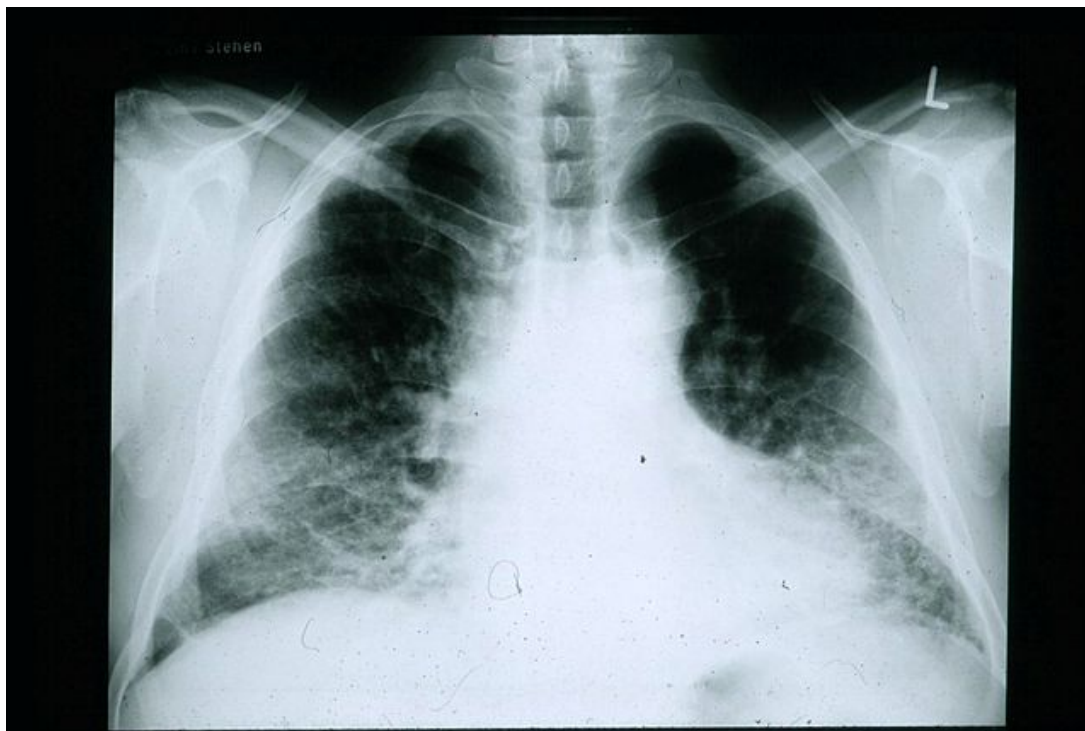


Usual Interstitial Pneumonia (UIP) and Idiopathic Pulmonary Fibrosis (IPF) — Symptoms and Treatments

[See online here](#)

Idiopathic pulmonary fibrosis (IPF) belongs to a group of diseases whose specific cause is not well known, which keeps clinicians and researchers worried: the often rapid progression of IPF is very distressing. Also the underlying causes are mostly unknown, pathophysiologic explanations and findings are still unsatisfying. With only a 5-year survival rate of 20-40 %, only quick decisions such as initiating a lung transplantation, might help prolong a patient's life.



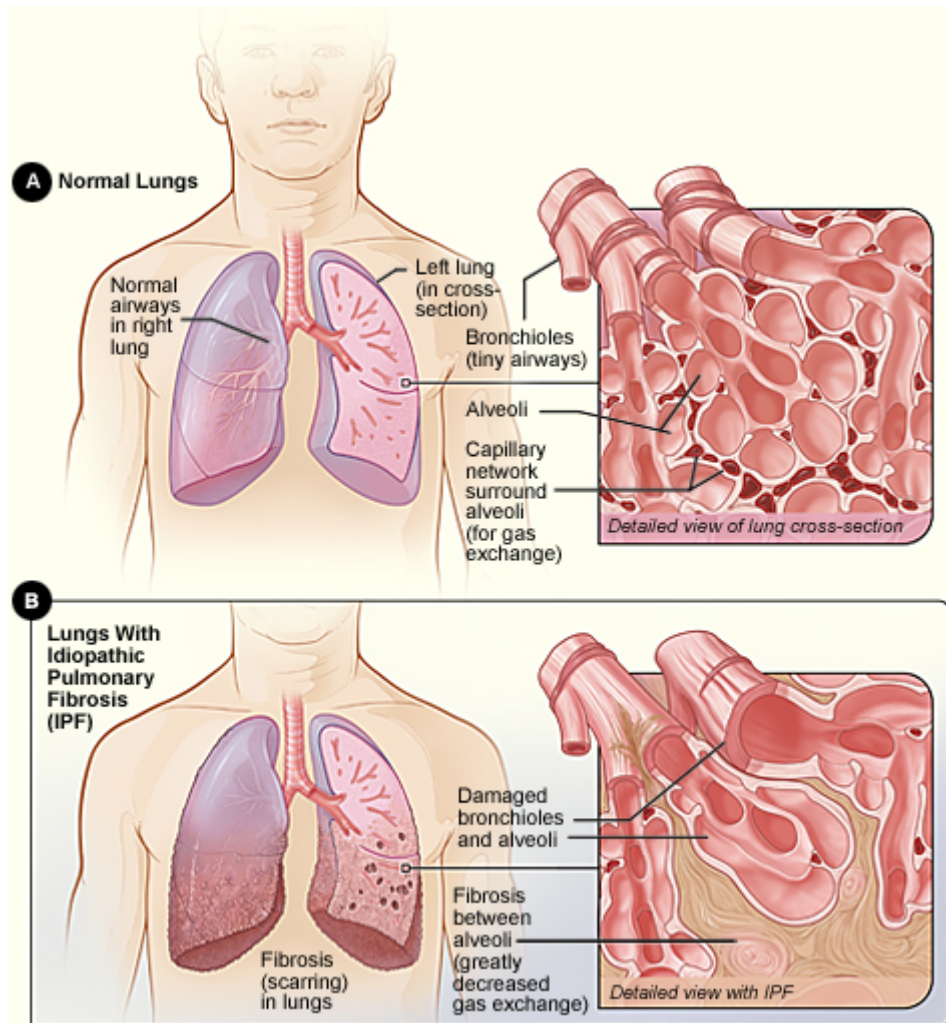
Definition of UIP

Usual interstitial pneumonia (UIP) is a **chronic lung disease characterized by the progressive scarring of both lungs**. The fibrosis involves the interstitium of the [lung](#) and is therefore rated among the 'interstitial lung diseases'.

In addition to the pathologic findings in the morphology of the lung, UIP may be from a known or unknown cause and should be investigated for possible underlying clinical conditions such as asbestosis, [autoimmune diseases](#), and drug toxicity. In most cases the cause is unknown. The clinical term for UIP of an unknown cause is **idiopathic**

pulmonary fibrosis (IPF).

IPF is the most common type of **interstitial lung diseases** and is characterized by chronic, progressive, irreversible, and usually fatal lung disease. Patients with IPF are usually middle-aged and share a similar histopathological picture with other forms of interstitial lung diseases.



[Image](#): "Figure A shows the location of the lungs and airways in the body. The inset image shows a detailed view of the lung's airways and air sacs in cross-section. Figure B shows idiopathic pulmonary fibrosis (scarring) in the lungs. The inset image shows a detailed view of the fibrosis and how it damages the airways and air sacs." by National Heart Lung and Blood Institute (NIH). License: Public Domain

Epidemiology of UIP and IPF

Spread of UIP and IPF

The epidemiology of UIP has been difficult to study because of its rarity and evolution in diagnostic and coding practices. Though uncommon, it is likely under-appreciated both in terms of its occurrence (i.e. incidence and prevalence) and public health impact (i.e. health care costs and resource utilization).

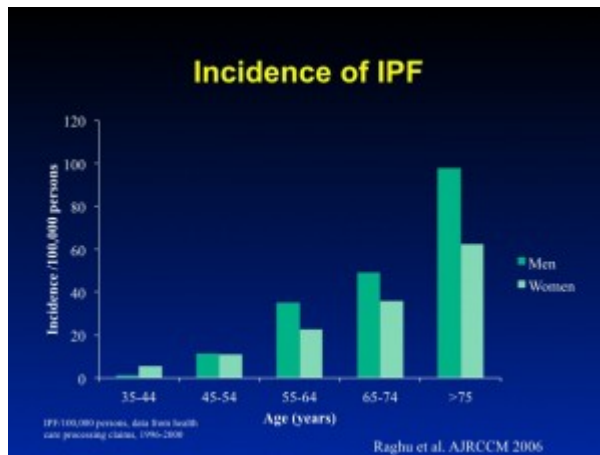


Image: "Incidence of IPF" by Rishirajmd. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Of the over 150 recognized types of interstitial lung diseases (ILD) in pulmonology practices, IPF is the most common with an estimated prevalence rate of **50 per 100,000**.

IPF prevalence and incidence increases with age, being higher among **men** with the median age at the time of diagnosis being 66 years, and appears to be on the increase in recent years. The disease occurs primarily in **middle-aged and older adults**.

Etiology of UIP and IPF

Causes of UIP and IPF

The etiology of IPF remains undefined. However, in the current hypothesis regarding the pathogenesis of idiopathic pulmonary fibrosis (IPF), **exposure to an inciting agent** like (tobacco) smoke, environmental pollutants, environmental dust, viral infections, wood and metal dust, [gastroesophageal reflux disease](#) or chronic aspiration in a vulnerable host may lead to the initial alveolar epithelial injury.

It has been hypothesized that no single etiologic agent serves as a common inciting agent but rather that affected patients might have common defects in their **reparative pathways** (i.e. abnormal wound healing).

There is currently no consensus upon the effect of [type 2 diabetes](#), obesity, and ischemic heart disease on the risk of IPF. Therefore, it is clear that risk factors for the disease can be only identified in a minority of the cases, hence the term 'idiopathic'.

Cigarette smoking is the best recognized and most accepted risk factor for IPF and increases the risk of IPF by about 2-fold. And because 1 type of IPF runs in families, **heredity** is also thought to play a role.

Risk factors are:

- More than 80% is sporadic
- Familiar: 2-20% cases
- Mucin gene MUC5B
- Telomerase and surfactant mutation
- Seen more in older individuals

Pathogenesis of IPF

Patients with IPF are thought to have an **inflammatory condition that is complicated by fibrosis**. It is currently believed that **fibroblasts** in IPF become recruited and activated by **epithelial-cell mediated pathways**, hence the link between inflammation and epithelial-mediated diseases has been established. In addition to activation of the fibroblasts responsible for the deposition of collagen and lung fibrosis in IPF by the epithelial cells, direct activation by the inflammatory process has also been described.

Epithelial cell injury is hypothesized to be the precursor step to the epithelial-mediated pathway of lung fibrosis. Chronic viral infection, smoking, and exposure to wood or metal dust are possible risk factors for epithelial cell injury. Additionally, familial cases of IPF seem to share certain **mutations in the surfactant protein C gene**, further emphasizing the role of epithelial injury in the pathogenesis of IPF.

In addition to epithelial cell injury, histological examination of the lung tissue from patients with IPF also shows **hyperplasia and hypertrophy of type 2 pneumocytes**. It seems that the insult to epithelial cells results in **uncontrolled epithelial cell activation** and a **dysregulated epithelial cell repair process**. The **upregulation of certain tumor-related genes** such as the Wnt and Shh pathways have been linked to IPF and uncontrolled epithelial cell activation.

The next step in the pathogenesis of IPF is the activation of the **coagulation pathway** in the lung microvasculature. As a result of this, **small thrombi** form, which contributes more to the pathogenesis of the disease. Injured epithelial cells also release mediators that activate fibroblasts. **Activated fibroblasts secrete collagen** in the extracellular matrix which contributes to fibrosis.

In addition to all of these pathologic changes, patients with IPF also have a characteristic **loss of Alveolar Epithelial Cells Type 1**, which are responsible for prompt gas exchange in the alveoli. It is currently hypothesized that the absence of these epithelial cells results in the **lack of anti-fibroblastic mediators**, which makes the fibroblasts to be left unchecked and highly active in the injured tissue.

Once fibrosis starts, lung remodeling ensues, which is also characterized by **angiogenesis**. New [blood vessels](#) that are abnormal form within the fibrotic lung tissue in some patients. It seems that this process is heterogeneous as other patients with IPF have **hypovascular fibrotic foci** and in this subset of patients, it is believed that the absence of angiogenesis is an important factor in inducing fibrosis.

Whether IPF is a condition that is **age-related** remains unclear. High resolution computed tomography of asymptomatic people older than 75 years reveals a similar picture but the disease is usually not progressive in this group of patients. Few studies have pointed out that **telomeres** are usually shorter in cells obtained from fibrotic tissue in IPF patients, hence linking IPF to cellular aging.

Pathology and Pathophysiology of UIP and IPF

There are 4 key features of UIP including interstitial fibrosis in a **'patchwork pattern'**, **interstitial scarring**, **honeycomb changes** and **fibroblast foci**. Fibroblastic foci are dense collections of myofibroblasts and scar tissue, and together with honeycombing, are the main pathological findings that allow a diagnosis of UIP.

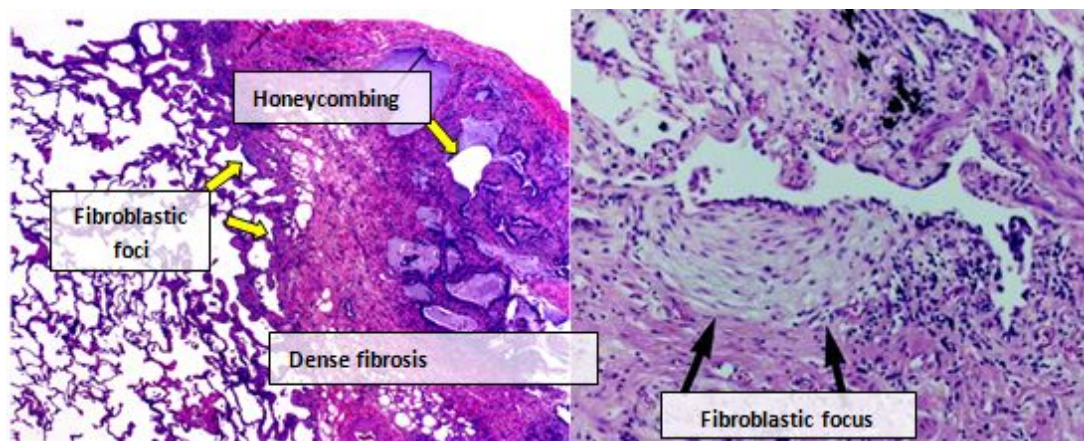


Image: "Photomicrograph of the histopathological appearances of usual interstitial pneumonia." by IPFeditor. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Lung tissue from people with IPF usually shows a characteristic histopathologic UIP pattern and is therefore the pathologic counterpart of IPF.

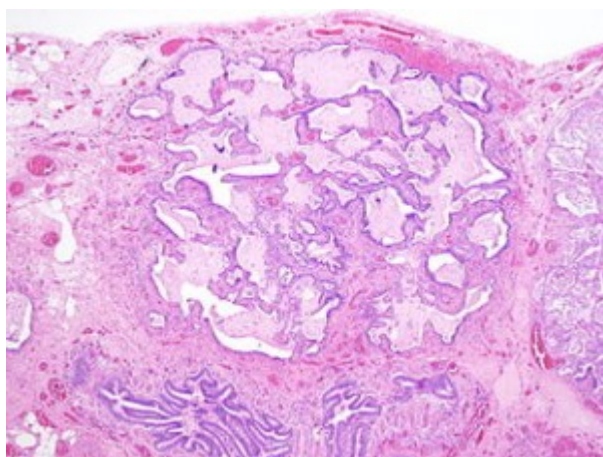


Image: "Honeycomb change on a surgical lung biopsy." by Mutleysmith. License: Public Domain

The gross appearance of the lungs in IPF shows characteristic fibrosis that is distributed along the inferior portions of the lobes with subpleural accentuation. The **pleural surface has a bosselated or cobblestone appearance**, and on cut sections, these regions correspond to areas of airspace enlargement and fibrotic retraction. This pattern of fibrosis has been termed gross honeycombing. The typical microscopic appearance of IPF has been termed usual interstitial pneumonia.

Although an understanding of the pathogenesis of IPF is incomplete, recent advances delineating specific clinical and pathologic features of IPF have led to a better definition of the molecular pathways that are pathologically activated by the disease.

The process of replacing a damaged epithelium after an injury with a new 1 plays an important role in physiological wound healing.

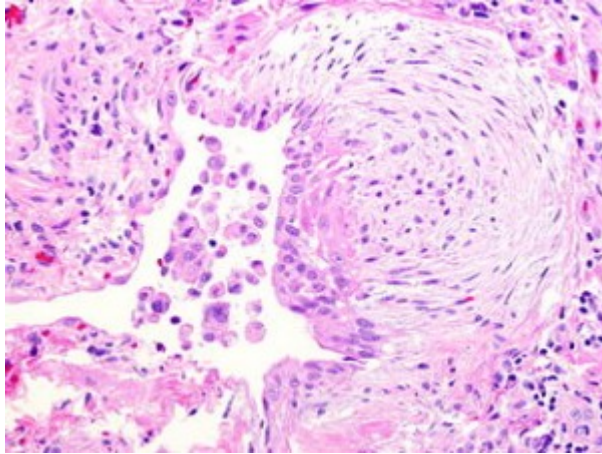


Image: "Fibroblast focus in UIP" by Mutleysmith. License: Public Domain

However, the current theory for the development of idiopathic pulmonary fibrosis says, that such injuries or damages to the alveolar epithelial cells can lead to an exaggerated activation of mesenchymal cells. These proliferate and form fibroblastic foci. Fibroblasts and myofibroblasts accumulate and lead to the irreversible fibrosis.

Symptoms of UIP and IPF

Signs of UIP and IPF

Patients presenting with symptomatic IPF are usually in the advanced stages of the disease and the median survival period after diagnosis is estimated to be 3.5 years.

The clinical symptoms of IPF are **nonspecific**. Most patients present with **exertional dyspnea** and a **nonproductive cough**. Such symptoms can be shared with a variety of other pulmonary and cardiac diseases. Dyspnea, which is the most prominent symptom in IPF, usually begins insidiously and is often progressive. Associated systemic symptoms can occur but are not common. Some of these systemic symptoms include **weight loss, low-grade fevers, fatigue, arthralgias** or **myalgias**.

The symptoms of IPF develop over time and may not even begin to appear until the disease has done serious damage to the lungs. The course of pulmonary fibrosis and the severity of symptoms can vary considerably from person to person.

Patients with **stable IPF** usually complain of having a **chronic cough** and **progressive dyspnea** over the years. Additionally, such patients usually have **decreased lung volumes and capacities** on [pulmonary function testing](#). Patients with accelerated IPF are usually male tobacco smokers. These patients present with a rapidly progressive disease and have a very short survival time after diagnosis.

Patients with stable IPF can also present with acute exacerbations. Patients usually present with worsening dyspnea and [hypoxemia](#). Possible causes of exacerbations should be excluded before attributing the acute exacerbation to the natural history of the disease. Examples of such causes are **infection, heart failure** and **pulmonary embolism**.

Patients with acute exacerbations due to IPF have characteristic imaging findings of bilateral ground-glass opacities that are superimposed on a pattern of honeycomb interstitial pneumonia on computed tomography.

Patients with IPF can have a complicated picture due to their smoking history with **chronic obstructive lung disease**. In these patients, in addition to the typical picture on computed tomography, focal and diffuse emphysema can also be identified.

Due to the ongoing epithelial injury, uncontrolled epithelial and fibroblast activity, and the overexpression of tumor-related genes, patients with IPF are at an increased risk of developing **lung cancer**.

Diagnostics of UIP and IPF

The diagnosis of IPF is usually made late in the disease process due to the non-specificity of the presenting symptoms. Therefore, the current consensus is to focus on **multidisciplinary approaches to diagnose IPF as early as possible** to provide a possible treatment for the patient.

History and physical findings

It is critical to obtain a complete history, including **medication history, drug use, social history, occupational, recreational, and environmental respiratory exposure history**, risk factors for **human immunodeficiency virus (HIV) infection** and review of systems, to ensure other causes of interstitial lung disease are excluded. **Amiodarone, bleomycin, and nitrofurantoin** are notable medications associated with pulmonary fibrosis.

Dry, inspiratory, bibasilar velcro-like crackles can be heard on auscultation. Assessment of velcro crackles on lung auscultation is a practical way to improve the earlier diagnosis of IPF. Fine crackles are easily recognized by clinicians and are a characteristic of IPF.

Many patients show a **pulmonary hypertension** while at rest. Then a **split 2nd heart sound** might be heard on auscultation, as well as a **dominant P2 component of S2**.

Digital clubbing is seen in 30–50% of patients with IPF and should be observed while examining the patient. **Cyanosis** and **peripheral edema** may be observed in the late phases of the disease.

Physicians should pay attention to historical clues that may suggest the presence of **obstructive sleep apnea** (OSA) because studies have demonstrated a high prevalence of OSA in patients with IPF.

Pulmonary function tests

The typical findings on pulmonary function tests in patients with idiopathic pulmonary fibrosis are a **restrictive ventilatory defect** and a **reduced diffusion capacity for carbon monoxide**.

Measurement of **static lung volumes using body plethysmography** typically reveals reduced lung volumes (restriction). Vital capacity, functional residual capacity, total lung capacity, and forced vital capacity (FVC) are all reduced. Additionally, the **static pressure-volume curve** is shifted downward and to the right as a result of decreased lung compliance.

Diagnostic imaging

HRCT scans

The radiological evaluation through high-resolution computed tomography (HRCT) is an essential point in the diagnostic pathway in IPF as HRCT findings are significantly more sensitive and specific for the diagnosis.

On HRCT images, idiopathic pulmonary fibrosis is characterized by **patchy, peripheral, subpleural, bibasilar reticular opacities**, and **honeycombing pattern of the lower lobes**. Typical HRCT of the chest of IPF demonstrates **fibrotic changes in both lungs**, with a predilection of the bases and the periphery.

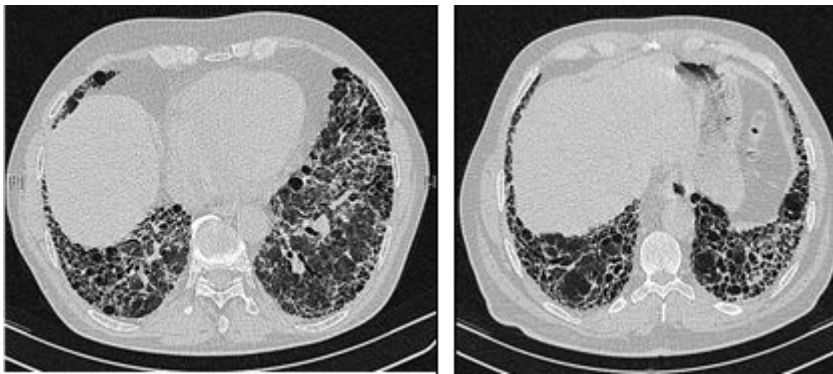


Image: "HRCT scans of the chest of a patient with IPF" by IPFeditor . License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)



Image: "A chest radiograph of a patient with Idiopathic Pulmonary Fibrosis (IPF)." by IPFeditor . License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Many patients with IPF have an abnormal [chest radiograph](#) at the time of diagnosis. The typical findings are **peripheral reticular opacities** (netlike linear and curvilinear densities) predominantly at the lung bases. **Honeycombing** (coarse reticular pattern) and **lower lobe volume loss** can also be seen.

Laboratory testing

Lung biopsy

Surgical lung biopsy specimen obtained using video-assisted thoracoscopic surgery (VATS) provides the best sample for which to distinguish usual interstitial pneumonia from other idiopathic interstitial cases of pneumonia.

Histopathological examination of a lung biopsy can provide more clues about the possibility of IPF. Patients with IPF show a similar histopathological picture to other typical interstitial lung diseases which include alternating zones of normal and abnormal lung tissue, dense fibrosis, mild fibrosis, and honeycombing patterns.

Laboratory testing to exclude connective tissue diseases such as **systemic lupus erythematosus** and **rheumatoid arthritis** is indicated. Rheumatoid factor, double-stranded DNA, antinuclear antibodies, C-reactive protein, and erythrocyte sedimentation rate are a few examples of possible **markers of inflammatory lung disease**. Unfortunately, there are **currently no reliable blood biomarkers** for the confirmation of the diagnosis of IPF.

Bronchoscopy with BAL

Bronchoscopy with Bronchoalveolar Lavage (BAL) and/or transbronchial biopsy is a well-tolerated diagnostic procedure for determining idiopathic pulmonary fibrosis. In the evaluation of patients with suspected IPF, the most important application of BAL is in the exclusion of other diagnoses.

Differential Diagnoses of UIP and IPF

Clinical pictures similar to UIP and IPF

UIP/IPF can be distinguished from other forms of diffuse parenchymal lung disease by clinical methods, including history, physical examination, laboratory studies, imaging, and pathologic analysis. You should especially keep in mind other pulmonary diseases such as **nonspecific interstitial pneumonia, acute interstitial pneumonia, respiratory bronchiolitis, interstitial lung disease, desquamative interstitial pneumonia,** and **cryptogenic organizing pneumonia**.

Make sure it is not associated with a connective tissue disease (serologies, rest of the history, and physical). Also, rule out any drug or occupational exposure.

Therapy of UIP and IPF

The goals of treatment in IPF are essential to **reduce the symptoms, stop disease progression,** prevent acute exacerbations, and **prolong survival**. Any underlying conditions that might help the disease to progress should be treated (e.g., [gastroesophageal reflux disease](#) (GERD), OSA, nicotine abuse, and side effects caused by medications).

The only definitive treatment that is known to prolong survival in patients with IPF is **lung transplantation**. Unfortunately, the 5-year survival rate after lung transplantation for IPF is only 44%. It is currently recommended to refer the patient for evaluation for possible lung transplantation immediately after the initial diagnosis.

Stem cell-based therapy for IPF is currently being investigated in several lung models of the disease with promising results.

Patients with IPF can present with **acute exacerbations** which should be treated promptly. **Broad-spectrum antibiotics** combined with **corticosteroids** are the mainstay of treatment for IPF-related acute exacerbations. Unfortunately, patients who develop acute exacerbations usually do not survive the episode.

Pharmacologic therapy

As we have explained, patients with IPF have an **increased risk of small-vessel occlusive disease** which puts them at risk of developing **pulmonary arterial hypertension**. Patients with pulmonary arterial hypertension are at an increased risk of **all-cause mortality** in IPF and therapeutic approaches against pulmonary arterial hypertension are recommended.

Therefore, **sildenafil** is recommended as 1st-line therapy for pulmonary arterial hypertension in IPF patients and its use has been associated with improved quality of life in advanced disease.

N-acetylcysteine (NAC)

Treatment with high doses of NAC **may repair an oxidant-antioxidant imbalance** that occurs in the lung tissue of patients with IPF. In addition, NAC reduced the decline in VC and DLCO over 12 months of follow-up when used in combination with prednisolone and azathioprine (triple therapy).

However, in 2011, a guideline for the treatment of IPF (composed and validated by an international group of leading respiratory societies) mentions a 'conditional recommendation against the use of NAC monotherapy'.

Our systematic review of the available evidence on IPF treatments points to the need for additional research and long-term studies of their safety and efficacy. Ganesh Raghu, a member of the committee, explained and further:

"The guidelines empower the clinician to make the most appropriate treatment choices for the patient confronted with IPF and encourage shared decision-making with the well-informed patient to choose the most appropriate treatment options tailored to the individual patient's needs".

Antifibrotic agents

Pirfenidone is an anti-fibrotic drug for the treatment of IPF. It works by reducing lung fibrosis through **down-regulation of the production of growth factors and procollagens 1 and 2**. Pirfenidone improves progression-free survival and, to a lesser effect, pulmonary function in patients with IPF.

Angiokinase inhibitors

Nintedanib inhibits multiple tyrosine kinases and targets growth factors, which have been shown to be potentially involved in pulmonary fibrosis.

Non-pharmacologic therapy

Long term oxygen therapy

Oxygen therapy or supplementary oxygen for home use is a strong recommendation for use in patients with clinically significant resting hypoxemia.

Respiratory rehabilitation

Pulmonary rehabilitation could alleviate the overt symptoms of IPF and improve functional status by stabilizing and/or reversing the extrapulmonary features of the disease. Respiratory rehabilitation programs may include **exercise training, smoking cessation, psychosocial assistance, and supportive care**.

Lung transplantation

Lung transplantation for IPF has been shown to confer a survival benefit over medical therapy. The most recent data suggest that **bilateral** lung transplantation is superior to single lung transplantation in patients with IPF.

Palliative care

Palliative care focuses on reducing symptoms and improving the comfort of patients rather than treating the disease.

Progression and Prognosis of UIP and IPF

IPF progression is associated with an estimated median **survival time of 2-5 years** following diagnosis. The **5-year survival** for IPF ranges between **20-40%**. In IPF patients, the overall mortality rate within 5 years is high but the annual rate of all-cause mortality in patients with mild to moderate lung impairment is relatively low. Respiratory failure resulting from disease progression is the most frequent cause of death.

Patients with IPF may suffer periods of acute respiratory decline either due to known complications, such as an infection, or an unknown cause (acute exacerbation of IPF). The rate of decline and progression to death in patients with IPF may take several clinical forms: **slow physiologic deterioration with worsening severity of dyspnea, rapid deterioration and progression to death, or periods of relative stability interspersed with periods of acute respiratory decline** sometimes manifested by hospitalizations for respiratory failure.

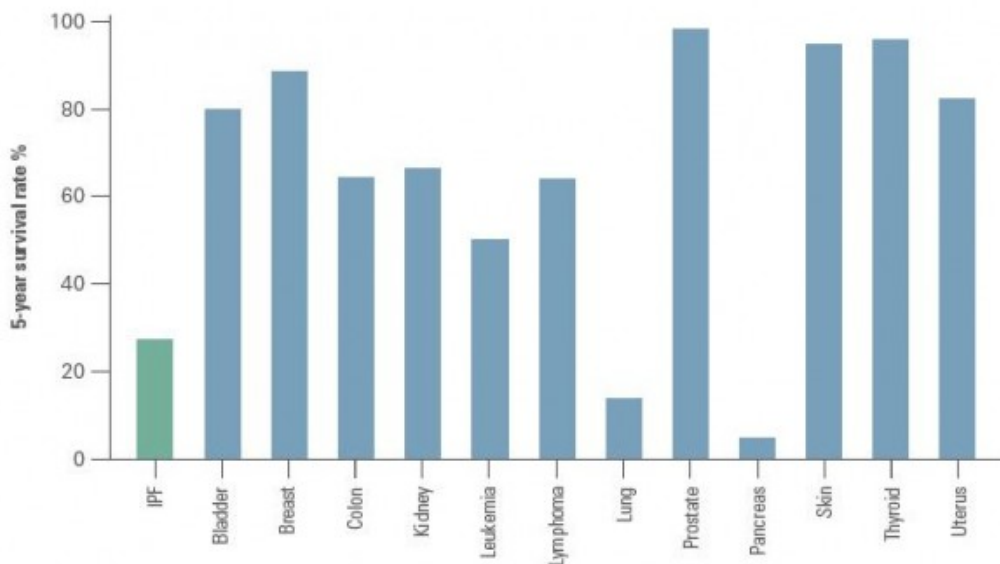


Image: "Comparison of the 5-year survival rate for Idiopathic Pulmonary Fibrosis (IPF) and common malignancies" by IPFeditor . License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

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