a population-based study. Am J Respir Crit Care Med. 2008;178(12): 1257–61.
14. Ponnuswamy A, Manikandan R, Sabetpour A, Keeping IM, Finnerty JP. Association between ischaemic heart disease and interstitial lung disease: a case-control study. Respir Med. 2009;103(4): 503–7.
15. Gribbin J, Hubbard R, Smith C. Role of diabetes mellitus and gastro-oesophageal reflux in the aetiology of idiopathic pulmonary fibrosis. Respir Med. 2009;103(6):927–31.
16. Raghu G, Freudenberger TD, Yang S, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J. 2006;27(1):136–42.
17. Song JW, Do KH, Kim MY, Jang SJ, Colby TV, Kim DS. Pathologic and radiologic differences between idiopathic and collagen vascular disease-related usual interstitial pneumonia. Chest. 2009;136(1):23–30.
18. Nozu T, Kondo M, Suzuki K, Tamaoki J, Nagai A. A comparison of the clinical features of ANCA-positive and ANCA-negative idiopathic pulmonary fibrosis patients. Respiration. 2009;77(4):407–15.
19. Hervier B, Pagnoux C, Agard C, et al. Pulmonary fibrosis associated with ANCA-positive vasculitides. Retrospective study of 12 cases and review of the literature. Ann Rheum Dis. 2009;68(3):404–7.
20. Kocheril SV, Appleton BE, Somers EC, et al. Comparison of disease progression and mortality of connective tissue disease-related interstitial lung disease and idiopathic interstitial pneumonia. Arthritis Rheum. 2005;53(4):549–57.
21. Yokoyama A, Kondo K, Nakajima M, et al. Prognostic value of circulating KL-6 in idiopathic pulmonary fibrosis. Respirology. 2006;11(2):164–8.
22. Takahashi H, Shiratori M, Kanai A, Chiba H, Kuroki Y, Abe S. Monitoring markers of disease activity for interstitial lung diseases with serum surfactant proteins a and D. Respirology. 2006;11(Suppl):S51–4.
23. Douglas W, Ryu J, Schroeder D. Idiopathic pulmonary fibrosis. Impact of oxygen and colchicine, prednisone, or no therapy on survival. Am J Respir Crit Care Med. 2000;161:1172–8.
24. Mogulkoc N, Brutsche MH, Bishop PW, Greaves SM, Horrocks AW, Egan JJ. Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation. Am J Respir Crit Care Med. 2001; 164(1):103–8.
25. Flaherty KR, Colby TV, Travis WD, et al. Fibroblastic foci in usual interstitial pneumonia: idiopathic versus collagen vascular disease. Am J Respir Crit Care Med. 2003;167(10):1410–5.
26. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. Ann Intern Med. 2005;142(12 Pt 1):963–7.
27. Selman M, Carrillo G, Estrada A, et al. Accelerated variant of idiopathic pulmonary fibrosis: clinical behavior and gene expression pattern. PLoS One. 2007;2(5):e482.
28. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2007;176(7):636–43.
29. Flaherty KR, Toews GB, Travis WD, et al. Clinical significance of histological classification of idiopathic interstitial pneumonia. Eur Respir J. 2002;19(2): 275–83.

30. King Jr TE, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med. 2001;164(7):1171–81.
31. Daniels CE, Yi ES, Ryu JH. Autopsy findings in 42 consecutive patients with idiopathic pulmonary fibrosis. Eur Respir J. 2008;32(1):170–4.
32. Rudd RM, Prescott RJ, Chalmers JC, Johnston ID. British Thoracic Society Study on cryptogenic fibrosing alveolitis: response to treatment and survival. Thorax. 2007;62(1):62–6.
33. Olson AL, Swigris JJ, Lezotte DC, Norris JM, Wilson CG, Brown KK. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. Am J Respir Crit Care Med. 2007;176(3):277–84.
34. Le Jeune I, Gribbin J, West J, Smith C, Cullinan P, Hubbard R. The incidence of cancer in patients with idiopathic pulmonary fibrosis and sarcoidosis in the UK. Respir Med. 2007;101(12):2534–40.
35. Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. Eur Respir J. 2006;27(1):143–50.
36. Bouros D, Nicholson AC, Polychronopoulos V, et al. Acute interstitial pneumonia. Eur Respir J. 2000;15: 412–8.
37. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006;174(7):810–6.
38. Gribbin J, Hubbard RB, Le Jeune I, Smith CJ, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax. 2006;61(11):980–5.
39. Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? Proc Am Thorac Soc. 2006;3(4):293–8.
40. Rosas IO, Ren P, Avila NA, et al. Early interstitial lung disease in familial pulmonary fibrosis. Am J Respir Crit Care Med. 2007;176(7):698–705.
41. Steele MP, Speer MC, Loyd JE, et al. Clinical and pathologic features of familial interstitial pneumonia. Am J Respir Crit Care Med. 2005;172(9):1146–52.
42. Olson AL, Swigris JJ, Raghu G, Brown KK. Seasonal variation: mortality from pulmonary fibrosis is greatest in the winter. Chest. 2009;136(1):16–22.
43. 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(9): 1322–8.
44. Garantziotis S, Schwartz DA. Host-environment interactions in pulmonary fibrosis. Semin Respir Crit Care Med. 2006;27(6):574–80.
45. Sweet MP, Patti MG, Leard LE, et al. Gastroesophageal reflux in patients with idiopathic pulmonary fibrosis referred for lung transplantation. J Thorac Cardiovasc Surg. 2007;133(4):1078–84.
46. Blondeau K, Mertens V, Vanaudenaerde BA, et al. Gastro-oesophageal reflux and gastric aspiration in lung transplant patients with or without chronic rejection. Eur Respir J. 2008;31(4):707–13.
47. Belperio JA, Weigt SS, Fishbein MC, Lynch 3rd JP. Chronic lung allograft rejection: mechanisms and therapy. Proc Am Thorac Soc. 2009;6(1):108–21.
48. Woodhead F, du Bois RM. Genetics of ILD. In: Lynch III JP, editor. Interstitial pulmonary and bronchiolar disorders. New York: InformaUSA; 2008. p. 43–91. 227.
49. du Bois RM. Genetic factors in pulmonary fibrotic disorders. Semin Respir Crit Care Med. 2006;27(6): 581–8.
50. Armanios MY, Chen JJ, Cogan JD, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med. 2007;356(13):1317–26.
51. Alder JK, Chen JJ, Lancaster L, et al. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. Proc Natl Acad Sci USA. 2008;105(35):13051–6.
52. Cronkhite JT, Xing C, Raghu G, et al. Telomere shortening in familial and sporadic pulmonary fibrosis. Am J Respir Crit Care Med. 2008;178(7): 729–37.
53. Young LM, Hopkins R, Wilsher ML. Lower occurrence of idiopathic pulmonary fibrosis in Maori and Pacific Islanders. Respirology. 2006;11(4):467–70.
54. Lynch III J, Weigt S, Suh R. Thoracic imaging for diffuse ILD and bronchiolar disorders. In: Lynch III JP, editor. Interstitial pulmonary and bronchiolar disorders. New York: InformaUSA; 2008. p. 13–42. 227.
55. Mejia M, Carrillo G, Rojas-Serrano J, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest. 2009;136(1):10–5.
56. Lama VN, Martinez FJ. Resting and exercise physiology in interstitial lung diseases. Clin Chest Med. 2004;25(3):435–53. v.
57. Lederer DJ, Arcasoy SM, Wilt JS, D'Ovidio F, Sonett JR, Kawut SM. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006;174(6):659–64.
58. Nadrous HF, Pellikka PA, Krowka MJ, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest. 2005;128(4):2393–9.
59. Nathan SD, Shlobin OA, Ahmad S, Urbanek S, Barnett SD. Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis. Chest. 2007;131(3):657–63.
60. Zisman DA, Ross DJ, Belperio JA, et al. Prediction of pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med. 2007;101(10):2153–9.
61. Zisman DA, Belperio JA, Saggar R, Saggar R, Fishbein MC, Lynch III J. Pulmonary Hypertension Complicating Interstitial Lung Disease. In: Humbert M, Lynch III JP, editors Pulmonary hypertension. New York: InformaUSA. 2009:236; pp264–291.

62. Nathan SD, Shlobin OA, Ahmad S, et al. Serial development of pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Respiration. 2008;76(3):288–94.
63. 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(3):746–52.
64. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med. 2003;167(5):735–40.
65. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest. 2007;131(3):897–9.
66. Mogulkoc N, Brutsche MH, Bishop PW, et al. Pulmonary (99 m)Tc-DTPA aerosol clearance and survival in usual interstitial pneumonia (UIP). Thorax. 2001;56(12):916–23.
67. King Jr TE, Schwarz MI, Brown K, et al. Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality. Am J Respir Crit Care Med. 2001;164(6):1025–32.
68. Nicholson AG, Colby TV, du Bois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med. 2000;162(6):2213–7.
69. Hubbard R, Johnston I, Britton J. Survival in patients with cryptogenic fibrosing alveolitis: a population-based cohort study. Chest. 1998;113(2):396–400.
70. Winterbauer R, Hammar S, Hallman K, et al. Diffuse interstitial pneumonitis. Clinicopathologic correlations in 20 patients treated with prednisone/azathioprine. Am J Med. 1978;65:661–72.
71. Nicholson AG, Fulford LG, Colby TV, du Bois RM, Hansell DM, Wells AU. The relationship between individual histologic features and disease progression in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2002;166(2):173–7.
72. Wells AU, Desai SR, Rubens MB, et al. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. Am J Respir Crit Care Med. 2003;167(7):962–9.
73. Flaherty KR, Mumford JA, Murray S, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2003;168(5):543–8.
74. 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(5):531–7.
75. Collard HR, King Jr TE, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2003;168(5):538–42.
76. 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(7):803–9.
77. Kawut SM, O'Shea MK, Bartels MN, Wilt JS, Sonett JR, Arcasoy SM. Exercise testing determines survival in patients with diffuse parenchymal lung disease evaluated for lung transplantation. Respir Med. 2005;99(11):1431–9.
78. Dal Corso S, Duarte SR, Neder JA, et al. A step test to assess exercise-related oxygen desaturation in interstitial lung disease. Eur Respir J. 2007;29(2):330–6.
79. Fell CD, Liu LX, Motika C, et al. The prognostic value of cardiopulmonary exercise testing in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2009;179(5):402–7.
80. Lynch DA, Godwin JD, Safrin S, et al. High-resolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. Am J Respir Crit Care Med. 2005;172(4):488–93.
81. Watters L, King T, Schwarz M, Waldron J, Stanford R. 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.
82. Yi CA, Lee KS, Han J, Chung MP, Chung MJ, Shin KM. 3-T MRI for differentiating inflammation- and fibrosis-predominant lesions of usual and nonspecific interstitial pneumonia: comparison study with pathologic correlation. AJR Am J Roentgenol. 2008;190(4):878–85.
83. Singh S, Wells A, Du Bois RM. Other imaging techniques for idiopathic interstitial pneumonias. In: Lynch III JP, editor. Idiopathic pulmonary fibrosis. New York: Marcel Dekker; 2004. p. 237–52. 185.
84. Nagai S, Handa T, Ito Y, Takeuchi M, Izumi T. Bronchoalveolar lavage in idiopathic interstitial lung diseases. Semin Respir Crit Care Med. 2007;28(5):496–503.
85. Ohshimo S, Bonella F, Cui A, et al. Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2009;179(11):1043–7.
86. Thannickal V, Flaherty K, Hyzy R, Lynch III JP. Emerging drugs for idiopathic pulmonary fibrosis. Expert Opin Emerg Drugs. 2005;10(4):707–27.
87. Selman M, Thannickal VJ, Pardo A, Zisman DA, Martinez FJ, Lynch 3rd JP. Idiopathic pulmonary fibrosis: pathogenesis and therapeutic approaches. Drugs. 2004;64(4):405–30.
88. Katzenstein A, Myers J. Idiopathic pulmonary fibrosis. Clinical relevance of pathologic classification. Am J Respir Crit Care Med. 1998;157:1301–15.
88a. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone Clinical Study Group in Japan. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35(4):821–9. Epub 2009 Dec 8.
88b. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis

(CAPACITY): two randomised trials. Lancet. 2011;377(9779):1760–9. Epub 2011 May 13.

88c. Luca Richeldi, M.D., Ph.D., Ulrich Costabel, M.D., Moises Selman, M.D., Dong Soon Kim, M.D., David M. Hansell, M.D., Efficacy of a Tyrosine Kinase Inhibitor in Idiopathic Pulmonary Fibrosis N Engl J Med 2011;365:1079–87.

89. Raghu G, Depaso W, Cain K, et al. Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. Am Rev Respir Dis. 1991;144:291–6.

90. Johnson M, Kwan S, Snell N, Nunn A, Darbyshire J, Turner-Warwick M. Randomized controlled trial comparing prednisolone alone with cyclophosphamide and low dose prednisolone in combination in cryptogenic fibrosing alveolitis. Thorax. 1989;44: 280–8.

91. Lynch III J, McCune J. Immunosuppressive and cytotoxic pharmacotherapy for pulmonary disorders. Am J Respir Crit Care Med. 1997;155:395–420.

92. Antoniou KM, Mamoulaki M, Malagari K, et al. Infliximab therapy in pulmonary fibrosis associated with collagen vascular disease. Clin Exp Rheumatol. 2007;25(1):23–8.

93. Raghu G, Brown KK, Costabel U, et al. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. Am J Respir Crit Care Med. 2008;178(9):948–55.

94. Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med. 2005;353(21):2229–42.

95. King Jr TE, Behr J, Brown KK, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2008;177(1):75–81.

95a. King Jr TE, Brown KK, Raghu G, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011:184;92–99.

95b. Raghu G, Brown KK, Bradford WZ, et al. Idiopathic Pulmonary Fibrosis Study Group. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2004;350(2):125–33.

95c. King Jr TE, Albera C, Bradford WZ, et al. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. Lancet. 2009;374(9685):222–8.

96. Lynch 3rd JP, Saggar R, Weigt SS, Ross DJ, Belperio JA. Overview of lung transplantation and criteria for selection of candidates. Semin Respir Crit Care Med. 2006;27(5):441–69.

97. Swigris JJ, Brown KK, Make BJ, Wamboldt FS. Pulmonary rehabilitation in idiopathic pulmonary fibrosis: a call for continued investigation. Respir Med. 2008;102(12):1675–80.

98. Trulock EP, Christie JD, Edwards LB, et al. Registry of the international society for heart and lung transplantation: twenty-fourth official adult lung and heart-lung transplantation report-2007. J Heart Lung Transplant. 2007;26(8):782–95.

99. Christie JD, Edwards LB, Aurora P, et al. Registry of the international society for heart and lung transplantation: twenty-fifth official adult lung and heart/lung transplantation report–2008. J Heart Lung Transplant. 2008;27(9):957–69.

100. Saydain G, Islam A, Afessa B, Ryu JH, Scott JP, Peters SG. Outcome of patients with idiopathic pulmonary fibrosis admitted to the intensive care unit. Am J Respir Crit Care Med. 2002;166(6): 839–42.

101. Mallick S. Outcome of patients with idiopathic pulmonary fibrosis (IPF) ventilated in intensive care unit. Respir Med. 2008;102(10):1355–9.

102. Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005;171(9):1040–7.

103. Walter N, Collard HR, King Jr TE. Current perspectives on the treatment of idiopathic pulmonary fibrosis. Proc Am Thorac Soc. 2006;3(4):330–8.

104. Kubo H, Nakayama K, Yanai M, et al. Anticoagulant therapy for idiopathic pulmonary fibrosis. Chest. 2005;128(3):1475–82.