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# PILOT™

Pulmonary Fibrosis Identification:
Lessons for Optimizing Treatment

## PILOT PRIMER 2013

# A PRACTICAL GUIDE TO IDIOPATHIC PULMONARY FIBROSIS

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# CME INFORMATION

## TARGET AUDIENCE

This activity is intended for pulmonologists, critical care clinicians, and other health care providers involved in the management of patients with IPF.

## STATEMENT OF NEED

IPF is a chronic progressive disease that is increasing in prevalence. Diagnosis is difficult, beyond the expertise of any one specialty, but has been codified in recent evidence-based guidelines. The understanding of the pathophysiology of IPF has progressed over the past decade, and this knowledge is intertwined with the clinical testing of candidate drugs. Several promising clinical candidates are in phase 3 evaluation and education of health care providers will enable both clinical trial enrollment and appropriate use of emerging medications after FDA approval. International guidelines for the diagnosis and treatment of IPF have been recently published, and provide a valuable resource for providers who manage patients with ILD. ***The PILOT™ Primer 2013: A Practical Guide to Idiopathic Pulmonary Fibrosis*** addresses these educational needs.

## LEARNING OBJECTIVES

Upon completion of this course, the participants should be able to:

- Discuss the latest research in IPF and the impact this information has on the current diagnosis and management approaches for this disease
- Explain the epidemiology of IPF and the importance of accurate and early diagnosis
- Indicate how to accurately diagnose IPF in conjunction with a multidisciplinary team
- Explain the pathophysiology of IPF and the therapeutic approaches to different steps in the disease process
- Describe the evidence-based diagnosis and management of IPF recommended in the 2011 ATS/ERS guidelines
- Incorporate effective communication techniques and educational tools to improve the patient's knowledge of their disease

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# INTRODUCTION

This primer gives an introduction to idiopathic pulmonary fibrosis (IPF) and highlights some of the critical issues in the diagnosis and management of patients with this disease. After a brief overview, the natural history of the disease is described, including the sudden worsening known as acute exacerbation (AE). Making the diagnosis can be difficult but is critical to management of IPF as well as other interstitial lung diseases (ILD). Comorbidities common to IPF patients are discussed, and best treatment practices aimed at optimizing patient comfort and quality of life (QOL) are described. An overview of emerging therapies and clinical trials will update the reader on the state of the art and provide background for when therapies become available. Patient education tools and other resources are shared to help you in practice.

# OVERVIEW OF IPF

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause occurring primarily in older adults. It is characterized by progressive dyspnea and declining lung function and is associated with a poor prognosis. Making the diagnosis of IPF is often difficult and requires clinical, radiologic, and sometimes histologic evidence as delineated in guidelines published in 2011.[1] No pharmacologic treatment for IPF has been approved by the US Food and Drug Administration. Lung transplantation may improve survival and QOL in select patients, and lifestyle modifications and management of comorbidities may improve certain outcomes.

IPF should be considered in patients over 50 years of age with unexplained insidious- and subacute-onset shortness of breath on exertion. It commonly presents with dry cough and bibasilar inspiratory Velcro™ crackles. Finger clubbing may be present. Male gender and cigarette smoking are risk factors for IPF.[1] Models of IPF pathogenesis have led to the development and testing of drugs aimed at various targets, and trials of many of them are ongoing.

# EPIDEMIOLOGY

- Estimated prevalence of IPF is 14 to 43 cases per 100,000 people in the United States[2]
- IPF is a disease of aging with a median age at diagnosis of 66[3]
- IPF is more common in men[2]
- Smoking is a risk factor for IPF[4]
- A number of environmental associations have been identified, including metal dusts, wood dusts, stone/sand, and exposure to livestock[5]
- Familial Interstitial Pneumonia (FIP) occurs when 2 or more individuals in a family have an idiopathic interstitial pneumonia (IIP). IPF is the most common form of IIP. Various studies have yielded estimates for IPF cases with a genetic component ranging from 1% to 19%. Genes identified include those coding for surfactant protein C, surfactant protein A2, telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC)[6]
- A polymorphism in the promoter of the MUC5B gene was found in 38% of subjects with IPF and 34% of patients with FIP and may be involved in the pathogenesis of disease[7]

# NATURAL HISTORY

- The prognosis of IPF is poor – patients have a median survival of 2 to 3 years from the time of diagnosis[8]
- In the US, from 1992-2003, mortality for IPF was 64 deaths per million men and 58 deaths per million women[7]
- The attributable mortality of IPF increased from 1992 to 2003 (and is probably still on the rise): mortality rates increased 28% in men and 41% in women, with most patients dying from the disease itself[7]
- Many predictors of shortened survival have been identified[10]
  - Older age
  - Male gender
  - Pulmonary hypertension
  - Degree of fibrosis on HRCT
  - A "typical" pattern for usual interstitial pneumonia (UIP) on HRCT
  - Impaired pulmonary function (FVC, $FEV_1$, and $DL_{CO}$) at diagnosis[9]
  - Decline in pulmonary function tests (PFT) over time (6 to 12 month changes in FVC and $DL_{CO}$)
  - The number of fibroblastic foci on pathology
- Though the typical clinical course is that of increasing shortness of breath accompanied by worsening pulmonary physiology **(Figure 1)** and progression of fibrosis on high-resolution computed tomography (HRCT) scans, there are several possible natural histories for IPF patients, including rapid or slow decline or periods of relative stability interposed with periods of acute decline[10,11]

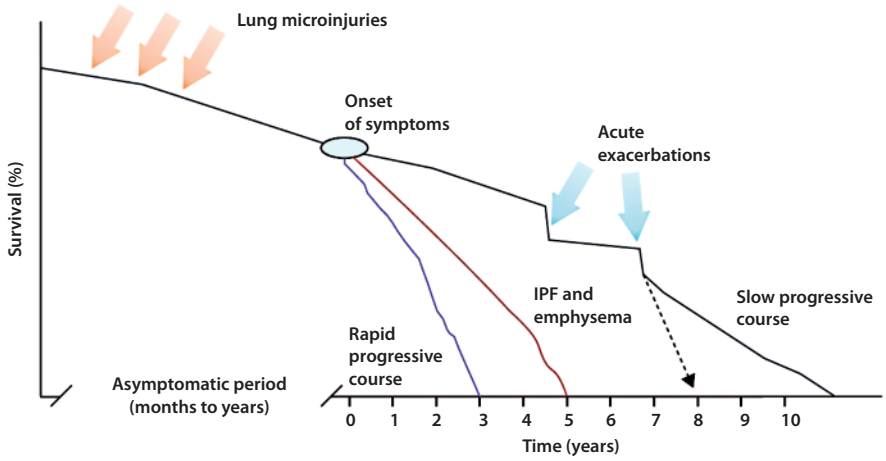


**Figure 1. Clinical progression of IPF.** The disease is believed to have a long asymptomatic period prior to diagnosis. Most patients follow a relatively slow clinical and functional decline (slowly progressive) after diagnosis. About 10% of these patients present with acute exacerbations that precede and possibly initiate the terminal phase of their disease. A few patients have a short duration of illness with a rapidly progressive clinical course (purple line). Heavy smokers might develop IPF combined with emphysema, with shorter survival compared with patients with IPF alone (red line).[10,12]

# ACUTE EXACERBATIONS

- Acute worsening may occur, either from secondary complications such as pneumonia, pulmonary embolism, pneumothorax, cardiac failure, or exacerbations of the underlying fibrotic lung disease[1]
- Etiology for AE are currently unknown
- The true incidence is hard to determine (due to retrospective trials and differing case definitions) but is estimated to be 4–19% per year[13]
- Potential risk factors include Japanese ethnicity,[13] low FVC, and never smoking[14]
- There are many case reports of AE following lung resection, surgical lung biopsy, lung cancer chemotherapy, and bronchoalveolar lavage (BAL)[13]
- Survival rates of patients with acute worsening with no identifiable etiology and of patients with an identified infectious agent are the same[14,15]
- In-hospital mortality is high (up to 50%) and one-year survival is 50%[14]

# DIAGNOSIS

- Impact: early referral to a tertiary center with expertise in IPF diagnosis improves survival[16]
- The likelihood of a correct diagnosis of IPF increases with agreement between the clinician, radiologist, and pathologist[17]
- Recognizing other forms of fibrosing lung disease is critical, as these diseases may respond to anti-inflammatory treatment and may have better outcomes
- Patients commonly present with progressive breathlessness with or without cough. The majority of patients have inspiratory dry crackles and 20 to 50% have clubbing[3]
- PFTs show restriction (with low lung volumes) and reductions in diffusion capacity that correlate with the extent of disease on HRCT **(Figure 2)**
- Hypoxemia is a universal finding at later stages of the disease and worsens as the disease progresses

**2011 ATS/ERS Diagnostic Criteria for IPF[1]**

- Exclusion of other known causes of interstitial lung disease
- Presence of
  - a usual interstitial pneumonia (UIP) pattern on high resolution computed tomography (HRCT), or
  - a combination of HRCT findings and characteristic findings on surgical lung biopsy
- The HRCT pattern for a "definite UIP pattern" consists of 4 features:
  - basilar and subpleural predominance
  - reticulation
  - honeycombing with or without traction bronchiectasis
  - absence of features inconsistent with UIP (ground glass abnormalities, profuse micronodules, discrete cysts, air trapping)

- Based on clinical and HRCT findings, confident diagnoses by radiologists have been observed to be accurate (correlates with histopathology) in 90% of IPF cases[18]

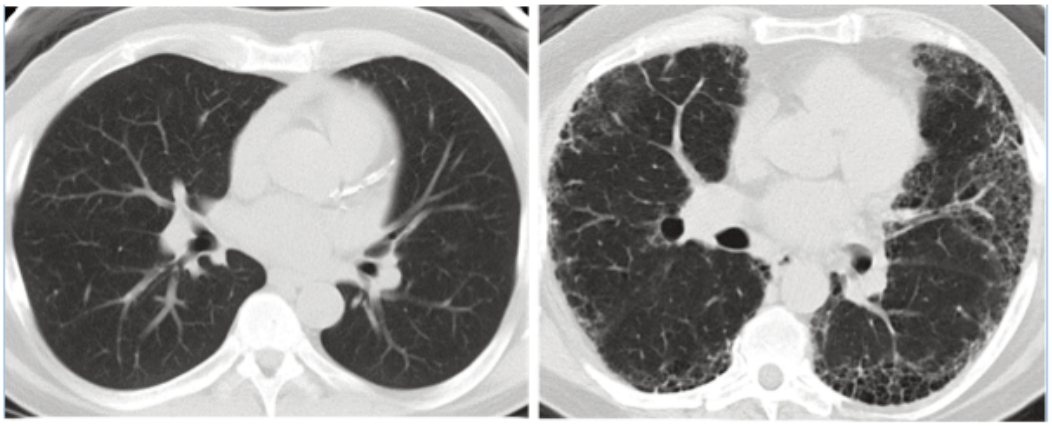

**Figure 2. HRCT images of normal lung (left) and UIP (right).** Courtesy of Dr. D Lederer.

## HISTOPATHOLOGY

- Usual interstitial pneumonia (UIP) is characterized by a patchy, subpleural, and paraseptal pattern of involvement with areas of scarring alternating with uninvolved lung parenchyma. The involved lung shows dense collagen with scattered foci of proliferating fibroblasts (called fibroblastic foci, **Figure 3**)[19]

- In cases with a "discordant" surgical biopsy (eg, a UIP pattern in one section and another pattern such as nonspecific interstitial pneumonia [NSIP] in another section), patients should be classified as having UIP[2]

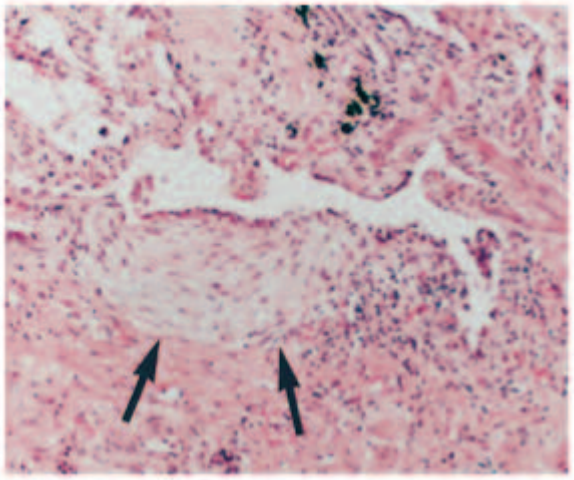

**Figure 3. Fibroblast focus in UIP (arrows).** Fibroblast foci represent areas of active fibrosis that contrast with adjacent areas of inactive collagen-type fibrosis.[19]

## DIAGNOSIS OF ACUTE EXACERBATIONS

In 2007 Collard et al proposed diagnostic criteria for AE of IPF[21]

### Diagnostic Criteria of Acute Exacerbations

1. Previous or concurrent diagnosis of idiopathic pulmonary fibrosis
2. Unexplained worsening or development of dyspnea within 30 days
3. HRCT with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with UIP
4. No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage
5. Exclusion of alternative causes, including the following:
   - Pneumonia
   - Left heart failure
   - Pulmonary embolism

Some patients may present with AE but without previous HRCT scans. In this case, the qualifier "new" can be dropped from the "new bilateral ground-glass abnormality" condition. Causes of acute lung injury include sepsis, aspiration, trauma, reperfusion pulmonary edema, pulmonary contusion, fat embolization, inhalational injury, cardiopulmonary bypass, drug toxicity, acute pancreatitis, transfusion of blood products, and stem cell transplantation. Patients with idiopathic clinical worsening who fail to meet all five criteria due to missing data should be termed "suspected acute exacerbations."

# PATHOPHYSIOLOGY[12]

- Current theory holds that the development of UIP is extremely complex and involves, among other features, epithelial cell injury and death, aberrant wound-healing including failure of myofibroblasts to undergo apoptosis, excessive extra-cellular matrix deposition, and failure of alveolar epithelial cells to normally repopulate denuded alveolar basement membrane **(Figure 4)**

- Several environmental factors might contribute to epithelial injury and apoptosis
  - Cigarette smoking
  - Chronic silent microaspiration
  - Chronic viral infection, mainly herpes
  - Inhaled dusts

## COMORBIDITIES

- **GERD/Reflux**
  - Very common in patients with IPF; often asymptomatic[22,23]
  - Restrictive lung disease mechanics may contribute to lower esophageal sphincter dysfunction
  - Untreated GERD may contribute to cough and progression of disease
  - There is accumulating evidence that treatment of GERD improves survival[24,25]
  - GERD is more common in patients with asymmetric IPF (AIPF) than in patients with symmetric disease (62.5% vs 31.3%, $P = 0.006$)[26]
    - Most patients with AIPF (62.5%) showed a predominance of fibrosis in the right lung
    - The angles of the mainstem bronchi predispose aspirated material toward the right lung
    - In 15/16 cases (94%) where sleeping habits were known, the patients fell asleep on the most involved lung side
  - Appropriate role of prokinetics or surgical intervention (fundoplication) is unclear

**CLINICAL PEARL**

*Pharmacologic and nonpharmacologic treatment should be considered; nonpharmacologic therapy includes*
- *Elevating the head of the bed 4 to 6 inches*
- *Avoiding meals for at least 3 hours prior to bedtime*

- **Obstructive Sleep Apnea (OSA)**
  - Very common in patients with IPF
  - Sleep questionnaires have lower sensitivity and specificity in patients with IPF than patients without IPF[27]
  - OSA likely contributes to poor QOL.[28] Poor sleep quality was significantly associated with decreased QOL in several domains
    - Physical functioning ($r = -0.58$, $P = 0.001$)
    - Energy ($r = -0.43$, $P = 0.015$)
    - Emotional well-being ($r = -0.40$, $P = 0.023$)
  - Severity of OSA is associated with increased risk of nocturnal GER[29]

**CLINICAL PEARL**

*Screening can be performed with polysomnography (PSG) or with a sleep questionnaire*

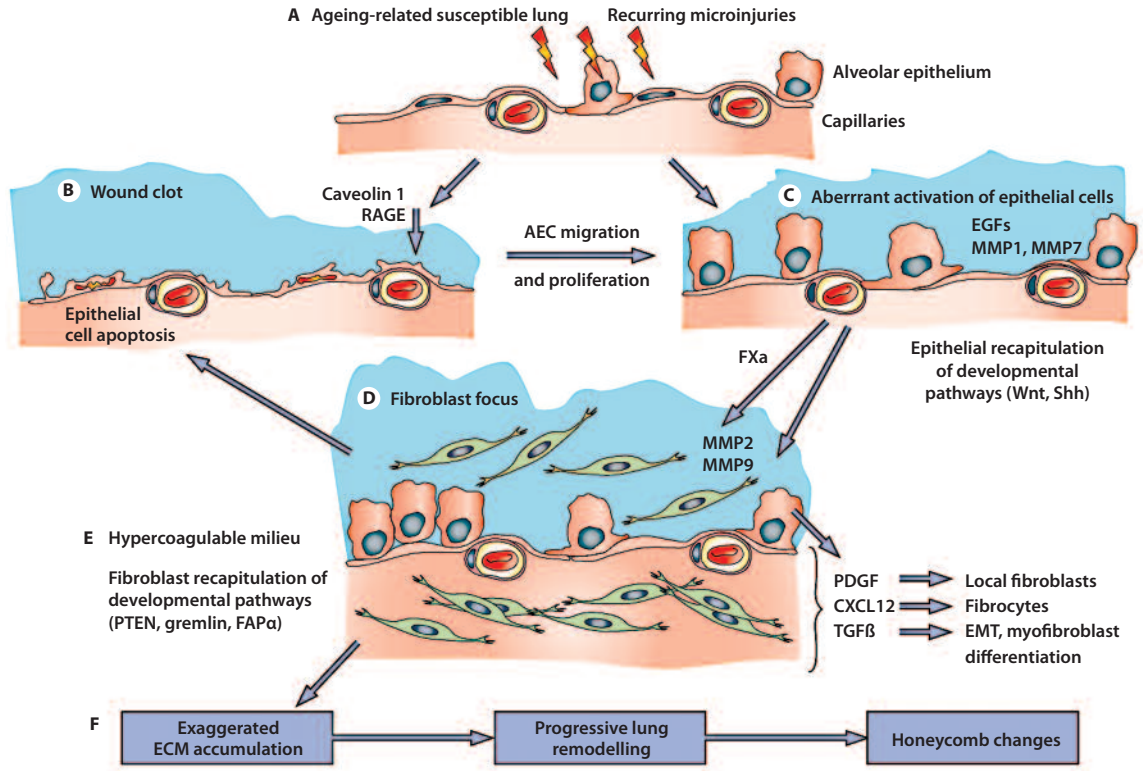


**Figure 4. Proposed mechanisms in the pathogenesis of IPF.[12]**

**(A)** Age-related susceptible lung is targeted by repetitive microinjury that provokes epithelial cell death. **(B)** Increased vascular permeability to proteins causes the formation of a provisional matrix (wound clot). **(C)** Bronchiolar and alveolar epithelial cell (AEC) migration and proliferation. Several epidermal growth factors participate in the proliferative response. Matrix metalloproteinases MMP1 and MMP7 also contribute to the epithelial cell migration. In this microenvironment, epithelial cells are abnormally activated and produce diverse growth factors and chemokines, inducing the migration of resident fibroblasts and bone marrow-derived progenitors of fibroblasts (fibrocytes) to the sites of microinjury. Additionally, they secrete and activate TGFβ1, which promotes epithelial-mesenchymal transition (EMT) and the differentiation of fibroblasts to myofibroblasts. **(D)** Fibrocytes, local mesenchymal cells, and myofibroblasts help form the fibroblast focus. MMP2 and MMP9 contribute to the activation of TGFβ and to the disruption of the basement membranes. **(E)** In the alveolar epithelium, the TF–FactorVIIa–FactorX complex is assembled, with activation of FX. In the hypercoagulable milieu degradation of the provisional matrix is decreased and a fibrogenic milieu is enhanced **(F)**. In the foci, myofibroblasts secrete excessive amounts of extracellular matrix proteins, mainly fibrillar collagens, and can also increase epithelial apoptosis. Several neighboring scars and over-secretion of enzymes (eg, MMP1) can provoke the formation of the honeycomb cysts through mechanical forces.

AEC = alveolar epithelial cells. CXCL12 = CXC chemokine ligand 12. ECM = extracellular matrix. EGF = epithelial growth factor. EMT = epithelial-mesenchymal transition. FVIIa = Factor VIIa. FX = Factor X. FXa = Factor X activated. FAPα = fibroblast activation protein α. MMP = matrix metalloproteinase. PDGF = platelet-derived growth factor. PTEN = phosphatase and tensin homologue. RAGE = receptor for advanced glycation end products. Shh = sonic hedgehog. TF = tissue factor. TGFβ = transforming growth factor β.

- **Pulmonary Hypertension (HTN)**
  - Common; associated with increased mortality[30,31]
  - Defined by the presence of a mean pulmonary artery pressure of > 25 mm Hg at rest on right heart catheterization[1]
  - Echocardiography is frequently inaccurate in patients with advanced lung disease[32]
  - Several endothelin receptor antagonists have been FDA-approved for treating pulmonary arterial hypertension (PAH) but have not been effective in improving functional status or progression-free survival in patient with IPF[33,34,35]
  - Subgroup analysis of the Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF)[36] shows that sildenafil may have a role in managing patients with IPF and right-sided ventricular dysfunction[37]

**CLINICAL PEARL**

*Prescribe supplemental oxygen and use at flows needed to maintain $SpO_2 \geq 89\%$ at all times; treat OSA (if present)*

- **COPD/Emphysema/Combined Pulmonary Fibrosis and Emphysema (CPFE)[38,39]**
  - Current or past tobacco use is common in IPF
  - Emphysema may be present in up to one-third of patients with IPF[9]
    - CPFE is characterized by preserved lung volumes with markedly decreased diffusing capacity
    - Unclear if CPFE represents a distinct phenotype
    - One-year survival of patients with CPFE is approximately 60%[40]
    - Longitudinal change in $FEV_1$ was predictive of mortality[9]

**CLINICAL PEARL**

*Treat emphysema (bronchodilators, inhaled steroids, possibly azithromycin) as you would if the patient did not have IPF*

- **Ischemic Heart Disease**
  - Many risk factors are shared with IPF such as tobacco use and advanced age[41]
  - Cause of death in 8.5% of IPF patients
  - Consider CAD as contributor to symptoms

**CLINICAL PEARL**

*Screen for heart disease and treat*

- **Venous Thromboembolism (VTE)**
  - Increased incidence in patients with IPF[42,43]
  - Warfarin was harmful in stable IPF patients without known thrombosis [44]

**CLINICAL PEARL**

*Be mindful of VTE risk; consider DVT/PE as a contributor to symptoms; use prophylaxis appropriately*

- **Mood Disorders[46,47,48]**
  - Common; dyspnea strongly linked to depression and functional status
  - Anxiety also contributes to QOL and respiratory symptoms

**CLINICAL PEARL**

*Screen and treat*

- **Cough[48,49]**
  - Often multifactorial; contributes to QOL
  - Low dose prednisone or thalidomide may have a role[50]

**CLINICAL PEARL**

*Treat each suspected contributing factor for 4-6 weeks to determine response*

- *Reflux*
- *Upper airway cough syndrome*
- *Airways disease*

# TREATMENT OF IPF

Patients with IPF have a short life expectancy and declining ability to maintain normal daily activity. No drugs are currently approved for the treatment of IPF in the US. Current goals of disease management are to maximize lung function and improve the QOL. Available treatment includes:

- Identification and treatment of common comorbidities
- Management of symptoms, such as cough and dyspnea
- Supportive care such as pulmonary rehab, oxygen supplementation, vaccinations
- Early evaluation for transplant

**Overview of pharmacologic treatment**

- No approved drugs in the US
- Pirfenidone is approved in Europe, Canada, Japan and elsewhere. It may have a role in slowing progression of disease. Because of inconsistent efficacy results,[58] the US FDA denied approval pending further study[51]
- NAC alone is often recommended, but its efficacy is unproven. The NAC and placebo arms of the IPFNet Prednisone, Azathioprine, and N-acetylcysteine in Patients With IPF (PANTHER-IPF) study are ongoing[62^^]

**CLINICAL PEARL**

*We recommend*

- *Accurate diagnosis to prevent treatment errors of omission or commission*
- *Participation in a therapeutic research trial if patients are eligible*
- *Early referral for lung transplant evaluation. Lung transplant is the only therapy proven to prolong survival in IPF, though many patients are not eligible due to age or comorbidities*

**Recent history of treatment trials**

- IPF researchers have conducted a number of large clinical trials **(Table 1)**
- Anti-inflammatory drugs appear to have no efficacy in stable IPF
- Among candidate therapies, corticosteroids, cyclophosphamide, interferon-γ, endothelin receptor antagonists, etanercept, imatinib, triple therapy with prednisone/azathioprine/NAC, and warfarin have been shown to be ineffective or harmful

## EMERGING THERAPIES (Table 2)

- **Pirfenidone**
  - CAPACITY trials yielded mixed results[58]
  - Being studied in ASCEND, a large phase 3 trial[64]
  - Orally bioavailable
  - Regulates the activity of TGF-β and TNF-α in vitro
  - Inhibits fibroblast proliferation and collagen synthesis
  - Reduces cellular and histologic markers of fibrosis in animal models

- **BIBF1120 (nintedanib)**
  - Being studied in 2 large phase 3 trials[61,65]
  - Tyrosine kinase inhibitor (PDGFR, VEGFR, FGFR)
  - Prevents development of lung fibrosis when administered before or during the fibrotic phase of the disease in a rat model

## TABLE 1: RECENT CLINICAL TRIALS OF PHARMACOLOGIC TREATMENTS FOR IPF

| Year | Study | Agent | N | Primary outcome | Result | Reference |
|---|---|---|---|---|---|---|
| 2004 | GIPF-001 | IFN-γ | 330 | Progression free survival | Negative | Raghu G; *NEJM* 2004[53] |
| 2005 | IFIGENIA | NAC | 184 | Δ FVC, $DL_{CO}$ | Positive | Demedts; *NEJM* 2005[54] |
| 2005 | Anticoagulant Therapy for IPF | Warfarin | 56 | Survival and hospital free survival | Positive | Kubo H; *Chest* 2005[55] |
| 2008 | BUILD-1 | Bosentan | 132 | Δ 6MWD | Negative | King TE Jr; *AJRCCM* 2008[33] |
| 2008 | NCT00063869 | Etanercept | 100 | Δ FVC, $DL_{CO}$ | Negative | Raghu G; *AJRCCM* 2008[56] |
| 2009 | INSPIRE | IFN-γ | 826 | Survival time | Negative | King TE Jr; *Lancet* 2009[57] |
| 2009 | CAPACITY I | Pirfenidone | 344 | Δ FVC | Negative | Noble PW; *Lancet* 2011[58] |
| 2009 | CAPACITY II | Pirfenidone | 435 | Δ FVC | Positive | Noble PW; *Lancet* 2011[58] |
| 2010 | Shionogi Pirfenidone | Pirfenidone | 275 | Δ FVC | Positive | Taniguchi H; *ERJ* 2010[59] |
| 2010 | BUILD-3 | Bosentan | 616 | Progression free survival | Negative | King TE Jr; *AJRCCM* 2011[34] |
| 2010 | Imatinib IPF | Imatinib | 119 | Progression free survival | Negative | Daniels CE; *AJRCCM* 2010[60] |
| 2011 | STEP-IPF | Sildenafil | 180 | Proportion with 20% improvement in 6MWD | Negative | Zisman DA; *NEJM* 20011[36] |
| 2011 | NCT00514683 | Nintedanib (BIBF 1120) | 432 | Annual decline in FVC | Helpful? | Richeldi L; *NEJM* 2011[61] |
| 2012 | PANTHER | Pred/Aza/NAC | 155 | Δ FVC | Harmful | Raghu G; *NEJM* 2012[62] |
| 2012 | ACE-IPF | Warfarin | 145 | Progression free survival | Harmful | Noth I; *AJRCCM* 2012[44] |
| 2013 | ARTEMIS-IPF | Ambrisentan | 492 | Progression free survival | Negative | Raghu G, *Ann Int Med*[35] |
| 2013 | MUSIC | Macitentan | 178 | Δ FVC | Negative | Raghu G, *ERJ*[63] |

**TABLE 2. CURRENT PHASE 2 AND 3 TRIALS IN IPF**

| Compound | Company | Study Phase | MOA | Estimated Completion Date |
|---|---|---|---|---|
| NAC | NHLBI | 3 | Anti-oxidant | Q3 2013 |
| Pirfenidone | InterMune | 3 | Anti-fibrotic | Q2 2014 |
| BI-1120 (Nintedanib) | Boehringer Ingelheim | 3 | Triple kinase inhibitor | Q4 2013 |
| FG-3019 | FibroGen | 2 | CTGF mAb | Jan 2014 |
| CC-930 | Celgene | 2 | JNK Inhibitor | Nov 2013 |
| STX-100 | Biogen Idec | 2 | αvβ6 Integrin Ab | June 2013 |
| BMS-986020 | Bristol-Myers Sqibb | 2 | Lysophosphatidic Acid $LPA_1$ Receptor antagonist | Feb 2015 |
| Tralokinumab | MedImmune | 2 | IL-13 mAb | Aug 2015 |
| SAR156597 | Sanofi-Aventis | 2 | IL-4/IL-13 Ab | June 2013 |
| Inhaled CO | Brigham & Women's Hospital | 2 | | July 2014 |
| GS-6624 (Simtuzumab) | Gilead | 2 | Lysyl oxidase-like 2 (LOXL2) mAb | July 2017 |
| Lebrikizumab | Hoffmann-La Roche | 2 | IL-13 mAb | May 2016 |
| PRM-151 | Promedior | 1 | Pentraxin (PTX-2), antifibrotic | Aug 2012 |
| IW001 | ImmuneWorks | 1 | Type V Collagen Oral Solution | Dec 2012 |

Abbreviations: MOA = mechanism of action; CTGF = connective tissue growth factor; mAb = monoclonal antibody; IL-13 = interleukin-13; JNK = c-Jun N-terminal protein kinase

**Issues for clinical trial design**

- How long should trials be?
- What is the best endpoint? (lung function, 6MWT, QOL, hospitalization, mortality, composite)
- Inclusion criteria (comorbidities, familial disease, rate of progression, time since diagnosis)
- Should placebo-controlled trials be conducted?
- Should pirfenidone be allowed as background therapy?

## TREATMENT OF ACUTE EXACERBATIONS

- In the absence of rigorous clinical evidence, patients with new ground-glass infiltrates are often treated with both antibiotics and steroids; this approach received a weak recommendation in the 2011 ATS/ERS guidelines.[1] If patients improve, continued immunosuppression is considered
- A minority of patients with acute exacerbations improve with combined steroids and antibiotics. These patients probably have a component of organizing pneumonia. Given the severity of acute exacerbations, this approach has potential benefits and few risks.
- Mechanical ventilation for patients with IPF and acute respiratory failure is associated with a high mortality rate[67]

**CLINICAL PEARL**

*Providers should have a lower threshold for evaluation and treatment of new respiratory symptoms in patients with IPF*

## NON-PHARMACOLOGIC MANAGEMENT OF IPF

Several lifestyle and general health approaches can be used to maximize lung function and improve the QOL.

- **Pulmonary Rehabilitation (PR)**
  - The 2011 ATS/ERS guidelines[1] have a weak recommendation for pulmonary rehabilitation in patients with IPF; pulmonary rehabilitation (PR) should be used in the majority of patients with IPF, but not using PR may be a reasonable choice in some patients
  - Patients with IPF attain greater and more sustained benefits from PR when disease is mild, so early referral to PR should be considered[68]
  - PR can increase functional performance (6-Minute Walk Distance, 6MWD)[69] but positive effects diminish after completion of intervention if patients do not continue exercising at home[68]
  - The ideal length of PR, and the best type of exercise program (endurance vs. interval vs. other type of aerobic training) for patients with IPF is unknown
- **Supportive Care**
  - Patients should have their oxygen needs periodically assessed at rest, with activity, and at night. Oxygen should be prescribed as necessary to maintain an oxygen saturation $SpO_2 \geq 89\%$
  - Appropriate vaccinations (annual influenza, pneumococcus, pertussis booster) are indicated to decrease the risk of respiratory infections
- **Collaborative care**[70,71]
  - The physiological symptoms of IPF and comorbidities are uncomfortable and disturbing for patients but also may impact caregivers as well. Frustration, anxiety, depression, and other reactions can stress social and familial relationships; caregivers may need psychosocial support
  - Education about the disease and its management, attention to relationships, and resources for end-of-life planning can be of great benefit for caregivers and family

# PATIENT EDUCATION TOOLS AND RESOURCES

Many patients with IPF want information about their disease.[72,73] Resources are available at a variety of web sites, listed below. Some resources are for direct patient consumption and some are designed as part of the provider's counseling effort.

- **Pulmonary Fibrosis Foundation**
  **http://www.pulmonaryfibrosis.org/patient**

- **Coalition for PF**
  **http://www.coalitionforpf.org/patients/**

- **PILOT**
  **http://www.pilotforipf.org/patient_tools.php**

  - **Patient Education Pamphlet**
    Download PDF >>

  - **GERD: Definition, Diagnosis, and Management of GERD**
    Download PDF >>

  - **Conditions Associated with IPF**
    Download PDF >>

  - **Emotional Well-Being**
    Download PDF >>

  - **Emotional Well-Being – Spanish**
    Download PDF >>

  - **Travel Hints for IPF Patients**
    Download PDF >>

  - **Oxygen and Travel: Oxygen arrangements, security information, and airline checklist**
    Download PDF >>

- **Clinical Trial Participation**
  **http://www.clinicaltrials.gov**

- **Participation Program for PF**
  **www.pulmonaryfibrosisresearch.org**

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