

2 0 0 5

PILOT™

Pulmonary Fibrosis Identification:
Lessons for Optimizing Treatment

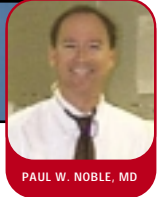
SPRING 2005

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.

PILOT™: A YEAR IN REVIEW

PAUL W. NOBLE, MD – YALE UNIVERSITY SCHOOL OF MEDICINE



PAUL W. NOBLE, MD

IPF is a progressive, chronic fibrosing interstitial pneumonia of unknown etiology. A diagnosis of IPF carries an extremely dismal prognosis with median survival reported as 2 to 3 years from the time of diagnosis. With no known cure, this disease presents major challenges to health care practitioners. Although recent research has provided important insights into the natural history of the disease, a thorough knowledge of the mechanisms operative at different stages of the disease remains to be elucidated. This knowledge could lead to development of targeted therapeutic interventions for specific stages of the disease.

Moreover, disease recognition, diagnosis, and therapeutic intervention may improve outcomes in patients with IPF. Early diagnosis allows for earlier referral and enrollment in clinical trials that are generally limited to patients with mild to moderate disease. Additionally, early recognition and diagnosis improves the ability of physicians to provide prognostic information. Recent evidence that even patients with relatively mildly impaired lung function can experience acute fatal events underscores the need for early and accurate diagnosis of IPF.

Initiated in 2004, the PILOT™ (Pulmonary Fibrosis Identification: Lessons for Optimizing Treatment) program was created to meet the need for increased physician awareness and knowledge of IPF. The program is supported by an educational grant from InterMune® Inc. to provide continuing medical education to the health care community. Development of educational content and materials is directed by a Steering Committee comprised of six pulmonologists, a radiologist, and a pathologist, all with expertise in IPF. Additionally, 4 multi-disciplinary working groups of experts oversee development of the 4 slide kit sections in the

PILOT™ Compendium, the primary educational tool in the program.

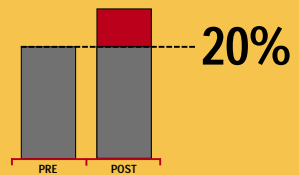
The PILOT™ Program focuses on the early and accurate diagnosis of IPF and addresses educational objectives critical to optimizing disease intervention and management by:

- Developing a series of educational tools designed to increase knowledge of the early and accurate diagnosis of IPF
- Identifying the evolving treatments available for the management of IPF with the overall intention of improving patient care
- Disseminating the core educational messages to a targeted audience, including pulmonologists, radiologists, pathologists, and primary care physicians
- Measuring the impact of PILOT™ activities on physician knowledge through the gathering and analysis of objective, measurable outcome data by pre- and posttesting

The PILOT™ 2004 Steering Committee and Working Groups met these goals through the completion of several initiatives, including the PILOT™ 2004 Compendium, which contained a slide set, faculty videos, interactive case studies, and a digital animation of a hypothetical mechanism of IPF pathogenesis. CME preceptorships at academic institutions offered an opportunity for community pulmonologists to conduct discussions with expert faculty at various centers of excellence.

including "New Concepts in Pathogenesis," "Acute Exacerbations," "The Role of HRCT in the Diagnosis of IPF," and "IPF Comorbidities."

IN 2004, PARTICIPANTS INCREASED THEIR KNOWLEDGE UP TO



Finally, a patient educational brochure was designed as a tool for physicians to educate IPF patients and their families. Topics covered in the brochure include understanding IPF, patient resources, tips for a healthy lifestyle, and what the patient needs to know about home oxygen therapy and pulmonary rehabilitation.

In an effort to provide physicians with updated clinical educational information and an opportunity for peer-to-peer interaction, CME dinner programs were conducted nationwide in 2004. By utilizing didactic presentations and a case study approach, the program provided physicians with the tools for a systematic approach to the early and accurate diagnosis of IPF. The effectiveness of these interactive sessions were measured by the administration of pre- and posttests focusing on the areas of pathogenesis, early and accurate diagnosis, and the latest clinical information. For 2004, posttest results indicated there was an overall increase in knowledge of approximately 20%. Ninety-eight percent of PILOT™ 2004 Dinner Program participants agreed that the activity enhanced their professional effectiveness and improved their ability to communicate with patients.



98% DESCRIBED THE PROGRAMS AS "CREDIBLE" AND "FREE FROM COMMERCIAL BIAS"

In addition, quarterly newsletters, distributed nationwide, provided up-to-date clinical information and expert opinions on topics,

Supported by an educational grant from



The France Foundation
A Continuing Medical Education Company

(Continued on next page)

(Continued from page 1)

A CME monograph focused on the early and accurate diagnosis of IPF by distinguishing IPF from other interstitial lung diseases through the systematic evaluation of clinical, radiographic, and pathologic findings.

The overwhelming success of the PILOT™ 2004 Dinner Programs and other educational initiatives demonstrates the impact of a comprehensive medical education program on physician knowledge of IPF. This success provides the groundwork for exciting new PILOT™ Programs in 2005.

The PILOT™ 2005 Compendium will include new content in the existing 4 sections in the form of slide files on CD-ROM, printed slides with speaker notes; new interactive cases on CD-ROM; new patient education tools; and recommended readings which include the most recent literature in the field. The slide kit section on emerging concepts in the pathophysiology and pathogenesis of IPF discusses recent findings that have led to an evolution in the conventional wisdom regarding the pathogenesis of IPF. The section on the early and accurate diagnosis of IPF reviews new findings

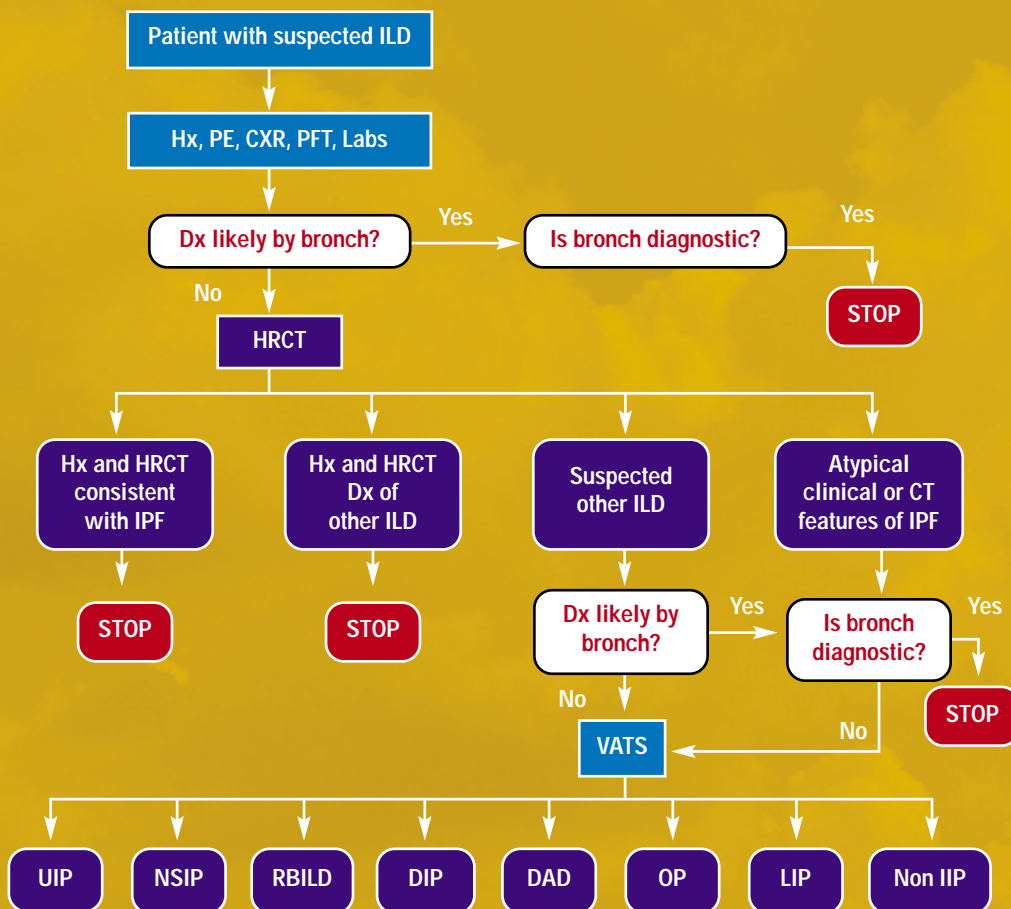
regarding a multidimensional and multi-disciplinary strategy for accurate diagnosis of IPF that utilizes clinical approaches but emphasizes radiological and pathological approaches. The disease management section reviews current and emerging strategies in the therapeutic management of patients with IPF, and includes a comprehensive review of recent and ongoing clinical trials. The 2005 educational resource section provides a practical patient education resource for health care practitioners, as well as new patient tools that focus on patient enrollment in clinical trials, lung transplantation, maximizing time with health care providers, and useful travel tips for patients with interstitial lung disease.

The PILOT™ Interstitial Lung Disease (ILD) CME Case Compendium explores a variety of ILDs, including IPF, through a compilation of 20 diverse cases that were contributed by practicing pulmonologists. These tools are designed to increase awareness and to provide a practical approach to diagnosis and treatment.

The PILOT™ 2005 Program promises to build on the success of the 2004 initiative to deliver state of the art, comprehensive continuing medical education to physicians involved in the diagnosis and management of patients with IPF. Additional information regarding the PILOT™ program, including a list of upcoming CME events and a link to PILOT™ information developed throughout the year can be obtained from the PILOT™ Web site, www.pilotforipf.org.

PILOT™ RESOURCE HUB

Approach to the ILD Patient



Martinez F, Flaherty K. Available at: http://www.chestnet.org/education/online/pccu/vol18/lessons03_04/lesson03.php. Accessed March 2, 2005.

**ON BEHALF OF THE
2005 PILOT™
STEERING
COMMITTEE, I
INVITE YOU TO GET
INVOLVED IN THIS
IMPORTANT
EDUCATIONAL
ENDEAVOR.**

IDIOPATHIC PULMONARY FIBROSIS: EMERGING CONCEPTS AND EVOLVING PARADIGMS

VICTOR J. THANNICKAL, MD – DIVISION OF PULMONARY AND CRITICAL CARE MEDICINE
UNIVERSITY OF MICHIGAN MEDICAL CENTER - ANN ARBOR, MICHIGAN



VICTOR J. THANNICKAL, MD

DIAGNOSIS

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, debilitating disease with a median survival of approximately 3 years. Despite recent advancements in definitions and classification of the idiopathic interstitial pneumonias (IIP)¹, making an accurate diagnosis can be challenging even for the experienced pulmonologist. An accurate diagnosis is important not only because of its prognostic implications, but

because there are a number of ongoing and future drug trials that may eventually prove beneficial for an otherwise

THERE IS GROWING CONSENSUS THAT A MULTIDISCIPLINARY APPROACH TO DIAGNOSIS THAT INVOLVES DYNAMIC INTERACTIONS BETWEEN CLINICIANS, RADIOLOGISTS, AND PATHOLOGISTS IMPROVES INTEROBSERVER VARIABILITY AND DIAGNOSTIC CONFIDENCE.

treatment-unresponsive process such as IPF. Several factors contribute to the difficulty in making an accurate diagnosis in IIP: the relative non-specificity of presenting symptoms, chest radiographic findings and physiological tests; lack of understanding of the natural history of the disease; lack of knowledge regarding etiology or causation (thus, a specific/sensitive test cannot be designed); lack of serological biomarkers; and the documented heterogeneity of the disease process, making even the "gold standard" of a surgical lung biopsy unreliable.² There is growing consensus that a multidisciplinary approach to diagnosis that involves dynamic interactions between clinicians, radiologists, and pathologists improves inter-observer variability and diagnostic confidence.³ The clinician that initially encounters the patient suspected of IPF must take the lead role in such interactions. Patients are typically older than 50 years of age and present with insidious onset of progressive dyspnea with/without a dry cough and "velcro-like" rales at end-inspiration that are most prevalent at the lung bases. Pulmonary function tests usually demonstrate restrictive physiology with abnormalities in gas exchange, although resting PFTs may be normal in early stages of the disease. Chest radiographs typically show (at least in moderate-severe disease)

reduced lung volumes with reticular opacities that are more prominent at the lung bases. It is important to exclude "secondary" causes of pulmonary fibrosis that may present in a similar manner, but that carry vastly different prognoses and implications for therapy.

A careful occupational, environmental, and drug history must be conducted. Clues to the presence of a systemic connective tissue disease must be sought. After secondary

causes have been excluded, the next step in the evaluation is to obtain a high-resolution computed tomography (HRCT) scan of the chest. The HRCT in IPF/UIP (usual interstitial pneumonia) is characterized by bibasilar and subpleural reticular abnormalities with

honeycombing, traction bronchiectasis and minimal ground-glass opacities. Consultation with an experienced radiologist may aid in the differential diagnosis. Recent studies suggest that, in a patient presenting with a clinical syndrome suggestive of IIP, HRCT findings typical of IPF/UIP, in particular honeycomb change in the bases, can be diagnostic of IPF and obviate the need for a surgical lung biopsy.^{4,5} A major advantage of the HRCT over surgical lung biopsy is the ability for more global assessment of lung involvement in a

heterogeneous disease such as IPF. In patients with atypical clinical and/or HRCT features, however, a surgical lung biopsy (preferably by video-assisted thoracoscopic surgery—VATS) may be necessary to make a confident and accurate diagnosis. Based on recent studies, it is anticipated that most patients will fall into this latter category. Sampling error can be minimized if biopsies are obtained from more than one lobe of the lung.⁶

PATHOGENESIS/DISEASE PROGRESSION
Evolving paradigms regarding the patho-

genesis of IPF will hopefully lead to development of more effective therapeutic interventions that target stage-specific aberrant pathways involved in IPF pathogenesis and progression. A comprehensive treatise of disease pathogenesis and mechanisms of pulmonary fibrosis is beyond the scope of this discussion and the reader is referred to recent reviews on this topic.^{7,8} Focus has shifted from an "inflammatory pathway" paradigm to fibrogenic mechanisms that appear to involve dysfunctional relationships between the regenerating epithelium and the activated mesenchyme (composed of myofibroblasts in the fibroblastic foci of UIP). Oxidant injury to alveolar epithelial cells in IPF has been recognized to occur and was previously thought to be related to inflammatory cells present in alveolar spaces.⁹ Recent in vitro studies from our laboratory support the concept that oxidant production by activated myofibroblasts is capable of inducing apoptosis/death of epithelial cells in an epithelial-fibroblast coculture system.¹⁰ In IPF, an apparent "apoptosis paradox" exists in that alveolar epithelial cells appear to undergo increased rates of apoptosis while adjacent myofibroblasts are resistant to apoptosis. We have demonstrated in an animal model of pulmonary fibrosis that targeting critical anti-apoptotic/pro-survival pathways in myo-

fibroblasts with systemic administration of a protein kinase inhibitor protects against fibrotic tissue responses.¹¹ Thus, better understanding and targeting of pro-fibrotic pathways in epithelial cells and myofibroblasts may offer more effective strategies for treatment of IPF.

Clinical observations in some patients with IPF suggest a more stepwise (as opposed to a linear) decline in lung function that results from multiple "exacerbations" of IPF during the course of the illness. Interestingly, such exacerbations may be due to non-infectious etiologies, may appear histopathologically indistinguishable from acute interstitial

THE HRCT HAS TAKEN ON GREATER UTILITY IN THE EVALUATION OF IIP AND CAN OBTAIN THE NEED FOR A VATS-LUNG BIOPSY WHEN THE CLINICAL AND RADIOGRAPHIC FEATURES ARE TYPICAL OF UIP/IPF

pneumonia (AIP) and may be responsive to high-dose corticosteroid therapy.¹² The natural history of IPF and the etiopathological factors responsible for acute exacerbations of IPF require further study.

PROGNOSIS

Emerging concepts regarding predictors of mortality may improve clinicians' ability to provide prognostic information. Prognostic information can be gathered from clinical/physiologic (baseline lung function, changes in lung function over time, etc), radiologic (HRCT and overall disease extent), and pathologic (UIP vs non-UIP) findings. A number of studies have shown that a more severe impairment in pulmonary function at time of diagnosis carries a worse prognosis than those with relatively preserved baseline lung function, as indicated primarily by the forced vital capacity (FVC). More recently, three independent studies show that a decline in FVC by $\geq 10\%$ as early as 6 months after diagnosis is predictive of increased mortality.¹³⁻¹⁵ A central feature of the pathophysiology of IPF is impaired gas exchange worsening with exercise. The 6-minute walk test (6MWT) primarily measures walking distance and desaturation (defined as oxygen saturation to $\leq 88\%$). Lama et al recently showed that desaturation during the 6MWT is independently predictive of higher mortality, even after adjusting for other factors, such as age, sex, smoking, baseline FVC, and resting oxygen saturation.¹⁶

In addition to its diagnostic utility, HRCT may provide important prognostic information in patients with IPF. In a study by Flaherty et al, patients with histopathologically-proven UIP/IPF who also had an HRCT that was typical or highly suggestive of UIP did significantly worse (median survival 2.08 years) than patients whose HRCT did not show definite/probable radiographic features suggestive of UIP (median survival 5.76 years). A number of studies have shown that a surgical lung biopsy showing UIP carries a worse prognosis than a biopsy showing non-UIP histopathology (eg, NSIP: non-specific interstitial pneumonia).¹⁷⁻¹⁹ Moreover, King et al demonstrated that a greater degree or extent of fibroblastic foci present on lung biopsy predicts increased mortality in UIP/IPF.²⁰

SUMMARY

Establishing an accurate diagnosis of IIP is essential. A thorough history and physical examination must exclude "secondary" causes of pulmonary fibrosis, in particular occupational/environmental lung disease,

drug exposures and connective tissue diseases; indolent and chronic cases of hypersensitivity pneumonitis can sometimes be difficult to exclude. The HRCT has taken on greater utility in the evaluation of IIP and can obviate the need for a VATS-lung biopsy when the clinical and radiographic features are typical of UIP/IPF. Emerging insights into pathogenesis, in particular the aberrant repair process involving epithelial cells and myofibroblasts, will provide opportunities for novel drug targeting and design. There must be a concerted effort by all physicians who encounter such patients to provide them with the opportunity to enter ongoing and future clinical trials, including those that are to be conducted by a recently assembled Clinical Research Network sponsored by the National Institutes of Health.

REFERENCES

1. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med.* 2002;165:277-304.
2. Wells AU. *Am J Respir Crit Care Med.* 2004;170:828-829.
3. Flaherty KR, King TE Jr, Raghu G, et al. *Am J Respir Crit Care Med.* 2004;170:904-910.
4. Hunninghake GW, Zimmerman MB, Schwartz DA, et al. *Am J Respir Crit Care Med.* 2001;164:193-196.
5. Flaherty K, Thwaite EL, Kazerooni EA, et al. *Thorax.* 2003;58:143-148.
6. Flaherty KR, Travis WD, Colby TV, et al. *Am J Respir Crit Care Med.* 2001;164:1722-1727.
7. Thannickal VJ, Toews GB, White ES, Lynch JP 3rd, Martinez FJ. *Annu Rev Med.* 2004;55:395-417.
8. Selman M, King TE, Pardo A. *Ann Intern Med.* 2001;134:136-151.
9. Cantin AM, North SL, Fells GA, Hubbard RC, Crystal RG. *J Clin Invest.* 1987;79:1665-1673.
10. Waghray M, Cui Z, Horowitz JC, et al. *FASEB J.* In press.
11. Vittal R, Horowitz JC, Moore BB, et al. *Am J Pathol.* 2005;166:367-375.
12. Kondoh Y, Taniguchi H, Kawabata Y, Yokoi T, Suzuki K, Takagi K. *Chest.* 1993;103:1808-1812.
13. Latsi PI, du Bois RM, Nicholson AG, et al. *Am J Respir Crit Care Med.* 2003;168:531-537.
14. Collard HR, King TE Jr, Bartelson BB, Vourlekis S, Schwarz MI, Brown KK. *Am J Respir Crit Care Med.* 2003;168:538-542.
15. Flaherty KR, Mumford JA, Murray S, et al. *Am J Respir Crit Care Med.* 2003;168:543-548.
16. Lama VN, Flaherty KR, Toews GB, et al. *Am J Respir Crit Care Med.* 2003;168:1084-1090.
17. Bjraker JA, Ryu JH, Edwin MK, et al. *Am J Respir Crit Care Med.* 1998;157:199-203.
18. Daniil ZD, Gilchrist FC, Nicholson AG, et al. *Am J Respir Crit Care Med.* 1999;160:899-905.
19. Flaherty KR, Toews GB, Travis WD, et al. *Eur Respir J.* 2002;19:275-283.
20. King TE Jr, Schwarz MI, Brown K, et al. *Am J Respir Crit Care Med.* 2001;164:1025-1032.

UPCOMING CME EVENTS

PILOT™ CME DINNER MEETINGS: EMERGING PERSPECTIVES ON IPF: PRACTICAL STRATEGIES FOR DISEASE MANAGEMENT

- April 4, 2005**
Atlanta, GA - Steven A. Sahn, MD
- April 5, 2005**
Columbia, SC - Charlie Strange, MD
Morristown, NJ - Paul W. Noble, MD
- April 11, 2005**
Louisville, KY - Steven A. Sahn, MD
Houston, TX - Paul W. Noble, MD
- April 12, 2005**
Nashville, TN - Marvin I. Schwarz, MD
- April 14, 2005**
Fair Oaks, CA - Kevin O. Leslie, MD
- April 20, 2005**
Troy, MI - Fernando J. Martinez, MD, MS
- April 26, 2005**
Virginia Beach, VA - Steven A. Sahn, MD
- May 3, 2005**
Miami Beach, FL - Marilyn K. Glassberg, MD
Cincinnati, OH - Paul W. Noble, MD
- May 9, 2005**
Columbus, OH - Steven A. Sahn, MD
- May 10, 2005**
Knoxville, TN - Paul W. Noble, MD
Charleston, WV - Jeffrey T. Chapman, MD
- May 17, 2005**
New York, NY - Kevin O. Leslie, MD
Paul W. Noble, MD
- May 18, 2005**
Kansas City, MO - Kevin O. Leslie, MD
- June 1, 2005**
Albany, NY - Paul W. Noble, MD
Cleveland, OH - Steven D. Nathan, MD
- June 7, 2005**
Portland, OR - Paul W. Noble, MD
Covington, LA - Joseph A. Lasky, MD
- June 14, 2005**
Indianapolis, IN - Robert M. Strieter, MD
- June 15, 2005**
Fort Wayne, IN - Robert M. Strieter, MD
- June 16, 2005**
Raleigh, NC - Charlie Strange, MD
- June 23, 2005**
Milwaukee, WI - Kevin K. Brown, MD
- July 19, 2005**
Jacksonville, FL - Kevin O. Leslie, MD
- July 20, 2005**
San Antonio, TX - Kevin O. Leslie, MD