

A PHYSICIAN'S GUIDE TO  
**IDIOPATHIC PULMONARY FIBROSIS**



Education. Support. Hope.

*Idiopathic pulmonary fibrosis (IPF) is a progressive and generally fatal interstitial lung disease characterized by a unique pattern of scarring, inflammation, proliferation of fibroblasts, and deposition of connective-tissue matrix proteins in the lungs. This scarring (fibrosis) and inflammation results in dyspnea and poor gas exchange, eventually leading to death.*

*Historically, a lack of agreed-upon guidelines along with clinical features that mimic other pulmonary diseases have made the correct diagnosis of IPF very difficult. A recently released international consensus statement (authored by the American Thoracic Society [ATS] and the European Respiratory Society [ERS] in collaboration with the American College of Chest Physicians [ACCP]) provides physicians with practical, up-to-date guidelines for the diagnosis and treatment of IPF.<sup>1</sup> In addition, a better understanding of the mechanisms behind IPF is driving exploration into novel treatment options—some of which are already in clinical trials.*

*This guide, intended for pulmonologists and specialists in related fields, highlights recent advances in the diagnosis, research, and treatment of IPF. It also suggests additional resources for healthcare professionals involved with this debilitating and elusive disease.*

## EPIDEMIOLOGY AND RISK FACTORS

Idiopathic pulmonary fibrosis is relatively rare, with an estimated 83,000 cases in the United States, and 15,000 new cases diagnosed annually.<sup>1</sup> Prevalence is on the rise.<sup>1a</sup> IPF is also referred to by its pathological corollary, usual interstitial pneumonia (UIP), and other names, such as cryptogenic fibrosing alveolitis. It is more common in males than females and is usually diagnosed in individuals between 50 and 70 years of age.<sup>1</sup> As one of the most prevalent interstitial lung diseases, or ILDs (approximately 200 disorders characterized by pulmonary fibrosis and inflammation of the interstitium), IPF has no distinct geographical distribution, nor does it occur more frequently in one particular race or ethnic group.<sup>1</sup> Clinical deterioration occurs in all patients and the 5-year survival rate from diagnosis ranges from 30% to 50%.<sup>2-6</sup>

Although its etiology is unknown, several potential risk factors have been identified. These risk factors include cigarette smoking, use of antidepressants, gastroesophageal reflux, occupational exposure to dusty environments, viral infection, and genetic predisposition.<sup>1</sup>

Clinicians are currently devoting considerable attention to the role of genetics in IPF and other ILDs. When the disease appears to run in families rather than occurring randomly, it is referred to as familial pulmonary fibrosis, or FPF. The manifestation, diagnosis, treatment, and prognosis of FPF are similar to those of the idiopathic form.

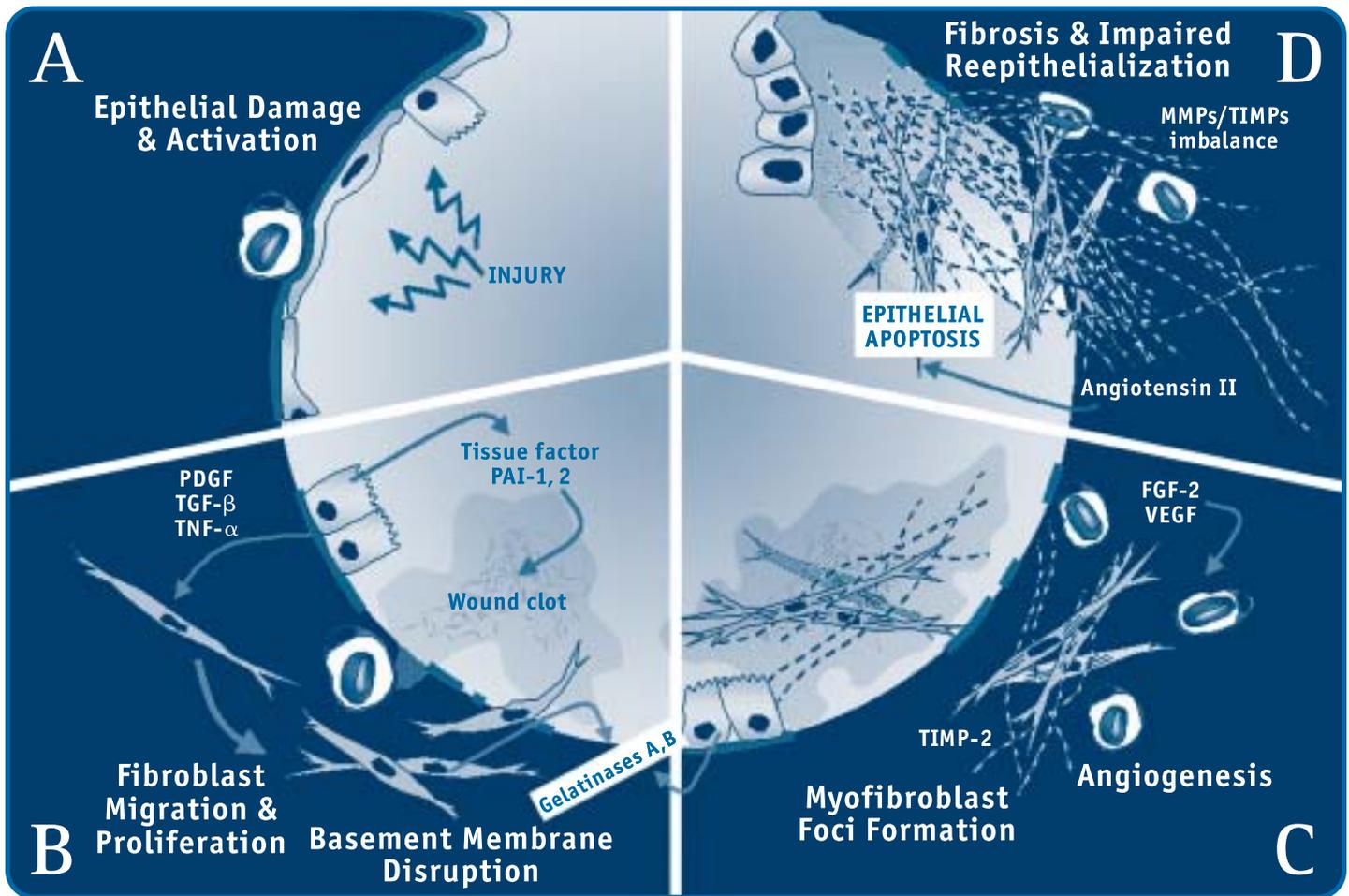
## PATHOGENESIS

As the word “idiopathic” implies, the cause of IPF remains a mystery. Research indicates, however, that changes in the lungs’ normal healing processes are involved. In ILDs, the lungs become chronically inflamed, promoting uncontrolled and exaggerated tissue repair (i.e., fibroproliferation and deposition of extracellular matrix).<sup>7</sup> Under the microscope, IPF lungs exhibit a unique pattern of alternating regions of normal tissue, interstitial inflammation, fibrosis, and “honeycombing” (cystic destruction). Although the exact mechanisms by which cellular injury occurs are unknown, activated alveolar macrophages and neutrophils appear to play a significant role in the pathogenesis of IPF.<sup>7</sup>

The body’s normal inflammatory response is characterized by four phases:

1. **Recognition**—In this phase, the expression of adhesion molecules used for leukocyte trafficking is increased
2. **Recruitment**—Neutrophils, lymphocytes, dendritic cells, and natural killer cells are trafficked in the presence of chemokines
3. **Removal**—Th1 and Th2 cytokines are produced
4. **Resolution**—Tissue integrity and function are restored via homeostatic mechanisms

**FIGURE 1. HYPOTHETICAL SCHEME FOR IPF PATHOGENESIS<sup>8</sup>**



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Multiple microinjuries damage and activate alveolar epithelial cells (A), which in turn induce an antifibrinolytic environment in the alveolar spaces, enhancing wound clot formation. Alveolar epithelial cells secrete growth factors and induce migration and proliferation of fibroblasts and differentiation into myofibroblasts (B). Subepithelial myofibroblasts and alveolar epithelial cells produce gelatinases that may increase basement membrane disruption and allow fibroblast-myofibroblast migration (C). Angiogenic factors induce neovascularization. Both intra-alveolar and interstitial myofibroblasts secrete extracellular matrix proteins, mainly collagens. An imbalance between interstitial collagenases and tissue inhibitors of metalloproteinases provokes the progressive deposit of extracellular matrix (D). Signals responsible for myofibroblast apoptosis seem to be absent or delayed in usual interstitial pneumonia, increasing cell survival. Myofibroblasts produce angiotensinogen that as angiotensin II provokes alveolar epithelial cell death, further impairing reepithelialization. FGF-2 = fibroblast growth factor-2; MMP = metalloproteinase; PAI-1, PAI-2 = plasminogen activator inhibitor-1, -2; PDGF = platelet-derived growth factor; TGF-β = transforming growth factor-β; TIMP = tissue inhibitors of metalloproteinases; TNF-α = tumor necrosis factor-α; VEGF = vascular endothelial growth factor.

**TABLE 1. CYTOKINE FUNCTIONS<sup>7</sup>**

**Th1 cytokines (e.g., interleukin [IL]-2 and interferon gamma):**

- Promote cell-mediated immunity
- Remove cellular antigens
- Decrease fibroblast procollagen mRNA, fibroblast proliferation, and fibroblast-mediated angiogenesis
- Down-regulate TGF- $\beta$

*The net effect of a predominantly Th1 response is tissue restoration.*

**Th2 cytokines (including IL-4 and IL-13):**

- Promote humoral immunity
- Produce antibody responses that can lead to fibroblast activation and fibrosis

*The net effect of a predominantly Th2 response is fibrosis.*

In IPF, one proposal is that the resolution phase is marked by a persistent imbalance between Th1 and Th2 cytokines (Table 1).<sup>7</sup> As Th2 cytokines become more prevalent, transforming growth factor beta (TGF- $\beta$ ) and other cytokine levels rise, causing fibroproliferation and excessive collagen accumulation.<sup>7</sup> The increased levels of Th2 vs. Th1 cytokines in the lungs are thought to be one mechanism behind the progression of pulmonary fibrosis.<sup>7</sup> IPF is also characterized by fibroblast/myofibroblast migration and proliferation to sites of injury, decreased myofibroblast apoptosis, and increased activity of, and response to, fibrogenic cytokines such as transforming growth factor beta-1, connective tissue growth factor, endothelin-1, tumor necrosis factor alpha, platelet-derived growth factor, and insulin-like growth factor (Figure 1).<sup>8</sup> Also, there appears to be failure of alveolar reepithelialization, failure to turn off collagen proliferation, and failure to break down collagen by naturally occurring metalloproteinases. Exactly what sets these abnormal tissue-repair processes in motion is unclear, although in some cases genetic factors seem to play a role.<sup>1</sup>

## DIAGNOSING IPF

Even though IPF is now considered a distinct disorder, its clinical features are nonspecific and resemble those of other interstitial lung diseases, making it difficult to diagnose (Table 2). There is also some confusion as to what constitutes IPF; until recently, there were no uniform diagnostic standards. Other diseases with similar symptoms were often diagnosed as IPF, despite widely varying prognoses. However, the recently released international guidelines<sup>1</sup> should help to eliminate much of the confusion surrounding the diagnosis of this disease.

A multidisciplinary approach is an absolute requirement for the definitive identification of IPF.<sup>9</sup> Because IPF's clinical and histopathologic features are found in a number of other disease states, accurate diagnosis is impossible without careful analysis of clinical and radiologic findings, serologic data, and lung biopsy specimens.

Patients diagnosed with IPF generally present with dyspnea and a dry cough. Chest x-rays and high-resolution computed tomography (HRCT) scans are abnormal (Figure 2), and a dry, "Velcro-like" crackling can be heard upon auscultation. Weight loss and fatigue may also occur over time. In late-stage IPF, clubbing may be observed.



*A complete patient history is necessary to exclude other known causes of interstitial lung disease, such as drug toxicities and environmental exposures.*

**TABLE 2. DIFFERENTIAL DIAGNOSES RELATED TO IPF**

**Systemic/rheumatic abnormalities**

- Progressive systemic sclerosis (PSS)
- Systemic lupus erythematosus (SLE)
- Sjögren’s syndrome (SS)
- Ankylosing spondylitis (AS)
- Rheumatoid arthritis (RA)
- Mixed connective tissue disease (MCTD)
- Polydermatomyositis
- Chronic aspiration pneumonia

**Drug/radiation-induced**

- Antibiotics
- Cardiovascular drugs
- Chemotherapeutic agents
- Radiation

**Malignancies**

- Lymphoma
- Lymphangitic carcinoma

**Sarcoidosis**

**Giant cell interstitial pneumonitis (GIP)**

- Hard metal pneumoconiosis

**Lymphangiomyomatosis (LAM)**

**Idiopathic interstitial pneumonias (IIPs)**

- Idiopathic pulmonary fibrosis (IPF)
- Nonspecific interstitial pneumonia (NSIP)
- Desquamative interstitial pneumonia (DIP)
- Respiratory bronchiolitis-associated interstitial lung disease (RBILD)
- Acute interstitial pneumonia (AIP)

**Occupational injuries**

- Inorganic fibrogenic disorders
- Inorganic nonfibrogenic disorders

**Bronchiolitis obliterans organizing pneumonia (BOOP)**

**Eosinophilic granuloma (EG)**

**Hypersensitivity pneumonitis**

- Organic dust
- Bacteria
- Animal protein
- Fungi

**Lymphocytic interstitial pneumonitis (LIP)**

- Lymphoma (low-grade)
- HIV infection

An IPF workup usually requires:

- A complete patient history and thorough physical exam (including laboratory and serologic tests; Table 3)
- Assessment of pulmonary function by spirometry, lung volumes, measurement of carbon monoxide diffusing capacity, and pulse oximetry at rest and exercise. If oxygen saturation is less than 89% at rest or exercise, an arterial blood gas test should be conducted to determine whether the patient needs supplemental oxygen.

- Chest x-ray and HRCT
- Lung biopsy. A surgical lung biopsy—open thoracotomy or, preferably, video-assisted thoracoscopy surgery (VATS)—should be conducted if not contraindicated, as surgical biopsies provide the best tissue samples for diagnosis. VATS is the preferred technique because it is associated with less morbidity, less prolonged chest tube drainage, and a reduced length of hospital stay vs. open-lung biopsy.<sup>1</sup> Bronchoalveolar lavage (BAL) should also be performed for cell count and flow cytometry.

**TABLE 3. LABORATORY/SEROLOGIC TESTS FOR SUSPECTED IPF\***

- Complete cell count
- Liver profile
- CPK and aldolase
- Urinalysis
- Antinuclear antibodies (ANA)
- Rheumatoid factor (RF)
- Erythrocyte sedimentation rate (ESR)
- Anti-topoisomerase I antibody (Scl-70)
- Anti-Jo1
- Angiotensin-converting enzyme (ACE)
- Hypersensitivity panel
- Quantitative immunoglobulin analysis
- Antineutrophil cytoplasmic antibodies (ANCA) level

\*Most tests are ordered to rule out diseases other than IPF and are based on clinical presentation and clinical suspicion.

In the absence of a definitive lung biopsy, the presence of *all four* major criteria and *three* minor criteria, as set forth in the current guidelines, increases the likelihood of a correct diagnosis of IPF (Table 4). However, the guidelines strongly emphasize the need for a lung biopsy, because this procedure is the *only* way to obtain definitive evidence of UIP—the pathological hallmark essential to the diagnosis of IPF.

For the first 30 years of its use, the term IPF was applied liberally to several idiopathic interstitial pneumonias (IIPs). Today, however, IPF is recognized as a clinical syndrome with the distinct histopathology of UIP. UIP is a specific subset of the IIPs, characterized by a heterogeneous, predominantly subpleural distribution of involvement. Alternating areas

of normal tissue, interstitial inflammation, fibrosis, and “honeycombing” (thickened collagenous septa surrounding airspaces lined by bronchial epithelium) are present (Figure 3). UIP is distinguished from other IIPs by the presence of fibroblastic foci at the junction of fibrotic and normal lung, subpleural “honeycomb” changes, and mild interstitial inflammation.<sup>9</sup> Other IIPs include<sup>10</sup>:

- Nonspecific interstitial pneumonia/fibrosis (NSIP/F)
- Desquamative interstitial pneumonia/respiratory bronchiolitis-associated interstitial lung disease (DIP/RBILD)
- Acute interstitial pneumonia (AIP)

**TABLE 4. IPF DIAGNOSTIC CRITERIA<sup>1</sup>**

#### Major Criteria

- Exclusion of other known causes of interstitial lung diseases, such as certain drug toxicities, environmental exposures, and connective tissue diseases
- Abnormal pulmonary function studies that include evidence of restriction (reduced vital capacity often with an increased FEV<sub>1</sub>:FVC ratio) and impaired gas exchange (increased AaPO<sub>2</sub> with rest or exercise or decreased DL<sub>CO</sub>)
- HRCT scan showing bibasilar reticular abnormalities with minimal ground-glass opacities
- Transbronchial lung biopsy or BAL showing no features to support another diagnosis

#### Minor Criteria

- Age >50 years
- Insidious onset of otherwise unexplained dyspnea on exertion
- Duration of illness ≥3 months
- Bibasilar inspiratory crackles (dry or “Velcro-like” in quality)

AaPO<sub>2</sub> = alveolar/arterial pressure difference for oxygen  
DL<sub>CO</sub> = diffusing capacity of the lung for carbon monoxide  
FEV<sub>1</sub> = forced expiratory volume in 1 second  
FVC = forced vital capacity

## TREATMENT

### Pharmaceutical Therapy

Current treatment options often involve the off-label use of anti-inflammatory drugs and are based on the concept that inflammation leads to injury and pulmonary fibrosis. Published guidelines suggest treatment with corticosteroids (prednisone or equivalent) and cytotoxic agents (azathioprine or cyclophosphamide) (Table 5).<sup>1</sup> The U.S. Food and Drug Administration has not yet approved any of these therapies for IPF because of a lack of clinical evidence of improved survival time or quality of life. This therapeutic approach to IPF has remained unchanged for 30 years, not because it is efficacious, but due to a lack of alternatives. One possible explanation for the lack of success of these drugs may be that fibrosis and T-helper (Th) cytokines—not inflammation—are the primary mechanisms responsible for the loss of lung function associated with IPF.

### Lung Transplantation

Unless contraindications exist, lung transplantation should be considered for IPF patients with severe functional impairment, oxygen dependency, and a deteriorating condition. Early wait-listing is important, because time to procure a donor organ may exceed 2 years, and corrective treatment may be necessary to improve the patient's medical condition.<sup>11</sup> Lung transplantation can reverse some of the symptoms and complications (e.g., pulmonary hypertension) associated with IPF; however, the 5-year survival rate after transplantation is only 50% to 60%.<sup>1</sup>

### Support Strategies

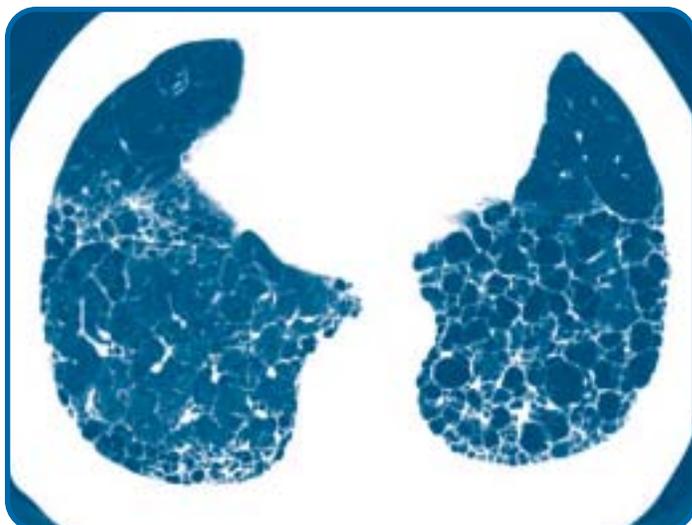
Because a healthy lifestyle may help slow disease progression, IPF patients should be encouraged to stop smoking, eat small and well-balanced meals, get adequate rest, and participate in an exercise regimen. They should enroll in a pulmonary physical rehabilitation program, if possible, and join a support group if one is available. Caregivers should also be encouraged to join a support group and/or to find other ways to help alleviate stress (e.g., exercise and relaxation techniques).

## FIGURE 2. IPF ABNORMALITIES—HRCT

### HRCT of normal lungs



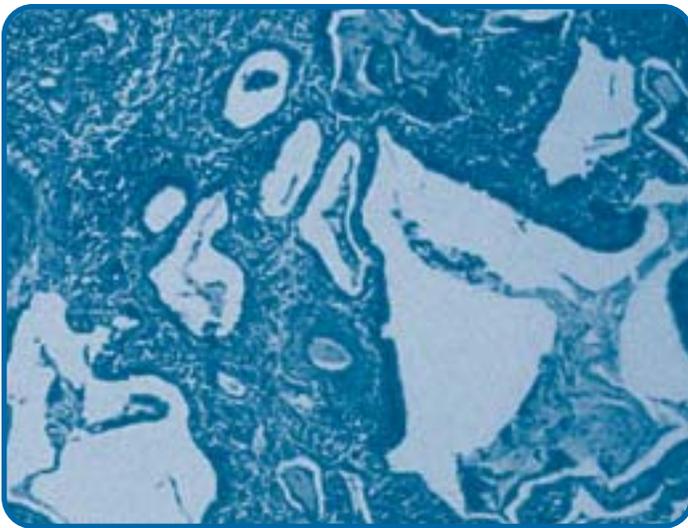
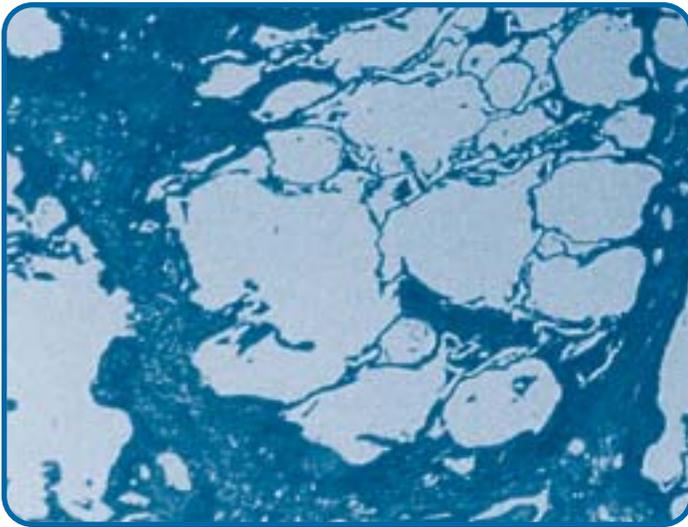
### HRCT showing IPF abnormalities



Images courtesy of J. Golden, MD

HRCT allows for earlier diagnosis of IPF, a narrowing of the differential diagnosis based on the CT pattern, and determination of the extent of associated emphysema.

### FIGURE 3. USUAL INTERSTITIAL PNEUMONIA



Images courtesy of K.O. Leslie, MD

These photomicrographs show areas of normal lung tissue with transition to the patchy interstitial inflammation, fibrosis, and “honeycombing” that characterize the temporal heterogeneity of UIP.

### Experimental Treatments

Because existing IPF therapies are only marginally beneficial, alternative treatments are clearly needed. Fortunately, recent advances in the understanding of the mechanisms underlying ILDs are leading to targeted interventions that may influence survival and quality of life. Researchers are evaluating a broad range of potential interventions targeted toward various steps in the disease process. The following therapies are currently under investigation in clinical trials:

- Interferon gamma
- N-acetylcysteine
- Etanercept
- Pirfenidone

One promising new treatment is interferon gamma-1b. This regulatory cytokine has antifibrotic and antifibrogenic effects and may regulate macrophage, fibroblast, and mast cell function; inhibit a variety of neutrophil-derived cytokines; and modify the balance of Th1 and Th2 cells in the lung.<sup>12,13</sup> A multicenter Phase III trial is currently being conducted to confirm the effectiveness of interferon gamma-1b in slowing or reversing the scarring associated with IPF and potentially improving lung function and patient survival (Principal Investigator: Ganesh Raghu, MD; University of Washington Medical Center. Sponsor: InterMune, Inc.).

Here is a partial list of other IPF trials/research programs currently under way:

- Genetic factors that may underlie pulmonary fibrosis (Principal Investigator: David Schwartz, MD; Duke University Medical Center).
- Mechanisms of pulmonary fibrosis and factors that influence prognosis and predict survival in ILD patients (National Institutes of Health–funded Specialized Centers of Research at: National Jewish Medical and Research Center, Denver, CO; University of Michigan, Ann Arbor, MI; and Boston University Medical Center).

## TABLE 5. COMBINED THERAPY FOR IPF PATIENTS<sup>1</sup>

Not approved by the FDA for the treatment of IPF.

### Corticosteroid (prednisone or equivalent)

- 0.5 mg/kg LBW\*/d orally for 4 wk
- 0.25 mg/kg/d for 8 wk
- Taper to 0.125 mg/kg/d or 0.25 mg/kg on alternate days
- Possible side effects include peptic ulcer disease, posterior capsular cataracts, increased intraocular pressure, hypertension, endocrine and metabolic alterations, musculoskeletal complications, and psychological effects

### PLUS

#### Azathioprine

- 2–3 mg/kg LBW/d orally (up to 150 mg/d)
- Dosing should begin at 25–50 mg/d, increasing by 25 mg increments every 1–2 wk until the maximum dose is achieved
- Possible side effects include hepatotoxicity and hematologic abnormalities

### OR

#### Cyclophosphamide

- 2 mg/kg LBW/d orally (up to 150 mg/d)
- Dosing should begin at 25–50 mg/d, increasing by 25 mg increments every 1–2 wk until the maximum dose is achieved
- Possible side effects include bladder injury, oncogenic potential, and hematologic abnormalities

Therapy should be continued for a minimum of 6 months. Response to treatment should be determined by symptoms and radiologic and physiologic findings. Close monitoring for adverse effects is mandatory. Because of the risk of hepatotoxicity from azathioprine and neutropenia from cyclophosphamide, complete cell counts and liver enzyme levels should be followed biweekly for the first 2 months, then monthly. *Pneumocystis carinii* pneumonia (PCP) prophylaxis with Bactrim® DS (one tablet three times per week) is advised.

\*LBW = lean body weight

## PROGNOSIS

Although many IPF patients can continue to live a normal life, particularly in the early stages of the disease, the prognosis is poor. Indicators of a longer survival among patients with IPF include<sup>1</sup>:

- Younger age
- Female gender
- Milder dyspnea (less functional impairment)
- Response to therapy
- Cigarette smoker at time of diagnosis (this result has not been explained)



An early response to therapy is associated with a better prognosis.

## RECOMMENDED READING

American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment (international consensus statement). *Am J Respir Crit Care Med.* 2000;161:646–664.

King TE Jr, ed. *New Approaches to Managing Idiopathic Pulmonary Fibrosis.* New York, NY: American Thoracic Society; 2000.

## ORGANIZATIONS

### *Coalition for Pulmonary Fibrosis (CPF)*

1685 Branham Lane, Suite 227

San Jose, CA 95118

(888) 222-8541 [www.coalitionforpf.org](http://www.coalitionforpf.org)

The Coalition for Pulmonary Fibrosis (CPF) is a 501 (c) (3) non profit organization, founded in 2001 to further education, patient support and research efforts for pulmonary fibrosis, specifically idiopathic pulmonary fibrosis (IPF). The CPF is governed by the nation's leading pulmonologists, individuals affected by pulmonary fibrosis, medical research professionals and advocacy organizations.

### *American College of Chest Physicians (ACCP)*

3300 Dundee Road

Northbrook, IL 60062-2348

(847) 498-1400 [www.chestnet.org](http://www.chestnet.org)

This organization is a leading resource for the improvement of cardiopulmonary health and critical care worldwide.

### *American Thoracic Society (ATS)*

1740 Broadway

New York, NY 10019

(212) 315-8700 [www.thoracic.org](http://www.thoracic.org)

An independently incorporated educational and scientific society, the ATS fights respiratory disease through research, education, patient care, and advocacy. The society publishes *The American Journal of Respiratory and Critical Care Medicine*.

### *Caring Voice Coalition*

POB 1384

Meridian, ID 83680

877-455-3374 [www.caringvoice.org](http://www.caringvoice.org)

Caring Voice Coalition (Caring Voice) is dedicated to building relationships with charitable organizations founded to help individuals and families affected by serious chronic disorders and diseases including IPF.

### *International Society for Heart and Lung Transplantation (ISHLT)*

14673 Midway Road, Suite 200

Addison, TX 75001

(972) 490-9495 [www.isHLT.org](http://www.isHLT.org)

This not-for-profit organization is dedicated to the advancement of the science and treatment of end-stage heart and lung diseases.

### *Mary D. Harris Memorial Foundation*

1500 Ashbury Street

Evanston, IL 60201

(847) 869-5276

This nonprofit organization supports efforts to find a cure for pulmonary fibrosis as well as educational initiatives that help to improve the lives of those living with the disease.

### *National Heart, Lung, and Blood Institute (NHLBI)*

National Institutes of Health

Bethesda, MD 20892 [www.nhlbi.nih.gov](http://www.nhlbi.nih.gov)

The NHLBI conducts and supports basic research, clinical investigations, and observational studies related to causes, prevention, diagnosis, and treatment of lung diseases, including IPF.

### *The Pulmonary Paper*

P.O. Box 877

Ormond Beach, FL 32175

(800) 950-3698 [www.pulmonarypaper.org](http://www.pulmonarypaper.org)

This nonprofit organization publishes a newsletter with the latest information on respiratory care and products for people with chronic lung problems.

### *Second Wind Lung Transplant Association*

300 South Duncan Avenue, Suite 227

Clearwater, Florida 33755-6457

888-855-9463 [www.2ndwind.org](http://www.2ndwind.org)

An independently incorporated educational and scientific society, the ATS fights respiratory disease through research, education, patient care, and advocacy. The society publishes *The American Journal of Respiratory and Critical Care Medicine*.

For a complete list of IPF-related patient resources, please visit <http://www.coalitionforpf.org/aboutus/resources.asp>

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The CPF relies on the contributions of individuals, corporations, and associations who share our commitment to improving IPF awareness and education. To learn more, or to make a contribution, please call (888) 222-8541.