

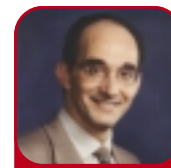
PILOT™

Pulmonary Fibrosis Identification: Lessons for Optimizing Treatment

WINTER 2004

PILOT™ MISSION STATEMENT

PILOT™ is a national education initiative designed to provide physicians with a comprehensive continuing medical education program that focuses on the early and accurate diagnosis of idiopathic pulmonary fibrosis (IPF), while addressing educational objectives critical to optimizing disease intervention and management.



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IPF COMORBIDITIES

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Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal condition that is associated with the pathologic features of usual interstitial pneumonia.¹ Estimates of the incidence and prevalence are somewhat lacking, but it is likely that there has been an underestimation of its true prevalence, especially in the elderly population. Elderly patients with IPF have also been noted to have a worse prognosis.² There are a number of possible explanations for this, including lead-time bias from the delay in diagnosis, less pulmonary reserve, a more aggressive disease course, or comorbidities. With regards to the latter, it appears that not only the elderly, but all patients with IPF might be at risk.

An appreciation for IPF-associated comorbidities is important, since they can have significant implications, not only for patients' quality of life, but also their overall prognosis. Deaths among IPF patients in randomized controlled studies, specifically the recently published interferon gamma-1b study, are mostly respiratory in nature.³ More than 80% of the deaths from this study were respiratory in origin, with IPF being directly responsible in 62% and 71% of these events in the treatment and placebo arms, respectively. However, these patients represent a highly select population, since significant comorbidities by necessity are exclusionary criteria for enrollment in such studies. Therefore, the proportion of deaths directly attributable to IPF might overestimate and misrepresent the true picture in a general population of IPF patients. A meta-analysis of six studies that looked at the cause of death in a total of 326 patients with IPF might provide a more accurate frame of reference.⁴

This study confirms that the majority of deaths are from respiratory failure due to IPF progression. However, cardiac disease, including heart failure and coronary artery disease accounted for 24% of the deaths. Other pulmonary conditions accounted for a further 16% of the deaths, with bronchogenic

carcinoma contributing 10%, pulmonary infection 3%, and pulmonary embolus 3% of all deaths. This meta-analysis encompassed studies from 1964–1983 and therefore one needs to be aware that the patient populations studied likely represented a heterogeneous group and not only patients with IPF/UIP by today's current definition.¹ Nonetheless, this study does underscore that not all patients' deaths are directly attributable to their IPF.

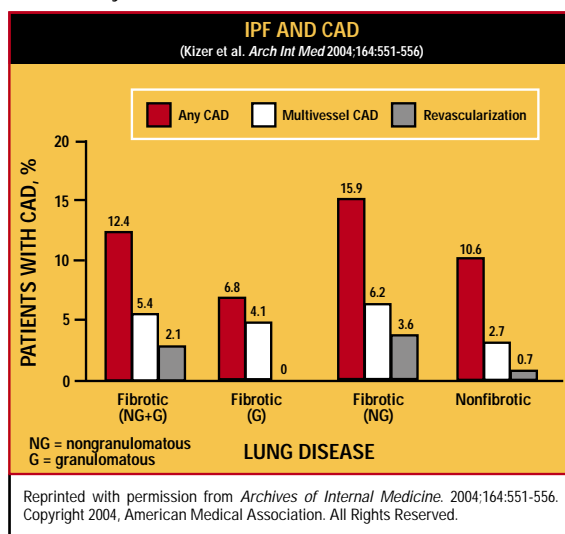
Since IPF is a condition that is localized to the lung, the question arises whether or not patients with IPF might have a higher predisposition to comorbidities or if such noted comorbidities are merely a function of the background prevalence of more common medical maladies. With regard to coronary artery disease, there have been recent data

this analysis was limited to only those patients who were of transplant age, it is likely that the prevalence might be even higher in older IPF patients. How does one explain this apparent association between two seemingly unrelated entities? While the lungs are the source of multiple cytokine derangements in IPF, it might be naive to think that their effects are only localized in the lung. Along these lines, elevations in interleukin (IL)-4, IL-8, IL-13, and tumor necrosis factor alpha, which are found in IPF, have also been shown to have pro-atherogenic effects.⁵ Therefore, this might help explain this apparent association and conceptually might also be the basis for other IPF-related comorbidities.

A higher propensity for pulmonary emboli has also been described in IPF.⁶ One possible mechanism might relate to microvascular injury, which occurs as part of the pathogenic sequence in IPF. Interestingly, a high incidence of antiphospholipid antibodies has also been noted in IPF patients.⁷ It is especially important to be aware of this potential complication since patients who present with acute SOB might have this wrongly attributed to progression of their IPF or to an "acute exacerbation." With the advent of contrast-enhanced spiral CAT scans, the ability to diagnosis pulmonary emboli in these patients has been greatly improved.

Patients with IPF may also be at higher risk for the development of bronchogenic carcinoma. Although the majority of these patients are current or ex-smokers, after accounting for this risk factor, the risk for the development of lung cancer appears to remain high, with a reported relative risk of 8.25.⁸ This association remains controversial, as there are other studies that have failed to show a similar association.⁹

An association between IPF and gastroesophageal reflux disease (GERD) has also been noted with more than 90% of IPF patients displaying abnormal esophageal pH



attesting to a higher incidence in IPF patients versus other forms of lung disease.⁵ Our own group has verified these findings by comparing the prevalence of CAD in 68 IPF lung transplant candidates to a similar group of COPD patients. While risk factors for CAD were not accounted for in this retrospective review, the prevalence of significant CAD was 29% in the IPF patients versus 10% in their COPD counterparts. Since

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monitoring.¹⁰ Interestingly, 75% of these patients did not manifest typical GERD type symptoms. There are now many different pulmonary maladies that have been shown to have an association with GERD, and therefore whether this represents a cause versus an effect of the disease remains uncertain. A common pathway to explain this association across this spectrum of diseases might be the increased pressure gradient across the diaphragm that accompanies the increased work of breathing. Nonetheless, cognizance of this relationship is important in the management of patients with IPF.

Another consideration is that patients with IPF might have been treated with steroids and cytotoxic agents, which certainly could have played a role in the emergence or potentiation of comorbidities. This is an important consideration for any potential therapy, where it is incumbent upon the physician to ensure that the preponderance of evidence suggests a net benefit that outweighs any potential detriment to the patient. For example, steroid therapy resulted in complications in 100% of 41 patients, with uncertain or no benefit documented.¹¹ Diabetes is only one of the concerns with steroid therapy, however, interestingly—a higher incidence of diabetes has been noted in steroid-naïve IPF patients.¹²

An unexplained and underappreciated fact is that among all lung transplant recipients, IPF patients tend to do the worst. The latest statistics from the International Society for Heart and Lung Transplantation attest to a 5-year survival of 53%, 47%, 45%, and 40% in patients with cystic fibrosis, COPD, sarcoidosis, and IPF, respectively.¹³ Whether some of this excess mortality in IPF patients is due to the impact of comorbidities is open to speculation and represents an area for future study. In conclusion, while proven effective therapies for IPF remain elusive, one of the few ways whereby clinicians might impact on the prognosis of this deadly condition is through the timely recognition and management of associated comorbidities.

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EDUCATING YOUR IPF PATIENTS ABOUT THEIR DISEASE

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Idiopathic pulmonary fibrosis (IPF) is a chronic and ultimately fatal disease characterized by a relentless decline in pulmonary function that is caused by fibrosis and scarring of the lungs. In the United States, there are currently 80,000 men and women suffering from IPF, with an estimated 30,000 new cases diagnosed annually. The average survival rate for patients with IPF is 2.5 to 5 years.¹² Unfortunately, the 5-year survival

rate from the time of diagnosis is only 30% to 50%,¹ which is worse than the survival rates for many cancers, including colorectal, breast, and prostate cancers. With such a dismal prognosis and limited treatment options, educating your IPF patients about their disease becomes a difficult task. A sensitive, but realistic and honest approach must be taken when discussing IPF with your patients and their families. It is

important to discuss not only the disease, but also the treatment options, including nonpharmacologic options, the value of clinical trials, and quality of life expectations. Although difficult, it is also crucial to discuss end-of-life issues so that patients and family members are prepared.

DESCRIBING IPF TO YOUR PATIENT

Patients should understand the early and late-stage symptoms of IPF. Although the disease is idiopathic, it may be beneficial to explain possible risk factors associated with the disease, such as occupational exposures, cigarette smoking, gastroesophageal reflux, infectious agents, and genetics.¹ Since the most common presenting symptoms of IPF are dyspnea and a nonproductive paroxysmal cough, IPF is often misdiagnosed as CHF, COPD, or other lung diseases. Therefore, patients are often frustrated by the time they are actually diagnosed with IPF. To help alleviate frustration, discuss the difficulty in diagnosing IPF, and review the types of tests

used in the diagnostic process, such as pulmonary function tests, HRCT scans, biopsies, and serological tests used to rule out other diseases. Because patients may be anxious about having a biopsy performed, explain the various procedures in more detail, including an explanation of video-assisted thoracoscopic surgery (VATS), the preferred biopsy technique in IPF, which is less invasive than open lung biopsy.

Prognosis should also be reviewed with patients and their families. Be sensitive to the ominous prognosis, encourage a positive outlook, remain honest, and establish realistic expectations. Emphasize that all patients are

unique and progress differently in the course of the illness. Some patients may deteriorate more rapidly as a consequence of an acute exacerbation^{3,4} or complicating infection, while others remain functional without experiencing a swift decline. For interested patients and family members, it is also helpful to provide credible educational resources. Additional patient education resources are available at the following web sites:

The Coalition for Pulmonary Fibrosis
www.coalitionforipf.org

The PILOT™ Website contains information for ordering IPF patient education brochures.
www.pilotforipf.org

IPF TREATMENT OPTIONS AND CLINICAL TRIALS

Discussion of IPF treatment options should focus on both pharmacologic and nonpharmacologic options. Patients should understand that several medications are available, but despite all of the studies being done, it is not clear which treatment is best. Patients should be educated about all treatments, including the benefits, risks, and side effects associated with each treatment. Oxygen supplementation and pulmonary rehabilitation are valuable non-pharmacological treatment options for IPF patients. A pulmonary rehabilitation program includes medical education, breathing techniques, exercise training, nutrition advice, and emotional support from a team of health care professionals. Pulmonary rehabilitation and oxygen supplementation treatments are intended to prolong life, reduce disability, and improve the level of patient functioning. Comorbidities (osteoporosis, sleep apnea, pulmonary hypertension, pulmonary emboli) that complicate the course of the illness, should be sought and treated appropriately.⁵⁻⁷ Since lung transplantation is another potential treatment option, discuss lung transplantation and the need for early referral for evaluation and listing, even before a significant decline in lung function is experienced.

Inform patients about the value of clinical trials. Patients should understand that a clinical trial tests a potential treatment for their disease, and that the medication may or may not be beneficial. Both the benefits and risks of enrolling in a clinical trial should be explained. Potential benefits for the patient

include gaining access to a promising therapy that is not yet approved for IPF, and obtaining medication and physician care for free or at a low cost. Potential risks for the patient include receiving placebo versus the active treatment, and experiencing unforeseen side effects. Recommended patient tips for selecting a clinical trial include:⁸

- Take the informed-consent form home and read it carefully.
- Determine what risks there may be, and what level of risk you are willing to accept
- Understand the type of trial you are considering
- Remember, you are allowed to quit at any time
- Know who is paying for the study
- Ask yourself whether you really have the time to commit to the trial

Additional Patient Resources include the following web sites:

American Association for Respiratory Care
www.aarc.org

American Association of Cardiovascular and Pulmonary Rehabilitation
www.aacvpr.org

National Home Oxygen Patients Association
www.homeoxygen.org

Clinical Trial Information
www.clinicaltrials.gov

Center Watch
www.centerwatch.com

SUPPORT GROUPS

Emotional support from other IPF patients is comforting to patients and family members. Interacting with other IPF patients helps patients and family members to understand that they are not alone and that resources exist to help cope with and better understand the disease. Physicians should help patients recognize the importance of finding a support group to help manage stress, anxiety, and depression. In addition, well-informed patients who understand their disease are in a better position to discuss all health care concerns and treatment options with their physician.

Additional information for pulmonary fibrosis support groups is available at the following web sites:

Coalition for Pulmonary Fibrosis
www.coalitionforipf.org

Pulmonary Fibrosis Foundation
www.pulmonaryfibrosis.org/groups.htm

TRAVELING AND RECREATIONAL ACTIVITIES FOR PATIENTS WITH IPF

Oxygen supplementation therapy should not infringe upon a patient's ability to travel and enjoy life. There are more than 2,500 locations to refill oxygen tanks, in over 1,600 cities in all 50 states.⁹ Although locations for oxygen tanks are plentiful, patients should be encouraged to plan ahead which includes identifying a convenient source of oxygen tanks in the area they will be traveling to. On-line resources for planning vacations are available for wheelchair-bound patients, patients who require portable oxygen and patients with other disabilities. Patients should carry any necessary medications and their physician's telephone number with them while they travel. Consider providing patients with a recent chest radiograph, which they may store in their suitcase. It may become useful in the event of an emergency. Finally, patients should be encouraged to enjoy life.

Additional information is available at:

Breathin' Easy
www.breathineasy.com

Accessible Journeys
www.disabilitytravel.com

Can Be Done
www.canbedone.co.uk

PILOT™ RESOURCE HUB

Medication	Study Phase	Design	Patients (N)	Primary Endpoints
IFN gamma (INSPIRE)	Phase III	Randomized 2:1, double-blind, placebo-controlled	600	Survival time
Bosentan (BUILD 1)	Phase II/III	Randomized, double-blind, placebo-controlled, parallel assignment	130	Change in 6-minute walk distance at 1 year
Pirfenidone	Phase II/III	Draft Protocol	N/A	Safety and efficacy
Etanercept	Phase II	Randomized, double-blind, placebo-controlled, parallel assignment	100	Safety and efficacy
Imatinib Mesylate	Phase II	Randomized, double-blind, placebo-controlled	100	Disease progression

Idiopathic Pulmonary Fibrosis: Ongoing Clinical Trials

END-OF-LIFE ISSUES

Setting realistic expectations for patients regarding survival, and remaining optimistic are essential components when discussing diseases with an ominous prognosis, such as IPF. The decreased survival and poor outcome of patients with IPF admitted to ICU who require ventilatory support has been consistently documented in several studies.¹⁰⁻¹² This information needs to be shared with patients and family members to help them in their decisions for advanced directives. Non-invasive ventilation may be used temporarily to alleviate the work of breathing. Goals of treatment include managing symptoms and relieving discomfort. Palliative care should be considered from the time of diagnosis, even while the patient pursues treatments to slow or stabilize the disease. Managing end-of-life care entails deciding whether and when to begin hospice care; these decisions can profoundly change the patient's and family's experiences of death. Research has found that when discussing end-of-life options, it is more effective to ask the patient "What makes you happy in this part of your life?" rather than "Do you want everything done?"¹³ Discussing hospice care is also important, since there are many common patient misconceptions, including the following, all of which are not true:¹⁴

- Patients enrolled in hospice must agree not to be resuscitated
- Patients enrolled in hospice lose their primary physicians
- Hospices would rather enroll cancer patients than patients with nonmalignant diseases
- Patients cannot be hospitalized and remain enrolled in hospice
- Patients cannot participate in research projects while enrolled in hospice

- Medicare beneficiaries can "use up" hospice eligibility, so it is important not to enroll too soon
- Hospice is not available to patients who live alone

Legal arrangements and advanced care planning should also be prepared early in the disease course so patients can assure that their wishes are followed. Patients should understand how to establish a do-not-resuscitate (DNR) order, if desired, and also a Durable Medical Power of Attorney. The ordinary Power of Attorney form authorizes an individual to make business and financial decisions, whereas a Durable Medical Power of Attorney authorizes a person to make medical decisions on the patient's behalf when the patient is unable to communicate his or her own wishes.¹⁵ Adequate planning and open discussion with family members and physicians allows patients to be better prepared and more comfortable with their end-of-life planning and helps to ensure that their wishes are followed.

Additional information is available at the following web sites:

Aging with Dignity
www.agingwithdignity.org

National Hospice and Palliative Care Organization
www.nhpco.org

Caregiving.com
www.caregiving.com

Well Spouse Foundation
www.wellspouse.org

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UPCOMING CME EVENTS

PILOT™ CME Dinner Meetings will start again in March 2005. Please visit us at

www.PILOTFORIPF.ORG
for updates.