

Reporters' Guide to Idiopathic Pulmonary Fibrosis



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IPF *slowly robs
its victims of
the ability
to breathe.*

Idiopathic pulmonary fibrosis (IPF) is a devastating illness for which there is no known cause or cure. It creeps up on its victims and slowly robs them of their ability to breathe.

Although relatively rare, affecting about 50,000 people in the United States, IPF is on the rise. Recent studies show that the disease is 5 to 10 times more prevalent than previously thought, occurring more often among men than women.

IPF's insidious nature and similarities to other diseases marked by inflammation and scarring of the lungs make it one of the most difficult pulmonary diseases to diagnose and manage. This is complicated by a lack of awareness and understanding of the disease. Once diagnosed, patients typically have only a few years to live.

Fortunately, recent advances in the understanding of the cellular and molecular biology underlying fibrotic lung diseases including IPF are leading to more targeted interventions that could improve a patient's quality of life and survival. A better understanding of IPF's development may result in promising new approaches to treatment.

The purpose of this guide is to help increase awareness of IPF and to serve as a resource for journalists who are interested in the disease. Guidelines for diagnosis and management, current

research and clinical studies are also included.

This guide was developed by the Coalition for Pulmonary Fibrosis, a national alliance of patients, physicians, medical professionals and organizations working toward advancing better diagnosis, understanding and treatment of pulmonary fibrosis. We hope you find the guide to be a valuable resource and encourage you to contact us if you are interested in pursuing coverage of IPF or would like to speak with physicians or patients. The guide is also accessible through the Coalition for Pulmonary Fibrosis Web site at www.coalitionforpf.org.

Sincerely,

A handwritten signature in black ink that reads "Talmadge E. King, Jr." in a cursive style.

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Definition and Characteristics of IPF

Idiopathic pulmonary fibrosis (IPF) is a chronic and generally fatal interstitial lung disorder. IPF is one of about 200 disorders called interstitial lung diseases (ILDs), so named because they involve inflammation and scarring of the interstitium or tissue layer between the air sacs (alveoli) of the lung and the blood vessels.

IPF is characterized by scarring that thickens and stiffens the interstitium, causing an irreversible loss of the tissues' ability to transport oxygen. Patients with IPF typically experience shortness of breath and a dry cough, which become progressively worse and debilitating.

Many ILDs have known causes such as exposure to asbestos or certain medications. However, the cause of IPF is unknown, hence the term *idiopathic*, which means "arising spontaneously from an obscure or unknown cause."

More specifically, IPF is defined as a specific form of chronic fibrosing interstitial pneumonia limited to the lung. A critical step in making a definitive diagnosis of IPF is the microscopic assessment of tissue obtained by a lung

biopsy. Physicians look for specific changes in lung tissue that indicate a condition called usual interstitial pneumonia (UIP). The hallmark of UIP is alternating areas of normal tissue, interstitial inflammation, fibrosis and "honeycombing"—abnormal holes in the lungs. If present, UIP strongly points to a diagnosis of IPF (see *Diagnosis*).

In 2000, the medical community issued an international consensus statement defining the diagnosis, evaluation, and management of patients with IPF. Prior to that, other diseases with similar symptoms were often called IPF, despite widely varying prognoses. This created confusion among patients and the medical community, and interfered with effective treatment.

Accurate diagnosis is critical because of the widely varying prognoses among other ILDs. In contrast to most other interstitial pneumonias, about two thirds of IPF patients die within five years.

Accurate diagnosis is critical because of the widely varying prognoses among other interstitial lung diseases (ILDs).



The surface of the lung of an IPF patient showing advanced honeycombing.

Patients are typically between 50 and 70 years old when diagnosed with IPF.

Epidemiology

Determining precise numbers of people afflicted with IPF has been difficult until recently due to the lack of standard diagnostic criteria and terminology (see *Terminology*). However, an estimated 50,000 people in the United States have IPF with an estimated 15,000 new cases (five cases for every 100,000 people) expected each year.

Earlier estimates for IPF varied from three to six cases per 100,000 individuals. A more recent study of interstitial lung disease in Bernalillo County, N.M., showed the prevalence of IPF was 5 to 10 times higher than previously thought, with 20.2 cases per 100,000 men and 13.2 cases per 100,000 women.

Males tend to present at a later state of disease progression than women, and typically present with more visible signs such as chest X-ray abnormalities and finger clubbing (enlargement of the fingertips). Women tend to present with more subjective complaints such as shortness of breath. Death rates for both men and women with IPF have increased

over the past 10 years, with the mortality rate per 100,000 estimated to be 3.3 for males and 2.5 for women.

Patients are typically between 50 and 70 years old when diagnosed with IPF. Approximately two-

thirds of patients with IPF are over the age of 60 at the time the disease arises, with the average age at diagnosis of 66 years.



Finger clubbing in an IPF patient

Symptoms

IPF, as with other interstitial lung diseases, affects each person differently and at different rates. Typical early symptoms of IPF include shortness of breath (dyspnea) during periods of activity and a dry cough. Other possible symptoms include weight loss and fatigue. With later-stage IPF, enlargement or clubbing of the fingertips may develop.

As the disease progresses, dyspnea in some patients may occur at rest, making even normal activities such as walking, talking on the phone and eating difficult.

Virtually all IPF patients have an abnormal chest X-ray or high-resolution computed tomography (CT) scan. A “Velcro-like” crackling noise can be heard in their lungs when they breathe.

Terminology

IPF is known by a number of other names, causing confusion for patients and physicians alike. Other terms for idiopathic pulmonary fibrosis include:

- Cryptogenic fibrosing alveolitis
- Diffuse fibrosing alveolitis
- Hamman-Rich syndrome
- Interstitial diffuse pulmonary fibrosis
- Usual interstitial pneumonia
- Alveolocapillary block

With the publication of an International Consensus Statement in 2000 by the American Thoracic Society and the European Respiratory Society, in collaboration with the American College of Chest Physicians, it is hoped that use of the IPF label will become more universal.

The diagnosis of IPF requires a high index of suspicion and a thorough and exhaustive history in order to rule out other diseases whose symptoms may mimic IPF.

Diagnosis

Until recently, there was no standard for the diagnosis of IPF. Consequently, other diseases involving inflammation and pulmonary fibrosis may have been called IPF if a cause could not be determined.

IPF is now recognized as a distinct clinical entity. In 2000, the American Thoracic Society and the European Respiratory Society, in collaboration with the American College of Chest Physicians, published an International Consensus Statement with a revised definition of IPF that also addresses its diagnosis and management (see *Definition and Characteristics of IPF*).

Diagnosis of IPF is a “diagnosis of exclusion.” In other words, other known causes of interstitial lung disease—such as environmental and occupational factors, legal and illegal drug use, arthritis, etc.—must first be ruled out. To exclude these other diseases that could mimic IPF, physicians must take a complete patient history, perform a thorough physical examination, assess pulmonary function, and examine chest X-rays and high-resolution computed tomographic images. Lung biopsy, with or without bronchoalveolar lavage (a “lung washing” technique used for the examination of cells and proteins from

inside the lung), is frequently required to rule out alternative diagnoses.

For IPF to be diagnosed correctly, the guidelines provide major diagnostic criteria—all four of which must be present—and four minor criteria, three of which when present increase the likelihood that the patient has IPF (see Table below). The guidelines emphasize the need for a surgical lung biopsy because it provides the best evidence for distinguishing UIP from other forms of interstitial pneumonia. UIP is the pathological hallmark essential to the diagnosis of IPF.

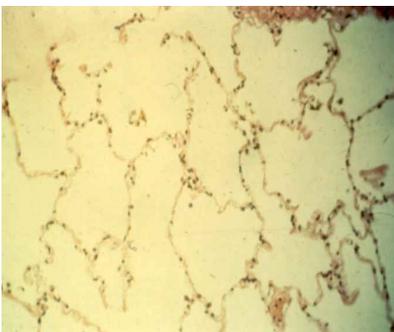
Criteria for a Diagnosis of Idiopathic Pulmonary Fibrosis

Major Criteria

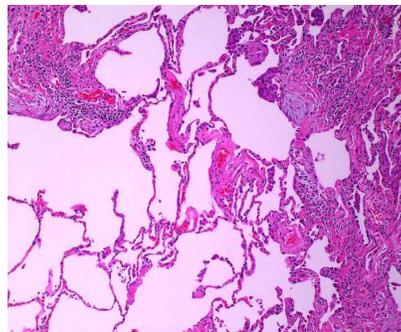
- Exclusion of other known causes of interstitial lung disease
- Abnormal pulmonary function studies that include evidence of restriction and impaired gas exchange
- Specific abnormalities on high-resolution computed tomography scans
- Lung biopsy specimen or bronchoalveolar lavage fluid showing no features to support an alternative diagnosis

Minor Criteria

- More than 50 years old
- Insidious onset of unexplained dyspnea on exertion
- Duration of illness greater than three months
- “Velcro” crackling sound heard in lungs during breathing



Normal lung



UIP/IPF



risk factors

The median survival of a 70-year-old diagnosed with IPF is less than two years while that of a 50-year-old patient is more than five years.

Potential Risk Factors

Although there is no known cause of IPF, the following risk factors for the disease have been identified:

- Cigarette smoking
- Occupational exposure to wood or metal dust
- Other family members with pulmonary fibrosis

Hereditary factors may contribute to the risk of developing IPF. Familial pulmonary fibrosis (FPF) is a form of pulmonary fibrosis that appears to run in families rather than occurring randomly. A study underway at Duke University Medical Center is seeking to find the cause of FPF. Specifically, it will attempt to determine if certain genes are associated with the development of pulmonary fibrosis.

Disease Progression and Patient Prognosis

Many patients, particularly in the early stages of the disease, can continue to go about their normal activities. Some respond to anti-inflammatory treatment (corticosteroids), and their loss of lung capacity may be slowed.

Physicians often recommend that patients follow the usual measures for maintaining health such as eating a healthy diet, maintaining proper weight, exercising regularly and getting enough rest. Patients who are smokers are advised to quit smoking.

Although the prognosis for IPF patients remains poor, a variety of factors can help physicians determine the risk of disease progression and effectiveness of treatment. For example, there is a clear relationship between age and prognosis. The median survival of a 70-year-old diagnosed with IPF is less than two years while that of a 50-year-old patient is more than five years.

Factors Indicating a Poorer Prognosis

- Male gender, although recent information indicates the effect may be small
- More severe dyspnea (shortness of breath)
- Certain features of a patient's X-ray or high-resolution computed tomographic scan, or the presence of "honeycombing"
- Oxygen-deficient blood (hypoxemia) at rest at the time of presentation
- Various abnormalities in the bronchoalveolar lavage fluid



treatment

Corticosteroids are standard therapy for IPF, primarily because of the lack of an effective alternative.

Treatment and Management

There are currently no effective treatments to extend patients' lives, nor is there a cure for IPF. The rarity of the disease, the difficulty of diagnosis, and the mystery surrounding its cause have been significant obstacles in developing an effective therapy.

Treatment for the disease is based on the concept that inflammation in the lung leads to fibrosis. Patients typically are treated with anti-inflammatory drugs, including corticosteroids and cytotoxic agents (e.g. azathioprine and cyclophosphamide). This approach has remained essentially unchanged for the past 30 years despite the fact that it has demonstrated little impact on long-term patient survival. In addition, it can be difficult for physicians to objectively determine the effectiveness of ongoing treatments.

Some patients may need supplemental oxygen to help reduce breathlessness and allow the patient to be more active. Lung transplantation is recommended for consideration for patients with severe functional impairment, dependency on oxygen and continued, rapid deterioration despite optimal medical management if they meet transplantation criteria established by the United Network for Organ Sharing. Successful transplantation frequently alleviates the requirement for supplemental oxygen. It may also increase lung capacity and reverse pulmonary hypertension and other conditions. However, only about half of patients survive more than five years after transplantation.

Pathogenesis

Whatever IPF's cause, it is known that the disease results from a normal tissue repair process gone awry. Normally, inflammation is the body's response to injury, followed by rapid restoration of healthy tissue.

With IPF, inflammation is chronic, and tissue repair is uncontrolled and exaggerated. An imbalance of "cytokines" —biologically active proteins in the body—appears to contribute to pulmonary fibrosis, and current research focuses on trying to regulate cytokines and thereby limit collagen accumulation and scarring. Both of these processes reduce elasticity of the lungs and impair their ability to transfer oxygen to the bloodstream.

Emerging Treatments

Researchers are exploring a number of new avenues for treating IPF. One approach targets the scarring process itself. Investigations have demonstrated that progressive scarring is accompanied by an imbalance in cytokines: Th2 cytokines, which promote the activation of scarring cells, are overproduced and outnumber Th1 cytokines, which promote normal tissue repair. It is believed that a persistent imbalance between these cytokines may be the mechanism behind pulmonary fibrosis.

Researchers are studying interferon gamma, one of the major Th1 cytokines, because of its potential to reduce collagen deposition during chronic inflammation. In a Phase II study, IPF patients who were resistant to steroid treatment were



Currently, there are a number of research studies and clinical trials underway in the United States.

treated for 12 months with interferon gamma-1b and prednisolone. The results were substantial improvement in lung function. A clinical study is currently underway to confirm the effectiveness of interferon gamma-1b in slowing and possibly reversing the scarring process.

Clinical Trials/Research

Because current therapy offers minimal benefit for patients with IPF, physicians and researchers are focusing future studies on new and better treatments. Participants at a 1998 workshop conducted by the National Heart, Lung, and Blood Institute identified a number of potential therapeutic interventions as targets for future studies. Among those suggested as warranting further investigation were pirfenidone, an antifibrotic agent; interferon gamma, which has a role in regulating fibroblast proliferation and collagen deposition; interferon beta, which has anti-inflammatory properties; and suramin, a prostate cancer treatment that appears to inhibit a number of growth factors.

Currently, there are a number of research studies and clinical trials underway in the United States. The following list highlights some of the major studies:[†]

Sponsor: Duke University Medical Center (also involves Vanderbilt University)

Principal Investigator:
Dr. David Schwartz

- study seeks to find the genes that may cause pulmonary fibrosis

Sponsor: InterMune, Inc.

Principal Investigator: Dr. Ganesh Raghu (University of Washington Medical Center)

- a multicenter Phase III study to determine the safety and efficacy of subcutaneous interferon gamma-1b in patients who are unresponsive to steroids

National Institutes of Health studies:

- Identification of genes associated with lung disease in patients with rheumatoid arthritis; specimen collection for individuals with lung disease associated with rheumatoid arthritis; lung disease associated with rheumatoid arthritis

In addition, the National Institutes of Health has designated and funded three institutions as Specialized Centers of Research (SCOR) for interstitial lung disease, a program focusing on the mechanisms of fibrosis in various types of lung diseases and designed to determine factors that influence prognosis and predict survival of ILD patients. These centers are National Jewish Medical and Research Center in Denver, Colo.; University of Michigan, Ann Arbor, Mich.; and Boston University Medical Center.

[†] List is not comprehensive.

Resources

A number of nonprofit health care associations and patient advocacy groups provide information on IPF and other chronic lung diseases, and support resources for patients and their families.

American Lung Association

www.lungusa.org

Coalition for Pulmonary Fibrosis

www.coalitionforpf.org

Chronic Lung Disease
Information Resource

www.cheshire-med.com/programs/pulrehab/rehinfo.html

National Heart, Lung & Blood Institute

www.nhlbi.nih.gov

National Jewish Medical and
Research Center

www.njc.org

Pulmonary Fibrosis Association

www.pulmonaryfibrosisassn.com

Second Wind Lung Transplant
Association

www.2ndwind.org

United Network for Organ Sharing
(UNOS)

www.unos.org

The Pulmonary Paper

www.pulmonarypaper.org



Glossary

Alveoli

Very small air sacs found in the lungs. The alveoli are lined with a single layer of cells that form a thin layer between the air and blood and facilitate a rapid and complete exchange of oxygen and carbon dioxide.

Azathioprine

A medication often prescribed for IPF patients that is used to inhibit the body's immune response.

Bronchoalveolar lavage

A “lung washing” technique used for the examination of cells and proteins from inside the lung. Usually done in conjunction with a fiberoptic bronchoscopy in which a fiberoptic probe is used to evaluate the lungs and airways.

Collagen

A family of closely related proteins found in tendons, bones, and connective tissues.

Computed tomography

Radiography in which a three-dimensional image of a body structure is constructed by computer from a series of plane cross-sectional images made along an axis — abbreviation *CT*.

Corticosteroids

Steroid hormones from the adrenal glands (an endocrine gland located near the kidneys).

Cyclophosphamide

An immunosuppressive and anti-inflammatory medication commonly prescribed for IPF patients.

Dyspnea

Shortness of breath or labored breathing.

Diffuse

Not concentrated or localized.

Epidemiology

1 : A branch of medical science that deals with the incidence, distribution, and control of disease in a population
2 : The sum of the factors controlling the presence or absence of a disease or pathogen.

Etiology

All of the causes of a disease or abnormal condition.

Familial

Tending to occur in more members of a family than expected by chance alone.

Fibrosis

The thickening and scarring of tissue (see *pulmonary fibrosis*).

Histopathology

1 : A branch of pathology concerned with the tissue changes characteristic of disease
2 : The tissue changes that affect a part or accompany a disease.

Hypoxia

A deficiency of oxygen reaching the tissues of the body.

Hypoxemia

Deficient oxygenation of the blood.

Idiopathic

Arising spontaneously or from an obscure or unknown cause.

Idiopathic pulmonary fibrosis (IPF)

A life-threatening disease characterized by progressive scarring, or fibrosis, of the lung tissue.

Incidence

Rate of occurrence or influence; *especially*, the rate of occurrence of new cases of a particular disease in a population being studied.

Inflammation

A local response to cellular injury that is marked by capillary dilatation, leukocytic infiltration, redness, heat, pain, swelling, and often loss of function and that serves as a mechanism initiating the elimination of noxious agents and of damaged tissue.

Interferon gamma-1b

A naturally occurring protein that prevents the formation of excessive scarring in the body and stimulates the human immune system.

Interstitial pneumonia

Any of several chronic lung diseases of unknown etiology that follow injury to the alveolar walls and result in inflammation and scarring of the lung tissue.

Interstitialium

The tissue layer between the alveoli and the blood vessels.

Pathogenesis

The origination and development of a disease.

Pathology

1 : The study of the essential nature of diseases and especially of the structural and functional changes produced by them **2** : The anatomic and physiological deviations from the normal that constitute disease or characterize a particular disease.

Phase I trial

The first phase of drug testing in humans. This phase usually involves 20 to 100 patients over several months, and mainly focuses on safety.

Phase II trial

The second phase of drug testing in humans. This phase involves up to several hundred patients and lasts as long as two years. Phase II trials focus mainly on effectiveness, but also on short-term safety.

Phase III trial

The third phase of drug testing in humans. This phase involves several hundred to several thousand patients and lasts from one to four years. Phase III trials focus on safety, dosage and effectiveness.

Prednisone

A corticosteroid used for its anti-inflammatory effects in the treatment of a variety of diseases including idiopathic pulmonary fibrosis (IPF).

Presentation

A presenting symptom or group of symptoms <clinical *presentation* of arthritis>.

Prevalence

Percentage of a population that is affected with a particular disease at a given time.

Prognosis

The prospect of survival and recovery from a disease as anticipated from the usual course of that disease or indicated by special features of the case.

Pulmonary fibrosis

The thickening and scarring of the lung tissue by the deposition of collagen and proteins. Causes may include certain medications, environmental exposure to asbestos, connective tissue disease, or may have no known cause.

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