NOVEMBER 2017
VOL. 17, ISSUE 6

IU Health Physicians

ADVANCED praxis CME

A JOURNAL OF CURRENT TRENDS IN MEDICINE FROM IU HEALTH PHYSICIANS, A PARTNERSHIP OF IU SCHOOL OF MEDICINE AND INDIANA UNIVERSITY HEALTH

CASE MANAGEMENT

Idiopathic Pulmonary Fibrosis

A 62-year-old white male with hypertension, hypercholesterolemia, a nonproductive cough, and progressive shortness of breath is hospitalized for pneumonia and placed on a short course of prednisone and supplemental oxygen. He improves on steroids but now requires around-the-clock oxygen. A former smoker (1.5 packs/day for seven years; quit at age 28), he has no family history of lung disease. Current medications are losartan, hydrochlorothiazide, atorvastatin, aspirin, albuterol inhaler, and oxygen at 3.0 L/minute per nasal cannula. (*continued on page 2*)

ACCREDITATION STATEMENT
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Indiana University School of Medicine (IUSM) and IU Health Physicians. IUSM is accredited by the ACCME to provide continuing medical education for physicians.

DESIGNATION STATEMENT
IUSM designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

FACULTY DISCLOSURE STATEMENT
In accordance with the ACCME Standards for Commercial Support, educational programs sponsored by IUSM must demonstrate balance, independence, objectivity, and scientific rigor. All faculty, authors, editors, and planning committee members participating in an IUSM-sponsored activity are required to disclose any **relevant financial interest or other relationship** with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services that are discussed in an educational activity.

The planning committee and those in a position to control the content of this activity have disclosed no relevant financial relationships.

OBJECTIVES
After reading this article, the reader should be able to:

- Discuss the clinical presentation and usual clinical course of idiopathic pulmonary fibrosis (IPF).
- Describe the comorbidities and complications commonly associated with IPF.
- Compare and contrast traditional and current IPF pharmacotherapy.
- Summarize the role of lung transplantation for IPF.
- Explain how extracorporeal membrane oxygenation (ECMO) can improve lung transplant outcomes.

Date of original release: November 2017

Date of expiration: November 2018

COMMERCIAL SUPPORT
This CME activity does not have any commercial support.

During a visit to his primary care physician, the patient complains of increasing dyspnea while mowing his lawn but reports no chest pain or palpitations. Interstitial changes are seen on chest X-ray *(Figure 1)*. On pulmonary function testing, his forced vital capacity is 1.83 L (58 percent of predicted), and diffusion capacity for carbon monoxide (DLCO) and lung capacity are 41 percent and 42 percent of predicted, respectively.

The patient is referred to a local pulmonologist, who notes mild clubbing of the fingers and diffuse chest crackles on physical examination. High-resolution computed tomography (HRCT) shows scattered coarse reticular opacities, mild ground glass opacifications in the mid lung and lower lobes, thickened interlobular septa throughout both lungs, and traction bronchiectasis *(Figure 2)*—all consistent with a diagnosis of pulmonary fibrosis.

Overview of Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing interstitial pneumonia of unknown etiology characterized by the progressive loss of lung function.[1] Its prevalence (14 to 42 cases per 100,000) increases with age, the majority of patients being males 55 to 80 years with a current or previous smoking history.[2] While the clinical course is highly variable and unpredictable, IPF has a poor prognosis: median survival time after diagnosis is just two to five years.[3]

Comorbidities and Complications

Because IPF generally affects older adults, comorbidities are common. These include emphysema, concurrent with IPF in approximately 30 percent of cases;[4] obstructive sleep apnea, identified in 60 to 88 percent of affected persons;[5,6] and gastroesophageal reflux disease (GERD), diagnosed in up to 90 percent of individuals with IPF.[7] Pulmonary hypertension is a severe complication of IPF that significantly contributes to morbidity and mortality.[8] Also impacting survival is the development of lung cancer, primarily squamous cell carcinoma followed by adenocarcinoma and independent of smoking history, which occurs in an estimated 10 percent of patients with IPF.[9]

Clinical Presentation, Risk Factors, and Diagnosis

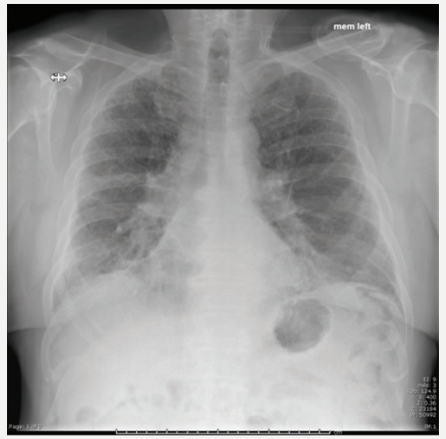
IPF typically presents with the gradual onset of non-specific symptoms, in particular a nonproductive cough and exertional dyspnea. Finger clubbing is common, and bibasilar crackles are virtually a universal finding.[2] Pulmonary function tests usually demonstrate restriction, but this may be masked by emphysema.

"Although the underlying causes of idiopathic pulmonary fibrosis remain unclear, an increased risk of the disease has been reported in persons with any smoking history or other types of particulate exposure (e.g., metal and wood dusts, stone, silica)," reports David Roe, MD, assistant professor of clinical medicine at Indiana University School of Medicine and medical director of Indiana University Health lung transplant program. "Genetic tendencies are increasingly recognized and currently account for about five to seven percent of IPF cases."

The diagnosis of IPF requires the exclusion of other known causes of interstitial lung disease and the presence of a usual interstitial pneumonia (UIP) pattern on lung HRCT or surgical biopsy.[1] The UIP pattern comprises basal, subpleural reticulation associated with architectural distortion, in particular honeycombing *(Figure 3, see page 4)*,* and traction bronchiectasis, and its demonstration on HRCT may be sufficient to establish the diagnosis without the need for lung biopsy. Pulmonary function testing, particularly forced vital capacity and DLCO, is an important surrogate of disease progression and predictor of mortality *(Table 1, see page 5)* and correlates with the extent of radiologic disease.[10]

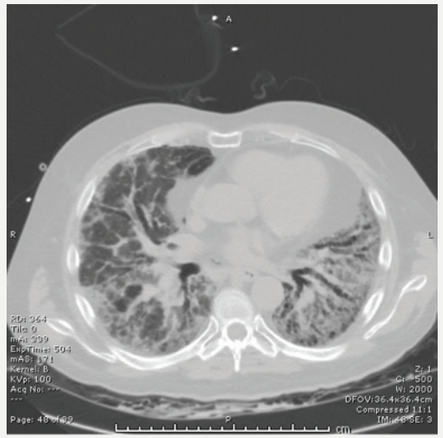
*Defined as clustered cystic spaces with well-defined 1.0 to 3.0 mm walls and usual diameters of 3.0 to 10.0 mm.[11]

Figure 1. Chest X-ray suggestive of pulmonary fibrosis



Radiographic demonstration of the low lung volumes and diffuse interstitial thickening characteristic of pulmonary fibrosis.

Figure 2. Chest CT demonstrating lung changes consistent with a diagnosis of IPF



The CT shows bilateral reticular opacities and bronchiectasis, predominantly basilar and peripheral in distribution, and some honeycombing, especially at the bases.

Treatment

The management of IPF is multifaceted *(Figure 4, see page 5)*, with the goals of: 1) slowing disease progression, 2) preserving quality of life (QoL), and 3) improving survival.

Pharmacologic Therapy

For several decades, glucocorticoids and immunosuppressants were the mainstays of IPF therapy because chronic inflammation was believed to cause persistent fibrosis in the early stages of the disease. This theory and treatment regimen were abandoned after a randomized, double-blind clinical trial found that compared with placebo, combination therapy with prednisone, azathioprine, and N-acetylcysteine actually increased the risk of hospitalization and death in patients with mild-to-moderate IPF.[12]

Current consensus is that fibrosis results from aberrant wound healing, specifically, the abnormal repair of alveolar epithelial injury.[2]

Antifibrotics. Two recently approved antifibrotic drugs—pirfenidone (Esbriet®), which inhibits transforming growth factor and also has anti-inflammatory and antioxidant effects; and nintedanib (Ofev®), an inhibitor of platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor—have been shown to safely slow declining lung function and reduce acute exacerbations in IPF.[13-15] Clinical practice guidelines recommend initiating treatment with one of these drugs in cases of mild-to-moderate disease.[16] At the present time, data are insufficient to choose between pirfenidone and nintedanib, and selection may be guided by drug availability and patient preference and tolerance.

Antacids. "The vast majority of patients with IPF have concomitant gastroesophageal reflux disease, a risk factor for aspiration that can cause pneumonitis and worsen idiopathic pulmonary fibrosis," Dr. Roe explains. "The empiric use of antacids, such as proton pump inhibitors or histamine-2 blocker receptor antagonists, may decrease this risk."

Lung Transplantation

IPF has become the most common indication for referral to a lung transplant service,[17] with transplantation shown to improve QoL and extend survival: median post-transplant survival is 4.5 years.[18] Patients with IPF are increasingly receiving bilateral rather than single lung transplant, and accumulating evidence suggests that this trend is linked to longer survival.[19]

"According to international guidelines, patients with idiopathic pulmonary fibrosis should be considered for lung transplantation at the time of diagnosis,"[20] Dr. Roe says. "Early referral is warranted, given the high mortality of the disease and the often lengthy waiting time for suitable donor organs."

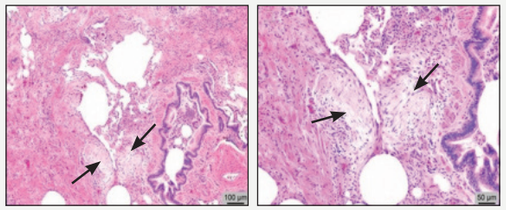
The number of patients with IPF referred to Dr. Roe and his team for transplant evaluation is growing, and these individuals are being transplanted at a higher rate owing to the severity of their disease. Of the 52 patients who received lung transplants at IU Health last year, more than half were patients with IPF.

Oxygen Therapy and Pulmonary Rehabilitation

Pronounced hypoxia during physical exertion is a frequent finding in IPF. Although no long-term data support the use of supplemental oxygen in this patient population, limited information suggests it may improve exercise capacity.

"Pulmonary rehabilitation, including aerobic conditioning, strength and flexibility training, nutrition counseling and other education, and psychosocial support is also beneficial for patients with idiopathic pulmonary fibrosis, alleviating symptoms and improving exercise tolerance, activities of daily living, and quality of life," emphasizes Dr. Roe. "In patients undergoing lung transplantation at IU Health, pulmonary rehabilitation is a component of care before and after transplant."

Figure 3. Honeycombing of the lung in IPF



Histologic specimen showing honeycombing distorting normal lung architecture and typical fibroblastic foci (black arrows).

The UIP pattern comprises basal, subpleural reticulation associated with architectural distortion, in particular honeycombing, and traction bronchiectasis, and its demonstration on HRCT may be sufficient to establish the diagnosis without the need for lung biopsy.

Because of the patient's advanced lung disease (as demonstrated on HRCT and pulmonary function testing), he is referred to IU Health lung transplant program at Methodist Hospital for evaluation and is subsequently placed on the waiting list for a donor organ. Two months later, he successfully undergoes bilateral lung transplantation and is supported by venovenous extracorporeal membrane oxygenation (ECMO) during the immediate post-transplant period.

TABLE 1. IPF CLINICAL PROGNOSTIC INDICATORS[25]

Six-month annual FVC decline	Prognosis
<5%	Stable disease
5-10%	Prognostically relevant decline
>10% of 50 m decline	Four- to eight-fold increase in mortality in one year

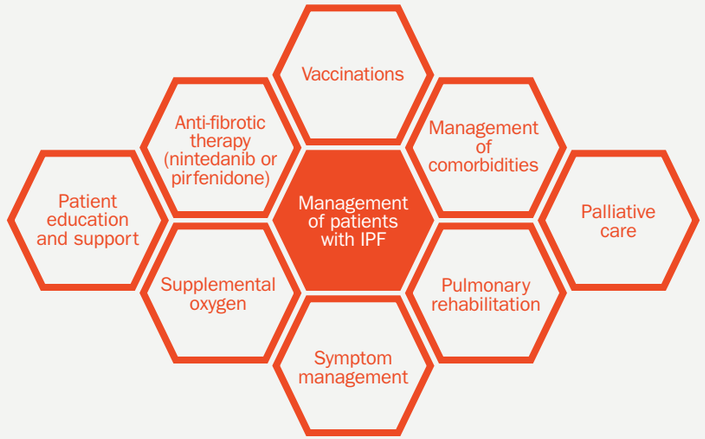
Despite improvements in donor lung preservation and surgical technique, 10 to 25 percent of patients undergoing lung transplantation experience primary graft dysfunction (PGD), the leading cause of early death.[21] Survivors of PGD tend to have a longer duration of mechanical ventilation, extended hospital stays, and lower lung function over time.

PGD reflects the summation of injuries inflicted on the donor lung(s) by the transplant process—retrieval, preservation, implantation, and reperfusion—and by factors such as acid aspiration, pneumonia, and microtrauma from mechanical ventilation. Recipient factors also play a role: persons with IPF have a higher incidence of PGD than do those with emphysema.

"Perioperative venovenous ECMO, which provides pulmonary support only, has the capacity to support gas exchange and stabilize the patient's condition until the new lungs recover," Dr. Roe explains. "Enhanced safety combined with increased experience has led to earlier deployment of ECMO following lung transplantation, thereby avoiding or minimizing the detrimental effects of ventilator support for primary graft dysfunction secondary to elevated airway pressures or high inspired oxygen concentrations."

The venovenous ECMO technique used by IU Health transplant specialists involves placement of a dual-lumen catheter (Avalon Elite®) in the right internal jugular vein *(Figure 5, see page 6)*. The catheter is designed to increase the efficiency of blood gas exchange by draining blood from both the upper and lower body while simultaneously reinfusing it directly into the heart. Bleeding, often related to the need for systemic anticoagulation and the most common complication of ECMO, is reduced by the use of modern circuitry.[22]

Figure 4. Multifaceted approach to the management of IPF [24]



The management of IPF is multifaceted with the goals of: 1) slowing disease progression, 2) preserving quality of life (QoL), and 3) improving survival.

The patient is hospitalized for three weeks. Following discharge home, he is enrolled for one month at the Center of Life for Thoracic Transplant (COLTT).* After completing the rehabilitation program, his overall lung function has normalized, supplemental oxygen is no longer required, and he is able to resume all daily activities. He returns to IU Health for weekly follow-up during the first post-transplant month, every two weeks for the next three months, and monthly thereafter for the first year.

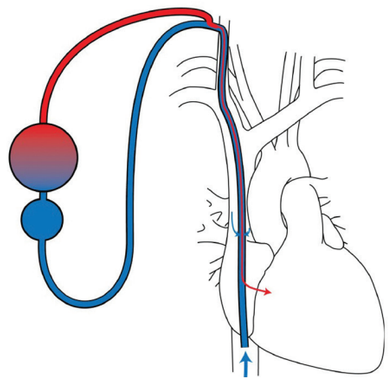
Future Management of IPF

Enhanced understanding of the pathogenic mechanisms of IPF (e.g., genetic susceptibility, abnormalities in telomere biology, increased epithelial apoptosis, cell senescence[23]) together with the efficacy of pirfenidone and nintedanib in slowing deteriorating lung function have raised hopes of finding a curative therapy. Ongoing investigational drug trials are focused on modifying disease progression via disparate targets, including the immune system, proinflammatory cascade, intracellular signaling, and myofibroblast activation. Strategies directed toward modulating the alveolar microenvironment (the lung microbiome) may represent another avenue for treatment, while the identification of specific IPF biomarkers may lead to more tailored therapies. For the near future, however, lung transplantation will remain the only treatment for IPF with the potential to increase long-term survival.

"Early disease detection and referral to a transplant center for initial consultation, even if lung transplantation is not yet needed, is key to improving outcomes for patients with idiopathic pulmonary fibrosis," Dr. Roe concludes.

**A new facility at IU Health Methodist Hospital staffed by a physical therapist and respiratory therapist. COLTT features include an indoor track; a variety of cardiovascular and weight-training equipment; an oxygen room, physical therapy room, and classroom for nutritional education; and patient support. Heart transplant recipients and patients on ventricular assist devices also have access to the center.*

Figure 5. Venovenous ECMO for lung transplantation



Deoxygenated blood is withdrawn from the superior vena cava and inferior vena cava (blue arrows) and pumped through an oxygenator to remove carbon dioxide and infuse oxygen. The blood is then pumped back across the tricuspid valve (red arrow) into the right ventricle and then to the lungs.

For more *Advanced Praxis*, visit iuhealth.org/ap

For free CME credit, visit iuhealth.org/ap and click on CME Credit Form

References

1. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med.* 2011;183(6):788-824.
2. King TE, Jr., Pardo A, Selman M. Idiopathic pulmonary fibrosis. *Lancet.* 2011;378(9807):1949-1961.
3. Raghu G, Chen SY, Hou Q, Yeh WS, Collard HR. Incidence and prevalence of idiopathic pulmonary fibrosis in US adults 18-64 years old. *Eur Respir J.* 2016;48(1):179-186.
4. Ryerson CJ, Hartman T, Elicker BM, et al. Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. *Chest.* 2013;144(1):234-240.
5. Gille T, Didier M, Boubaya M, et al. Obstructive sleep apnoea and related comorbidities in incident idiopathic pulmonary fibrosis. *Eur Respir J.* 2017;49(6).
6. Lancaster LH, Mason WR, Parnell JA, et al. Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. *Chest.* 2009;136(3):772-778.
7. Raghu G, Freudenberger TD, Yang S, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. *Eur Respir J.* 2006;27(1):136-142.
8. Buendia-Roldan I, Mejia M, Navarro C, Selman M. Idiopathic pulmonary fibrosis: Clinical behavior and aging associated comorbidities. *Respir Med.* 2017;129:46-52.
9. Tomassetti S, Gurioli C, Ryu JH, et al. The impact of lung cancer on survival of idiopathic pulmonary fibrosis. *Chest.* 2015;147(1):157-164.
10. Arcadu A, Byrne SC, Pirina P, Hartman TE, Bartholmai BJ, Moua T. Correlation of pulmonary function and usual interstitial pneumonia computed tomography patterns in idiopathic pulmonary fibrosis. *Respir Med.* 2017;129:152-157.
11. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology.* 2008;246(3):697-722.
12. Raghu G, Anstrom KJ, King TE, Jr., Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med.* 2012;366(21):1968-1977.
13. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet.* 2011;377(9779):1760-1769.
14. King TE, Jr., Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370(22):2083-2092.
15. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370(22):2071-2082.
16. Raghu G, Rochwerg B, Zhang Y, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2015;192(2):e3-19.
17. Yusen RD, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report–2014; focus theme: retransplantation. *J Heart Lung Transplant.* 2014;33(10):1009-1024.
18. Kistler KD, Nalysnyk L, Rotella P, Esser D. Lung transplantation in idiopathic pulmonary fibrosis: a systematic review of the literature. *BMC Pulm Med.* 2014;14:139.
19. Schaffer JM, Singh SK, Reitz BA, Zamanian RT, Mallidi HR. Single- vs double-lung transplantation in patients with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis since the implementation of lung allocation based on medical need. *JAMA.* 2015;313(9):936-948.
20. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014–an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2015;34(1):1-15.
21. Trulock EP, Edwards LB, Taylor DO, Boucek MM, Keck BM, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: twenty-second official adult lung and heart-lung transplant report–2005. *J Heart Lung Transplant.* 2005;24(8):956-967.
22. Lafc G, Budak AB, Yener AU, Cicek OF. Use of extracorporeal membrane oxygenation in adults. *Heart Lung Circ.* 2014;23(1):10-23.
23. Macagno F, Varone F, Leone PM, et al. New treatment directions for IPF: current status of ongoing and upcoming clinical trials. *Expert Rev Respir Med.* 2017;11(7):533-548.
24. Raghu G, Richeldi L. Current approaches to the management of idiopathic pulmonary fibrosis. *Respir Med.* 2017;129:24-30.
25. Soo E, Adamali H, Edey AJ. Idiopathic pulmonary fibrosis: current and future directions. *Clin Radiol.* 2017;72(5):343-355.

David Roe, MD

Medical Director, Lung Transplant Program, IU Health

Assistant Professor of Clinical Medicine, Department of Internal Medicine, IU School of Medicine

droe@iuhealth.org

Dr. Roe received his medical degree from Southern Illinois University in Springfield, did a residency in internal medicine and pediatrics at Michigan State University, and completed a fellowship in pulmonary/critical care medicine at IU School of Medicine. He is currently medical director of the lung transplant and ECMO programs at IU Heath and medical director of the critical care unit and advanced heart and lung care clinic at Methodist Hospital. His clinical interests focus on lung transplantation, ECMO, and interventional bronchoscopy. Among his research interests are frailty in lung transplant recipients, chronic lung allograft dysfunction, and lung transplantation protocol development.

A fellow of the American College of Physicians and the American College of Chest Physicians and member of the American Thoracic Society and other professional organizations, Dr. Roe is a reviewer for the *Journal of Intensive Care Medicine* and serves as a co-investigator for two ongoing clinical trials. The author of several peer-reviewed journal articles, he is frequently invited to lecture on lung transplantation and ECMO at local and national medical conferences.

IU Health Physicians

340 West Tenth Street, FS 5100
Indianapolis, IN 46202

IU Health Physicians is the most complete, multi-specialty practice group in Indiana. A unique partnership between Indiana University School of Medicine faculty physicians and private practice physicians, IU Health Physicians gives its highly skilled doctors access to innovative treatments using the latest research and technology.

We hope that you find each topic's case management to be informative and valuable. If you have any questions, we welcome you to contact either *Advanced Praxis* or the featured physician at the numbers/email addresses below.

Referral information: 1-800-622-4989 or iuhealth.org/find-a-doctor

Dr. David Roe, featured physician: droe@iuhealth.org

Kara Anderson, publisher of *Advanced Praxis*: advancedpraxis@iuhealth.org