



## RESPIRATORY

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# Idiopathic Pulmonary Fibrosis

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CROMSOURCE is an international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialized in clinical development and staffing solutions.

## Definition and Epidemiology

Idiopathic pulmonary fibrosis (IPF) is defined as a specific, chronic and progressive form of pulmonary interstitial fibrosis of unknown etiology that is characterized by irreversible loss of lung function. Although periods of transient clinical stability may be observed, continued progression of the disease is inevitable. The prognosis is poor, with a 5-year survival rate that is similar to the rates for several malignancies. It occurs mainly in adult and elderly patients, it is limited to the lungs, and it is associated with the histological or radiological pattern of “usual interstitial pneumonia” (UIP)<sup>1</sup>. Definition and framing of IPF are shown below in table one.

**Table One: IPF definition and framing**

<b>Definitions</b>	<ul style="list-style-type: none"> <li>• Chronic and progressive form of pulmonary interstitial fibrosis</li> <li>• Unknown etiology</li> <li>• Mainly affects adult and elderly patients</li> <li>• The histological or radiological pattern of “usual interstitial pneumonia” (UIP)</li> </ul>
<b>Diagnosis</b>	<ul style="list-style-type: none"> <li>• Exclusion of known causes of interstitial lung disease (i.e. environmental or occupational exposures, autoimmune diseases and drug toxicity)</li> <li>• UIP pattern in High Resolution Computerized Tomography (HRCT) scan in patients not subjected to Surgery Lung Biopsies (SLB)</li> <li>• Specific combination of radiological and histological pattern in patients subjected to SLB</li> <li>• Multidisciplinary approach among experts: pneumologists, radiologists and pathologists particularly interested in pulmonary interstitial diseases</li> </ul>
<b>Clinical pattern</b>	<ul style="list-style-type: none"> <li>• Disease course is variable and unpredictable</li> <li>• Lung function declines over years in most of the patients</li> <li>• Only few patients remain stable or have rapid worsening symptoms</li> <li>• Episodes of acute exacerbation of the disease are possible in few patients despite previous stability</li> </ul>
<b>Progression</b>	<ul style="list-style-type: none"> <li>• Worsening of respiratory symptoms</li> <li>• Lung function decline</li> <li>• Radiological pattern worsening</li> <li>• Acute exacerbations</li> <li>• Median survival time from diagnosis is 2-4 years</li> </ul>
<b>Comorbidity</b>	<ul style="list-style-type: none"> <li>• Gastroesophageal Reflux (GERD)</li> <li>• Obesity</li> <li>• Pulmonary hypertension</li> <li>• Obstructive Sleep Apnea (OSAS)</li> <li>• Pulmonary Emphysema</li> </ul>

IPF is the most common type of idiopathic interstitial pneumonia. Although the disease has been considered rare, it is as common as stomach, brain and testicular cancers. Incidence of IPF has risen over time, and in Europe and North America is estimated to range between 2.8 and 18 cases per 100.000 people per year. Little data is available for world wide variation, but incidences may be lower in Asia and South America, where it is estimated to range from 0.5 to 4.2 cases per 100.000 individuals per year<sup>2</sup>.

IPF is more common in men and is rare in people younger than 50 years old, the median age of diagnosis is about 65 years old. Although disease course is variable and somewhat unpredictable, the median survival time from diagnosis is 2-4 years.

IPF is now generally regarded as a consequence of multiple interacting genetic and environmental risks factors with repetitive local micro-injuries to ageing alveolar epithelium playing a central role. These micro-injuries initiate aberrant epithelial-fibroblast communication, the induction of matrix-producing myofibroblasts, and considerable extracellular matrix accumulation and remodeling of lung interstitium. Some risk factors that have been identified are: a smoking habit, environmental and occupational exposure, chronic viral infections, GERD and genetic factors<sup>3</sup>.

## Clinical Presentation

Mainly clinical features are chronic dry cough and reduced exercise tolerance (exertional dyspnea). During a physical examination, fine, high-pitched bibasilar inspiratory crackles are usually heard. Careful attention to signs of connective tissue disease is essential to rule out associated diseases. In established disease pulmonary function test (PFT) identify restrictive disease (reduced total lung capacity) and abnormal gas exchange, reduced capacity for carbon monoxide diffusion.

## UIP Pattern Definition and IPF Diagnosis

High-resolution CT scan (HRCT) of the chest is recognized to be the best technique to study interstitial pulmonary diseases. At HRCT UIP pattern is characterized by the presence of “honeycombing” with the typical peripheral and bibasilar distribution. Various studies have shown that the positive predictive power of HRCT in this subset of patients is 90-100%. In these cases, the HRCT is a UIP pattern diagnostics so that surgical lung biopsy it is not indicated. By contrast when the radiological honeycombing feature is not present, but the high resolution CT of the chest images are still compatible with the diagnosis of IPF, the HRCT can be read as a “possible UIP”. Furthermore, when aspects not compatible with UIP diagnosis are present, HRCT is described as “inconsistent with UIP diagnosis”. In these cases of atypical HRCT for UIP (possible UIP or inconsistent with UIP) surgical lung biopsy may be indicated to define whether or not the presence of the UIP pattern. Surgical lung biopsy can also reveal typical pathological aspects of the UIP pattern (fibroblastic foci and honeycombing and patchy fibrosis in the absence of compatible pathological aspects for other diagnoses) or present compatible but non-diagnostic aspects of UIP<sup>4</sup>.

**Diagnosis of IPF is obtained by combining the HRCT with the pathological pattern.**

For the pathological framework, the guidelines recognize the possibility of expressing three different levels of diagnostic certainty ranging from the:

- UIP pattern
- Probable UIP pattern (when there are no aspects compatible with the UIP pattern: only honeycombing or marked fibrosis associated with patchy involvement of lung parenchyma or associated with fibroblastic foci)
- Possible UIP pattern (when there are no aspects of the UIP pattern, but also aspects compatible with other diagnoses)

A multidisciplinary approach is particularly important when deciding to perform additional diagnostic assessments, integrating biopsy results with clinical and HRCT features, and establishing a working diagnosis of IPF if lung tissue is not available<sup>5</sup>.

## Clinical Management: Disease Progression

Accurate prognostication is difficult because the natural history of idiopathic pulmonary fibrosis is highly variable. IPF evolves with a progressive decline in lung function. A restrictive ventilatory defect, defined by a reduction in static, Total Lung Capacity (TLC), and /or operating, Vital Capacity (VC), lung volume, is typical in patients with IPF. Some patients progress rapidly, others quite slowly, and others have sudden worsening after periods of stability.

IPF parenchymal and vascular lesions are responsible of reducing lung diffusion capacity so that lung diffusing capacity is almost always reduced in patients with IPF. Cortes-Telles and coworkers in their study found that the lung carbon monoxide diffusion capacity (DLCO) was reduced in 98% of IPF patients at the time of initial evaluation, although 27% of these subjects had normal TLC and 56% had normal Forced Vital Capacity (FVC)<sup>6</sup>. The severity of lung function impairment at the time of diagnosis and the decline of lung function over time both tightly associated with survival in IPF. Impairment of operating lung volumes, static lung volumes and carbon monoxide transfer are associated with worse prognosis in IPF, with the strongest associations observed with FVC, TLC and DLCO, respectively. Other factors have been shown to affect the disease progression: a minority of patients have acute exacerbations of the disease or rapid worsening triggered by concomitant events like pulmonary embolism, pneumonia, pneumothorax or heart failure. Prognostic factors that negatively affect survival rate are: old age, being male, and other associated diseases like coronary heart disease, pulmonary embolism and lung cancer.

In table two the main negative prognostic factors are summarized. It is strongly recommended to identify those patients that are at high risk of mortality at two years from the diagnosis in order to evaluate the possibility of lung transplantation.

**Table Two: Factors Associated with an Increased Risk of Mortality in IPF**

Baseline factors	Longitudinal factors
<b>Dyspnea severity</b> <b>DLCO &lt; 40% predicted</b> <b>Oxygen saturation &lt; 88% at 6MWT</b> <b>HRCT honeycombing area extension</b> <b>Pulmonary Hypertension</b>	Increasing dyspnea FVC reduction > 10% of baseline value DLCO reduction > 15% of baseline value Worsening of Fibrosis at HRCT scan



## Clinical Management: Treatment

During the past ten years notable advances have been made in pharmacotherapeutic approaches to IPF. Once randomized controlled trials identified that various putative therapies (eg. prednisolone and azathioprine, acetylcysteine, and warfarin) were ineffective or harmful two large phase III development programs identified the first effective disease-modifying therapies for IPF - nintedanib and pirfenidone. Both drugs have been shown to be safe and effective in the treatment of IPF and they are now approved worldwide for idiopathic pulmonary fibrosis treatment, which has improved patient care. In placebo-controlled, randomized trials, each drug has been shown to slow the rate of FVC decline by approximately 50% over the course of one year. Both have shown some efficacy in reducing severe respiratory events. Pooled data and meta-analysis suggest

that these two agents may reduce mortality. If the treatment of IPF can be started at the time of diagnosis patients have a better chance of slowing down irreversible destruction of the lungs.

**Nintedanib** is a tyrosine kinase inhibitor that suppresses multiple signaling receptors implicated in fibrosis pathogenesis, including fibroblast growth factors receptor and platelet-derived growth factor receptor. In comparison with placebo in two phase III clinical studies conducted over 52 weeks, nintedanib resulted with significantly less decline in forced vital capacity (FVC) than in the placebo (47,9% vs 55,1%). In the INPULSIS -2 trial, a significant difference in time to first exacerbation was identified. A prespecified sensitivity analysis based on pooled data from both trials of confirmed or suspected acute exacerbations adjusted centrally by investigators masked to treatment group showed a statically significant benefit of nintedanib ( $p < 0.001$ )<sup>7</sup>.

The most common side effects with nintedanib (which may affect more than 1 in 10 people) include diarrhea, vomiting and increased blood levels of certain liver enzymes (a sign of possible liver problems).

Nintedanib must not be used in patients who are hypersensitive (allergic) to nintedanib, peanut or soy, or any of the other ingredients.

Patients should initially be prescribed 150 mg of nintedanib, to be taken by mouth twice daily. The medication should be taken with food and can be continued indefinitely.

Patients taking nintedanib commonly have diarrhea, which can often be managed with antidiarrheal agents. The dose can be decreased to 100 mg bid if unmanageable side effect occur. Liver function should be tested at baseline, monitored monthly for the first three months, and then monitored as clinically indicated. Since nintedanib is associated with a small increase in the risk of bleeding this agent should be used with great caution, if at all, in patients receiving full-dose anticoagulant therapy.

**Pirfenidone** is an orally administered pyridine with combined anti-inflammatory, antioxidant and antifibrotic actions, including inhibition of collagen synthesis, down-regulation of TGF- $\beta$  and tumor necrosis factor alpha, and a reduction in fibroblast proliferation. The clinical efficacy of Pirfenidone has been studied in four phase III, multicenter, randomized, double-blind, placebo-controlled studies in patients with IPF. The first study conducted by Taniguchi and coworker reported a significant reduction (56.3%) in the relative decline in vital capacity in Japanese patients with idiopathic pulmonary fibrosis treated with pirfenidone. In this study 275 subjects were blindly randomized to high-dose pirfenidone, low-dose pirfenidone or placebo.

Progression-free survival (defined as change in vital capacity of >10% from baseline or death) also showed a significant difference between groups, favoring pirfenidone. These results were compelling and suggested that pirfenidone slows the progression of disease. However, important study design issues challenge the validity of this conclusion. Three areas are of particular concern:

1. The change in primary end-point during the course of the trial
2. The handling of missing data
3. The absence of patient-reported outcomes

Two subsequent phase III trials (CAPACITY studies) compared pirfenidone with a placebo over 72 weeks. The effect of pirfenidone on FVC decline was discordant in these two trials: one trial conformed the initial phase III results, where the other trial found no significant differences between the groups. A fourth study compared oral pirfenidone versus placebo over 52 weeks in patients with idiopathic pulmonary fibrosis with a FVC of 50-90% predicted and a DLCO of 30-90% predicted. The primary end point was the change in FVC or death at week 52. Secondary end points were the 6-minute walk distance, progression-free survival, dyspnea, and death from any cause or from idiopathic pulmonary fibrosis. In the pirfenidone group, as compared with the placebo group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died; there was also a relative increase of 132.5% in the proportion of patients with no decline in FVC ( $P<0.001$ ). Pirfenidone reduced the decline in the 6-minute walk distance ( $P=0.04$ ) and improved progression-free survival ( $P<0.001$ ). There was no significant difference between groups in dyspnea scores ( $P=0.16$ ) or in rates of death from any cause ( $P=0.10$ ) or from idiopathic pulmonary fibrosis ( $P=0.23$ ). However, in a prespecified pooled analysis incorporating results from phase III trials, conducted in 1247 patients, reported that fewer subjects died and had a decrease in 6MWT in the pirfenidone group than in the placebo group. Gastrointestinal and skin-related adverse events were more common in the pirfenidone group than in the placebo group but rarely led to treatment discontinuation<sup>8</sup>.

In practice patients should initially be prescribed a titrated daily dose of pirfenidone over a 14-day period as follows:

- Days 1 to 7: one capsule, three times a day (801 mg/day)
- Days 8 to 14: two capsules, three times a day (1602 mg/day)
- Day 15 onward: three capsules, three times a day (2403 mg/day)

The recommended maintenance daily dose of pirfenidone is three 267 mg capsules three times a day with food for a total of 2403 mg/day. Doses above 2403 mg/day are not recommended for any patient.



**Table 3: Comparison Nintedanib vs Pirfenidone**

Variable	Nintedanib (Ofev)	Pirfenidone (Esbriet)
<b>Mechanism of action</b>	Tyrosine kinase inhibitor Inhibition of the activation of FGFR and PDGFR signaling cascades.	Pirfenidone attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as, transforming growth factor-beta (TGF- $\beta$ ) and platelet-derived growth factor (PDGF).
<b>Efficacy</b>	Slow FVC decline by 50%	Slow FVC decline by 50%
<b>Reference product used in phase 3 clinical studies</b>	PLACEBO	PLACEBO
<b>FDA approved dose</b>	150 mg bid by mouth	801 mg bid by mouth
<b>Common side effects</b>	Diarrhea	Anorexia, nausea, photosensitivity
<b>Need for liver function monitoring</b>	Yes	Yes
<b>Clinical strategies to minimize side effects</b>	Use of antidiarrheal agents, temporary dose reduction to 100 mg bid	Slow dose increase over 14-day period, medication to be taken with food, use of antacids, use of antiemetic agents, sun avoidance

Since no head-to-head comparison of data is available to recommend pirfenidone or nintedanib. A network of meta-analysis results have shown similar benefit<sup>9, 10</sup>. New trials are needed to assess timing of initiation therapy, how to better define the patients response to treatment and when the therapy should be discontinued<sup>11</sup>. Recently Vancheri and coworkers studied the safety of combining the two drugs. Preliminary results showed that Nintedanib with add-on pirfenidone had a manageable safety and tolerability profile in patients with IPF, in line with the adverse event profiles of each drug. Further research into combination regimens in the treatment of IPF are expected in the future<sup>12</sup>.



## Clinical Management: Lung Transplantation

Approximately only half of 2000 lung transplantations performed each year in United States are performed for interstitial lung diseases. The medical complexity of the surgery and post-surgical treatment and the restricted supply of donor organs are the reasons why only a minority of patients receive a transplant. In selected patients with IPF, lung transplantation can prolong survival and improve quality of life; however only about 50% survive for more than five years.

Lung transplantation should be discussed with individual patients at the time of diagnosis or no later than objective evidences of disease progression are available, since the evaluation process and waiting time can last for months to years<sup>13</sup>.

## Clinical Management: Acute Respiratory Deterioration

Patients with IPF might have acute respiratory deteriorations, with development of new or worsening dyspnea and increase oxygen requirement. Each year, approximately 10 to 20% of patients with IPF have an acute exacerbation, characterized by worsened hypoxemic respiratory failure, with bilateral ground glass opacities, consolidation or both on HRTC imaging<sup>14</sup>. A clinical event like an infection may be a possible trigger factor but frequently exacerbation is idiopathic. Acute exacerbation is more common in patients with physiologically and functionally advanced disease. In patients with acute respiratory deterioration, identification of any potentially treatable causes is a priority and these should be managed appropriately. In case of acute exacerbation a short course of high-dose glucocorticoids is conditionally recommended by international guidelines even though the efficacy and safety of this treatment in these circumstances have not been demonstrated in clinical trials.

## Clinical Management: Symptom Focused Therapy

Patients with IPF suffer a symptom burden and impaired Quality of Life (QoL) that increases in the terminal stages of their disease. Therefore, all patients with progressive idiopathic fibrotic interstitial lung diseases should receive the best supportive care to improve symptom control, including dyspnea and cough. In patients with chronic cough possibly contributing comorbidities, such as gastro-esophageal reflux disease, should be considered. Opiates might reduce anxiety, dyspnea and cough. Symptoms are often refractory to standard pharmacological intervention. Pulmonary rehabilitation has a positive effect on 6MWD test and a trend towards significance in improving QoL and dyspnea<sup>15, 16</sup>.

## Conclusions

Approval of disease-modifying therapies for IPF have increased the focus on early and accurate diagnosis with the aim of improving long-term treatment outcomes. The diagnostic certainty of IPF depends on the presence or absence of specific radiological/morphological diagnostic criteria. Therefore, the involvement of a multidisciplinary team is highly recommended rather than only clinicians or radiologists.

Prediction of disease progression for individual patients is not possible because of considerable interpatient heterogeneity, however, an advanced stage of disease at the time of diagnosis, rapid progression and the frequency of acute exacerbations negatively affect the prognosis.

In the future more therapeutic trials are required to assess if combination therapy might be more effective than single treatment and for subjects with uncertain IPF diagnosis (possible or probable) because an approved pharmacological treatment is not available. In addition, new primary objectives such as hospitalization and survival time/death rate should be considered as strategic end points for effective future treatments for phase III trials.

## References

- 1 Raghu G., Remy-Jardin M., Myers JL. et al.  
Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guidelines  
Am. J. Respir. Crit. Care Med. 2018; 198 (5): e44-e68.
- 2 Hutchinson J., Fogarty A., Hubbard R., et al.  
Global incidence and mortality of idiopathic pulmonary fibrosis: ma systematic review.  
Eur. Respir. J 2015; 46: 795-806.
- 3 Richeldi L., Collard HR., Jones MG.  
Idiopathic pulmonary fibrosis  
Lancet 2017; 389: 1941-52.
- 4 Lederer D., Martinez FJ.  
Idiopathic pulmonary fibrosis  
N. Engl. J. Med. 2018; 378: 1811-23.
- 5 Lynch DA., Sverzellati N., Travis WD., et al.  
Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper.  
Lancet Respir. Med. 2018; 6: 138-53.
- 6 Cortes-Telles A., Forkert L., O'Donnell DE., et al  
Idiopathic pulmonary fibrosis: new insights on functional characteristics at diagnosis.  
Can. Respir. J. 2014; 21: e55-e60.
- 7 Richeldi L., Bois duRM., Raghu G., et al.  
Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis.  
N. Engl. J. Med. 2014; 370: 2071 – 82.
- 8 King 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.
- 9 Canestaro WJ., Forrester SH., Raghu G., et al.-  
Drug treatment of idiopathic pulmonary fibrosis: systematic review and network meta-analysis.  
Chest2016; 1498: 756-66.
- 10 Rochweg B., Neupane B., Zhang Y., et al.  
Treatment of idiopathic pulmonary fibrosis: a network meta-analysis.  
BMC Med 2016; 14: 18.
- 11 Raghu G. and Selman M.  
Nintedanib and pirfenidone: new antifibrotic treatments indicated for idiopathic pulmonary fibrosis offer hopes and raises questions.  
Am. J. Respir. Crit. Care Med. 2015; 191: 252-4.

12 Vancheri C., Kreuter M., Richeldi L., et al.

Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis. Results of the INJOURNEY Trial. Am. J. Respir. Crit. Care Med. 2018 Feb 1; 197(3): 356-363.

13 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 International Society for Heart and Lung Transplantation. J.Heart Lung Transplant 2015; 34: 1-15.

14 Collard HR., Ryerson CJ., Corte TJ. Et al.

Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am. J. Respir. Crit. Care Med. 2016; 194: 265-75.

15 Bajwash S., Ross JR., Peacock JL., et al.

Interventions to improve symptoms and quality of life of patients with fibrotic interstitial lung disease: a systematic review of the literature. Thorax 2013; 68: 867-79.

16 Ryerson CJ., Cayou C., Topp F., et al.

Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. Respir. Med. 2014; 108: 203-10.

## About The Author



**Renato Testi** graduated from the University of Padua with a degree in Chemistry, before gaining his MD from the University of Verona. After a couple of years at Padua University as an assistant in the Organic Chemistry Department, Renato joined Laboratory Glaxo S.p.A. (Italy) as Head of Chemistry from 1974 to 1979. In 1979 he moved to the Medical Department as a Medical Advisor, subsequently becoming Medical Respiratory Leader in the same company Glaxo Smith Kline SpA (Italy) from 1979 to December 2004. In this role Renato supported clinical development and marketing activities of several drugs in respiratory medicine.

In 2006, Renato became a Clinical Research Physician at Centro Ricerche Cliniche, Policlinico BG Roma, Verona focusing on performing medical activities and screening visits for volunteers involved in clinical trials in Phase I to III. Renato joined CROMSOURCE in 2010 as a Medical Monitor in the Clinical Research division. Here Renato has managed clinical trial activities, medical oversight and monitoring procedures for many international clinical trials in both asthma and COPD.

Renato continues practising as a physician specialised in respiratory medicine, currently at Respiratory Physiopatology Unit - Policlinico BG Roma, Verona University.

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