REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Idiopathic Pulmonary Fibrosis

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THE FAMILY OF INTERSTITIAL LUNG DISEASES IS CHARACTERIZED BY cellular proliferation, interstitial inflammation, fibrosis, or a combination of such findings within the alveolar wall that is not due to infection or cancer.[1] Interstitial fibrosis is the predominant phenotype in most cases. The majority of patients with interstitial fibrosis ultimately receive a diagnosis of chronic hypersensitivity pneumonitis (due to mold or bird exposure), pulmonary sarcoidosis, an underlying autoimmune disease, or if no cause is identified, an idiopathic interstitial pneumonia (see Glossary) (Fig. 1). The most common idiopathic interstitial pneumonia is idiopathic pulmonary fibrosis (IPF), a chronic, progressive, fibrotic interstitial lung disease of unknown cause, often with characteristic imaging and histologic appearances (described below), that occurs primarily in older adults.[2] IPF is of particular clinical interest because it is often misdiagnosed and managed inappropriately with immunosuppressive therapy, it is associated with a high mortality rate, and therapies that slow disease progression are now available.

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EPIDEMIOLOGY

IPF occurs worldwide. The prevalence of the disease appears to be increasing, although it is unclear whether this reflects increased recognition or a true increase in incidence. The incidence of IPF appears to be higher in North America and Europe (3 to 9 cases per 100,000 person-years) than in South America and East Asia (fewer than 4 cases per 100,000 person-years).[3] In the United States, the prevalence of IPF has been reported to range from 10 to 60 cases per 100,000, although in one study, the prevalence was 494 cases per 100,000 in 2011 among adults over the age of 65 years, which was twice as high as the prevalence recorded 10 years earlier.[4-6] Increasing rates of hospital admissions and deaths due to IPF also suggest an increasing burden of disease.[3,7,8]

CLINICAL PRESENTATION

Clinicians should consider interstitial lung disease in the differential diagnosis for adults presenting with unexplained exertional dyspnea, chronic dry cough, or Velcro-like crackles on examination (Table 1). Exertional dyspnea typically progresses over a period of months to years. In practice, patients with interstitial lung disease often initially receive a diagnosis of heart failure or chronic obstructive pulmonary disease,[9] suggesting that clinicians frequently fail to consider interstitial lung disease in patients with dyspnea. In some cases, patients have presented with dyspnea and dry cough up to 5 years before interstitial lung disease was diagnosed.[9] Early recognition and accurate diagnosis are likely to improve outcomes through avoidance of potentially harmful therapies (e.g., glucocorticoids for IPF)[10] and prompt initiation of therapies that are effective even in the early stages of disease.[11,12]

Spirometry should be performed and lung volumes and the diffusing capacity

Glossary

Chronic hypersensitivity pneumonitis: An interstitial lung disease characterized by peribronchiolar and interstitial chronic inflammatory infiltrates and interstitial fibrosis with or without poorly formed granulomas.

Ground-glass opacities: Hazy areas of increased lung attenuation on CT imaging.

Honeycombing: Thick-walled, linear clusters of cysts on CT, which are often subpleural. Honeycombing represents lung fibrosis.

Idiopathic interstitial pneumonia: Any one of nine interstitial lung diseases of unknown cause.

Mosaic attenuation: Ground-glass opacities alternating with lucent (or hyperlucent) lung on CT. Mosaic attenuation is suggestive of small-airway involvement (e.g., hypersensitivity pneumonitis).

Proteostatic dysregulation: Abnormalities in the synthesis, trafficking, folding, or turnover of intracellular proteins.

Reconstruction kernel: The algorithm used to generate CT images. Higher (sharper) kernels provide better spatial resolution and are preferred for high-resolution CT imaging.

Reticulation: Short, irregular, linear opacities on CT. Reticulation typically represents fibrosis.

Traction bronchiectasis: Dilated bronchi on CT due to peripheral retraction resulting from lung fibrosis.

of the lung for carbon monoxide (DLco) should be measured in patients with suspected interstitial lung disease. These studies typically identify a reduced forced vital capacity (FVC), a reduced total lung capacity, and a reduction in DLco.[2] However, spirometric results and lung volumes can be normal during the early stages of interstitial lung disease or when emphysema is also present.[13] Chest radiographs may be normal or show nonspecific findings in early disease. In more established disease, bilateral reticular infiltrates, hazy opacities, and reduced inspiratory lung volumes on chest radiographs should prompt consideration of interstitial lung disease. In IPF, bilateral reticulation is often predominant in the lower lung zones.

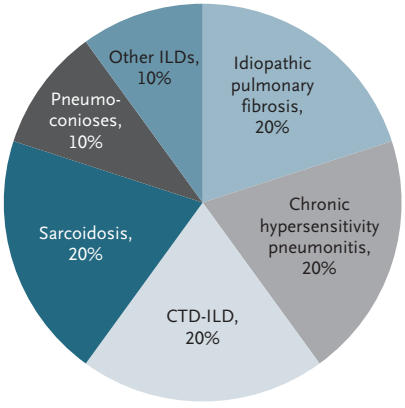

Figure 1. Estimated Relative Distribution of Specific Interstitial Lung Diseases (ILDs) in the United States.

These estimates are based on our experience and are likely to be heavily influenced by regional variation in referral patterns and the true underlying prevalence of each disease (which is unknown). Regardless of the exact prevalence of each condition, idiopathic pulmonary fibrosis, chronic hypersensitivity pneumonitis, connective-tissue disease–related ILD (CTD-ILD), and pulmonary sarcoidosis are the most common interstitial lung diseases seen in our clinical practices.

PATHOBIOLOGIC FEATURES AND RISK FACTORS

A favored conceptual model of the pathogenesis of IPF posits that recurrent, subclinical epithelial injury superimposed on accelerated epithelial aging leads to aberrant repair of the injured alveolus and deposition of interstitial fibrosis by myofibroblasts (Fig. 2). Senescence of alveolar epithelial cells and fibroblasts appears to be a central phenotype that promotes lung fibrosis.[14] Shortened telomeres, oxidative injury, proteostatic dysregulation and endoplasmic reticulum stress, and mitochondrial dysfunction lead to decreased alveolar epithelial-cell proliferation and secretion of profibrotic mediators.[14,15] Mutations in *TERT*, *TERC*, *PARN*, and *RTEL1* — genes involved in the maintenance of telomere length — are associated with an increased risk of IPF.[16,17] Variations in genes (*DSP*, *AKAP13*, *CTNNA*, and *DPP9*) that are responsible for cell adhesion, integrity, and mechanotransduction (the generation of electrical signals from a mechanical stimulus) also confer a predisposition to IPF.[18,19]

A single-nucleotide polymorphism (rs35705950) in the promoter region of *MUC5B* substantially increases the risk of IPF.[20] *MUC5B* codes for mucin 5B, a glycoprotein required for airway clearance and innate immune responses to bacteria.[21]

Table 1. Clinical Presentation of Idiopathic Pulmonary Fibrosis (IPF).*

History
Chronic exertional dyspnea (nearly universal)†
Chronic cough without purulence
Fatigue
Physical examination
Bilateral Velcro-like crackles†
Clubbing
Acrocyanosis
Physiological findings
Low DLco†
Resting hypoxemia or exertional desaturation
Normal or low FVC
Chest radiograph
Nonspecific changes or bilateral basal reticular abnormalities

* DLco denotes diffusing capacity of the lung for carbon monoxide, and FVC forced vital capacity.
† This finding is nearly universal in IPF. Other findings are often absent in the early stages of the disease.

The rs35705950 minor allele leads to overexpression of mucin 5B in small-airway epithelial cells,[22] a universal finding in patients with IPF (regardless of the *MUC5B* genotype).[20] Although the mechanism linking mucin 5B overexpression and IPF risk remains unknown, some researchers have hypothesized that aberrant mucociliary clearance may lead to alterations in the lung microbiome and innate immune responses that promote IPF.[23,24]

Indeed, innate immune cells, such as monocyte-derived alveolar macrophages, appear to be critical for the development of lung fibrosis.[25] In one study, bacterial DNA could not be detected in lung tissue from patients with IPF,[26] but other work has identified an abundance of prevotella, veillonella, and escherichia in bronchoalveolar-lavage fluid from such patients. In addition, both an increased overall bacterial burden and an abundance of streptococcal and staphylococcal organisms have been associated with an increased risk of disease progression in patients with IPF.[27,28] Additional elegant microbiome work[29] and the finding that the risk of IPF is increased by genetic variation in *TOLLIP*, a gene encoding a protein in the toll-like receptor pathway that inhibits responses to microbes,[30] suggest a complex relationship among IPF risk, microbiome diversity, host defense pathways, and disease progression.[23,29]

Animal models of lung fibrosis do not recapitulate IPF. Nevertheless, these models have been useful for identifying pathways leading to lung fibrosis, including those involving transforming growth factor β (TGF-β), connective-tissue growth factor, fibroblast growth factor 2, platelet-derived growth factor, microRNAs, impaired autophagy, activation of developmental pathways, matrix metalloproteinase 7 (MMP-7), lysyl oxidase–like 2 (LOXL2), and lysophosphatidic acid (LPA) (Fig. 2). Mechanical contributions of the matrix to cell behavior (e.g., matrix stiffness and stress and strain forces) have also been highlighted.[31]

A number of nongenetic risk factors for IPF have been identified. Older age, male sex, and cigarette smoking are considered risk factors for IPF.[32] Observational data have implicated gastroesophageal reflux,[33] obstructive sleep apnea,[34] air pollution,[35] herpesvirus infection,[36] and certain occupational exposures in interstitial lung disease.[32] The investigation of subclinical disease with the use of computed tomographic (CT) imaging in population-based and high-risk cohorts has proved to be a powerful tool that may help identify new targetable risk factors for incident IPF, potentially leading to preventive interventions.[37-40]

DIAGNOSIS

When the history and physical examination suggest interstitial lung disease, a high-resolution CT scan of the chest should be obtained to determine whether the disease is present and to identify specific radiologic patterns that aid in narrowing the differential diagnosis.[2] High-resolution CT protocols should include both inspiratory and expiratory imaging, thin reconstructions (≤1.25 mm), a moderately sharp reconstruction kernel, and a small reconstruction field of view. Although inspiratory imaging should be contiguous, expiratory imaging can be noncontiguous to minimize radiation exposure. Imaging with the patient in the prone position should be performed only if there are subtle dependent opacities of unclear clinical significance.

Once interstitial lung disease has been identified on high-resolution CT studies, a focused history taking and physical examination should be performed to identify disorders that are known to cause interstitial lung disease, such as chronic hypersensitivity pneumonitis, or to be associated with it, such as connective-tissue dis-

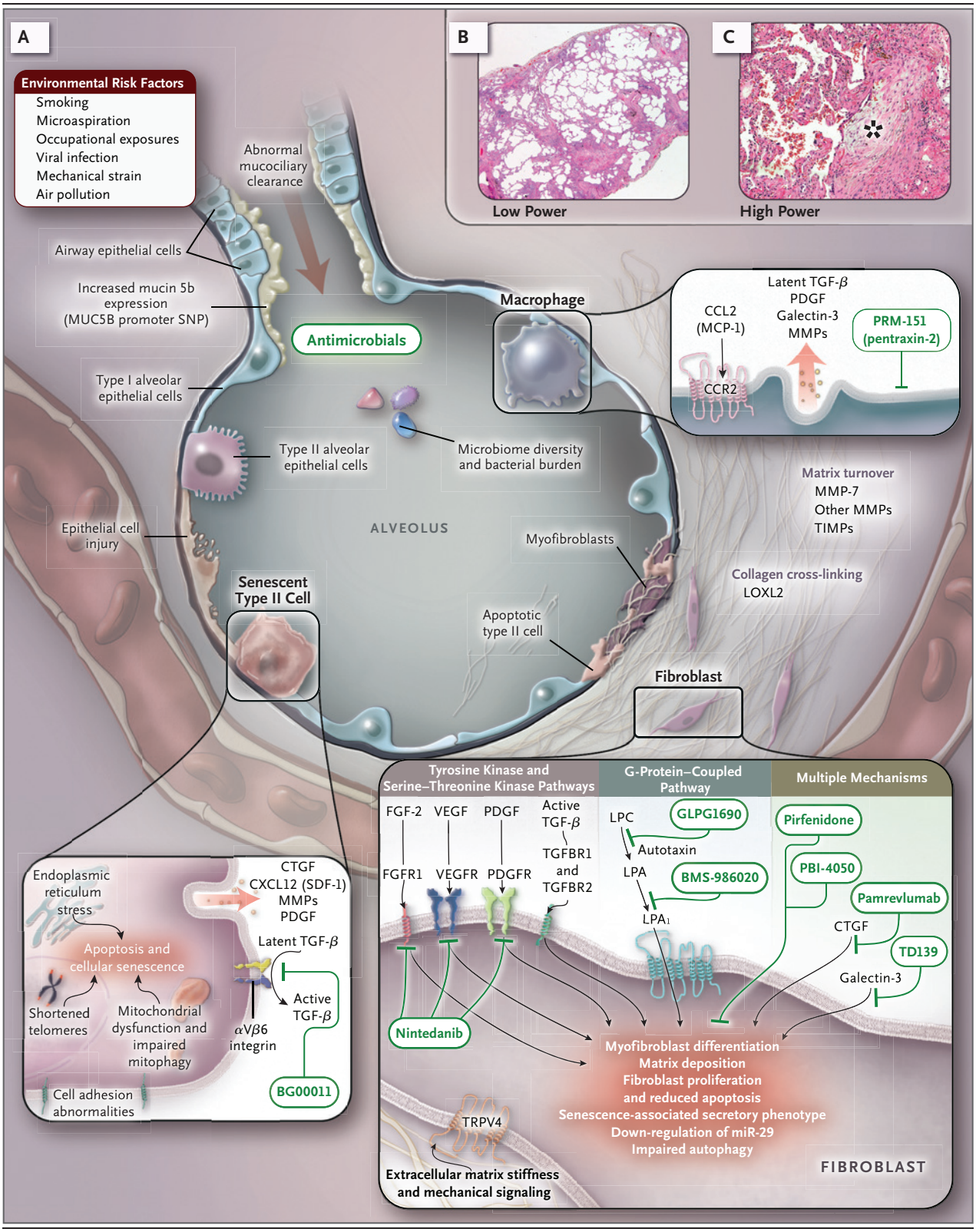

Figure 2 (facing page). Pathobiologic Features of Idiopathic Pulmonary Fibrosis.

Panel A shows a conceptual model of the pathobiology of idiopathic pulmonary fibrosis, which is characterized by recurrent epithelial-cell injury, senescent alveolar epithelial cells, profibrotic mediators leading to matrix deposition by myofibroblasts, microbiome changes, and host defense abnormalities. Potential therapeutic interventions are shown in green. Histologic features of usual interstitial pneumonia are shown in Panels B and C at low magnification and high magnification, respectively (hematoxylin and eosin). The photomicrographs show a marked patchy fibrosis in a peripheral, lobular (paraseptal) distribution. Fibroblastic foci (asterisk) are typically a prominent (but nonspecific) feature. Notably absent are features that would suggest an alternative interstitial lung disease, such as granulomas, hyaline membranes, organizing pneumonia, and marked inflammation. AEC denotes alveolar epithelial cell, CTGF connective-tissue growth factor, CCL2 chemokine (C-C motif) ligand 2, CCR2 chemokine (C-C motif) receptor 2, CXCL12 C-X-C motif chemokine ligand 12, FGF-2 fibroblast growth factor 2, FGFR1 fibroblast growth factor receptor 1, LOXL2 lysyl oxidase–like 2, LPA lysophosphatidic acid, LPA_1 lysophosphatidic acid receptor type 1, LPC lysophosphatidylcholine, MCP-1 monocyte chemoattractant protein 1, MMP matrix metalloproteinase, PDGF platelet-derived growth factor, PDGFR platelet-derived growth factor receptor, SDF-1 stromal-cell–derived factor 1, TGF-β transforming growth factor β, TGFBR1 TGF-β receptor type 1, TIMP tissue inhibitor of metalloproteinases, TRPV4 transient receptor potential cation channel subfamily V member 4, VEGF vascular endothelial growth factor, and VEGFR vascular endothelial growth factor receptor.

ease (Table 2), which are more common in younger and middle-age adults with interstitial lung disease. We routinely question patients about exposure to dampness, mold, or birds in the home or workplace, which can cause chronic hypersensitivity pneumonitis. We also look for signs and symptoms of autoimmune conditions, and we routinely test for antinuclear antibodies; rheumatoid factor; anti–cyclic citrullinated peptide antibodies; antibodies against Scl-70, Ro, La, U1-RNP, and Jo-1; creatine kinase; and myoglobin. In selected cases, a more extensive panel of antisynthetase antibodies should be considered. However, the presence of autoantibodies is not sufficient to rule out IPF. Input from a rheumatologist should be sought when the history, physical examination, or serologic testing suggests autoimmune disease.

If no cause can be identified, IPF should be included in the differential diagnosis, particularly for patients who are more than 50 years of age.

Table 2. Fibrotic Interstitial Lung Diseases (ILDs) of Known Cause That Mimic IPF.*

Condition	Examples or Causes	Clues from the Patient History	Findings Inconsistent with IPF†		Serologic Testing
			Physical	HRCT	
Chronic hypersensitivity pneumonitis	Mold, avian antigens, mycobacteria, isocyanates (specific exposures are often not identifiable)	Microbes in the home or workplace from forced-air heating, humidifiers, hot tubs, water damage, or visible mold; indoor or caged birds, down or feather bedding, agricultural exposure	Inspiratory squeaks	Peribronchovascular distribution, mosaic ground-glass attenuation, expiratory gas trapping, ground-glass opacities	Hypersensitivity pneumonitis panel in selected cases
Connective-tissue disease–related ILDs	Rheumatoid arthritis, systemic sclerosis, idiopathic inflammatory myopathy (e.g., antisynthetase syndrome), Sjögren's syndrome	Joint pain, stiffness, or swelling; skin thickening or tightening; rash; dry eyes; dry mouth; heartburn; muscle pain or tenderness; Raynaud's phenomenon	Synovitis, joint deformities, rheumatoid nodules, sclerodactyly, mechanic's hands, Gottron's papules, Raynaud's phenomenon	Ground-glass opacities, pleural involvement	ANA; rheumatoid factor; anti-CCP, anti-Ro, anti-La, anti-U1RNP, and anti-Jo-1 antibodies; CK; myoglobin
Drug-induced ILDs	Amiodarone, methotrexate, nitrofurantoin, chemotherapeutic agents	Medication history	None	Ground-glass opacities	None
Pneumoconiosis (occupational ILDs)	Asbestosis, coal workers' pneumoconiosis, silicosis, berylliosis	Occupational history and exposures	None	Pleural plaques, progressive massive fibrosis, nodules	Lymphocyte-proliferation test for berylliosis

* ANA denotes antinuclear antibodies, anti-CCP anti–cyclic citrullinated peptide antibodies, CK creatine kinase, and HRCT high-resolution CT.
† Crackles are noted on lung examination in nearly all cases. Reticulation with or without traction bronchiectasis is common.

The findings on high-resolution CT can be used to infer whether the histologic pattern of IPF is present, thereby obviating the need for a lung biopsy in some cases. This pattern, termed "usual interstitial pneumonia" (UIP), consists of heterogeneous paraseptal fibrosis with architectural distortion (Fig. 2). The term UIP is also used to describe a high-resolution CT pattern characterized by bilateral reticulation and honeycombing that is predominantly peripheral and in the lower lobes (Fig. 3A, 3B, and 3C), which has a high positive predictive value for a histologic UIP pattern. Therefore, if no cause is identified, a typical UIP pattern on high-resolution CT is diagnostic of IPF.

A "probable UIP" pattern on high-resolution CT, defined as bilateral reticulation that is predominantly peripheral and in the lower lobes, with traction bronchiectasis but without honeycombing (Fig. 3D, 3E, and 3F), is also suggestive of an underlying histologic UIP pattern.[41] In studies performed at tertiary care centers with multidisciplinary discussions used for diagnosis, a probable UIP pattern on high-resolution CT was diagnostic of IPF in older adults who had substantial traction bronchiectasis or reticulation.[42,43] IPF may therefore also be confidently diagnosed on the basis of these findings, without the need for a lung biopsy.

Atypical features on high-resolution CT, including upper-lung or midlung predominance, peribronchovascular predominance, subpleural sparing (Fig. 3G, 3H, and 3I), predominant consolidation, extensive ground-glass opacities, extensive mosaic attenuation (Fig. 3J, 3K, and 3L), and diffuse nodules or cysts, should raise suspicion of an interstitial lung disease other than IPF.[41] Identifying these features can be difficult, and referral to a center that specializes in interstitial lung disease may help establish an accurate diagnosis without a lung biopsy.

When the combination of clinical and imaging data is not diagnostic, a thoracoscopic lung biopsy can be considered if the results are expected to influence therapy. Biopsy samples should be taken from multiple lobes, and surgeons should avoid sampling the most severely affected areas, since samples from these areas typically show advanced, nondiagnostic fibrosis.

Figure 3 (facing page). High-Resolution CT Images of the Chest Showing Various ILD Patterns.

Panels A, B, and C show the pattern of usual interstitial pneumonia (UIP): predominant peripheral and lower-lobe reticulation (blue arrows) and honeycombing (yellow arrows), as well as traction bronchiectasis (green arrow). This pattern is diagnostic of idiopathic pulmonary fibrosis if no known cause is identified. Panels D, E, and F show features of "probable UIP": predominant peripheral and lower-lobe reticulation (blue arrows) and traction bronchiectasis (green arrow) without honeycombing. A probable UIP pattern with substantial bronchiectasis, reticulation, or both in older adults strongly supports a diagnosis of IPF if no known cause of ILD is identified. Panels G, H, and I show CT features that are most consistent with a non-IPF diagnosis: a predominance of ground-glass opacities (black arrows) and reticular abnormalities in the lower lung, with subpleural sparing. Although not diagnostic, this pattern is commonly seen when a histologic pattern of nonspecific interstitial pneumonia is present. Panels J, K, and L show CT features that are highly suggestive of hypersensitivity pneumonitis: sharply defined mosaic attenuation and ground-glass opacities (black arrows) with mild reticulation. Images are shown from left to right as axial, coronal, and sagittal reconstructions.

The procedure should not be performed in high-risk patients, including those with high oxygen requirements (e.g., >2 liters per minute), pulmonary hypertension, rapid disease progression, severely reduced FVC or D_{LCO}, multiple coexisting conditions, or frailty.[44] Transbronchial lung cryobiopsy has been increasingly advocated as a replacement for thoracoscopic biopsy. Although experience with this technique is growing, current data do not support its use.[45-48] Surgical biopsy remains the standard procedure for obtaining lung tissue to establish a diagnosis of interstitial lung disease.

If a histologic UIP pattern is found in the absence of a known cause, IPF can often be confidently diagnosed.[41] In other circumstances, despite the availability of extensive clinical data, confirmation of the diagnosis remains challenging, particularly for nonexpert clinicians.[49] Face-to-face multidisciplinary discussions involving clinicians, radiologists, and pathologists are now widely used to increase diagnostic agreement.[50] The reproducibility of an IPF diagnosis established by multidisciplinary discussion is good and improves prognostication.[51]

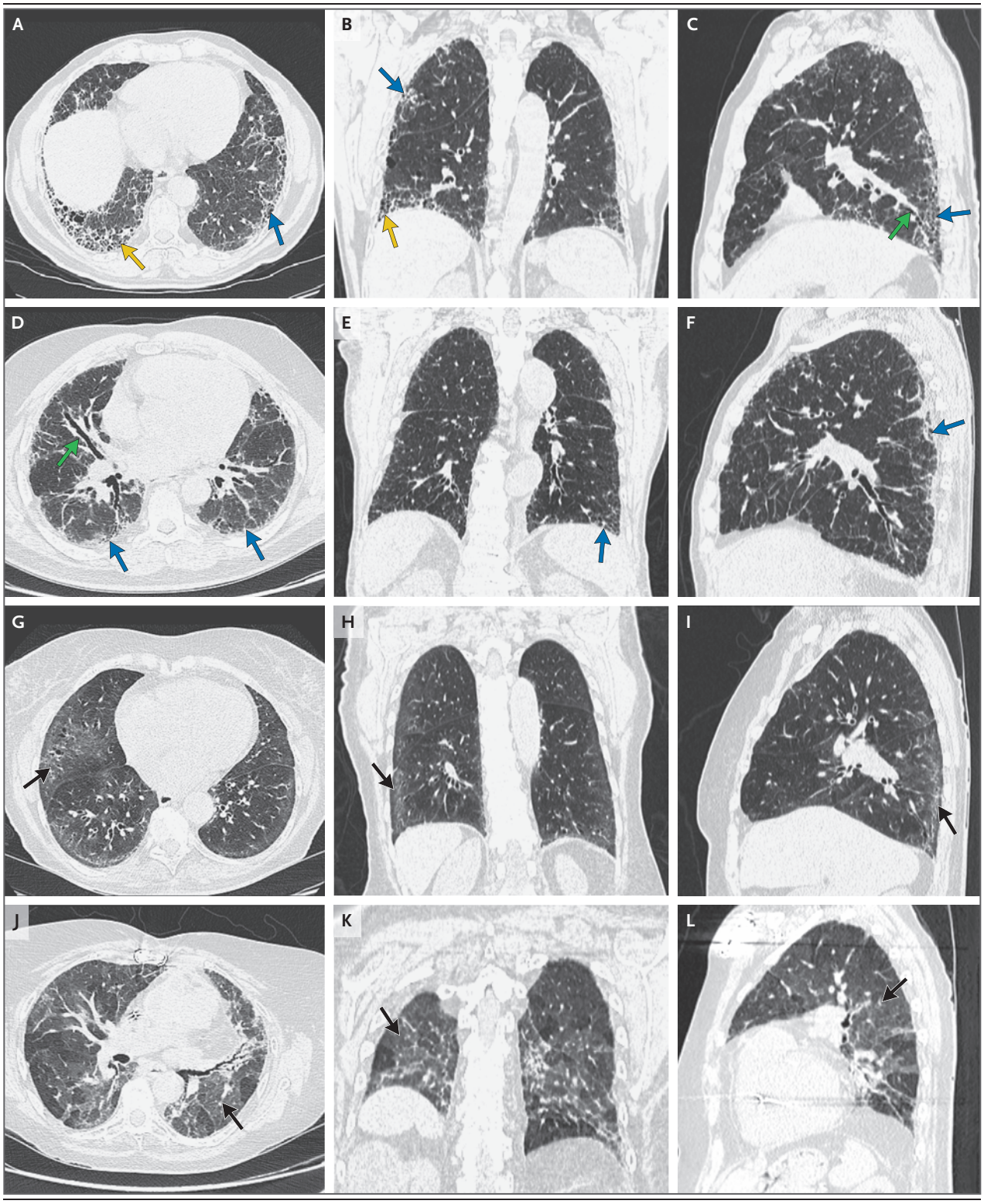

Table 3. Pharmacologic Management of IPF.*

Variable	Nintedanib	Pirfenidone
Mechanism of action	Tyrosine kinase inhibition	Inhibition of TGF-β production and downstream signaling, collagen synthesis, and fibroblast proliferation (selected list)
Efficacy	Slows FVC decline by 50%	Slows FVC decline by 50%
FDA-approved dose	150 mg by mouth twice daily	801 mg by mouth thrice daily
Common side effects	Diarrhea	Anorexia, nausea, photosensitivity
Enzyme metabolism	Ester cleavage (major), CYP 3A4 (minor)	CYP 1A2 (major), other CYP enzymes (minor)
Cautions	Risks of both bleeding and arterial thrombosis; risk of gastrointestinal perforation (rare); anticoagulant and prothrombotic drugs should be avoided	CYP 1A2 inhibitors (e.g., fluvoxamine and ciprofloxacin) can raise pirfenidone levels; CYP 1A2 inducers (e.g., omeprazole and smoking) can lower pirfenidone levels
Need for liver-function monitoring	Yes†	Yes‡
Clinical strategies to minimize side effects	Use of antidiarrheal agents, temporary dose reduction to 100 mg twice daily	Slow dose increase over 14-day period, medication to be taken with food, use of antacids, use of antiemetic agents, sun avoidance

* Nonpharmacologic management includes smoking cessation, age-appropriate vaccination, supplemental oxygen, pulmonary rehabilitation, evaluation for lung transplantation, diagnosis and management of depression and anxiety, weight and nutrition management, and support and education. CYP denotes cytochrome P450, FDA Food and Drug Administration, and TGF-β transforming growth factor β.

† Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin should be measured before the start of treatment, monthly for the first 3 months of treatment, and then as clinically indicated. Nintedanib should be discontinued when the AST or ALT level is more than 3 times the upper limit of the normal range if there is clinical evidence of hepatic dysfunction or the bilirubin level exceeds the upper limit of the normal range. If no clinical signs or symptoms are present, an AST or ALT level that is 3 to 5 times the upper limit of the normal range should prompt a reduction in the dose to 100 mg twice daily and additional evaluation as clinically indicated. An AST or ALT level that is more than 5 times the upper limit of the normal range should always prompt discontinuation of nintedanib, regardless of whether there are clinical signs or symptoms of hepatic dysfunction. Liver function should be closely monitored until the levels return to baseline values.

‡ AST, ALT, and bilirubin should be measured before the start of treatment, monthly for the first 6 months of treatment, and then every 3 months. Pirfenidone should be permanently discontinued when the AST or ALT level is more than 3 times the upper limit of the normal range if there is clinical evidence of hepatic dysfunction or the bilirubin level exceeds the upper limit of the normal range. If no clinical signs or symptoms are present, an AST or ALT level that is 3 to 5 times the upper limit of the normal range should prompt careful monitoring of liver function and additional evaluation as clinically indicated. An AST or ALT level that is more than 5 times the upper limit of the normal range should always prompt discontinuation of pirfenidone, regardless of whether there are clinical signs or symptoms of hepatic dysfunction.

Molecular diagnostic markers, including circulating matrix metalloproteinases,[52] combinations of circulating proteins,[53] and a peripheral-blood transcriptomic signature,[54] have been explored because of the diagnostic challenge. A gene-expression signature developed with the use of a machine-learning approach has been applied to surgical lung-biopsy samples to enhance the identification of a UIP pattern[55]; this approach has been extended to transbronchial lung-biopsy samples.[56] It remains unclear how such molecular approaches will be integrated into clinical practice, and their use cannot be recommended until further data are available.

NONPHARMACOLOGIC MANAGEMENT

Nonpharmacologic management strategies help patients with IPF live healthier, more normal lives, and the importance of these approaches cannot be overemphasized. Smoking cessation should be a priority for patients who are actively using tobacco products. Influenza, pneumococcal, and other age-appropriate vaccines should be administered.

SUPPLEMENTAL OXYGEN

Clinical practice guidelines strongly recommend supplemental oxygen for patients with IPF.[2] Oxygen administration reduces exertional dyspnea and improves exercise tolerance.[57] An oxyhemoglobin saturation of 88% or less at rest, during exertion, or during sleep should prompt initiation of home oxygen therapy. The oxygen prescription should be informed by 6-minute walk tests or treadmill testing of oxygen saturation, as well as by nocturnal oximetry or polysomnography when indicated (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

PULMONARY REHABILITATION

Pulmonary rehabilitation, a structured exercise program designed for adults with advanced lung disease, has been shown to improve exercise capacity and health-related quality of life for patients with IPF.[58]

LUNG TRANSPLANTATION

More than 2000 lung transplantations are performed in the United States each year, approximately half of which are performed for interstitial lung disease.[59] Thus, only a minority of patients with IPF receive a transplant. Lung transplantation can prolong survival and improve quality of life for highly selected candidates[60,61]; however, only 66% of transplant recipients with IPF survive for more than 3 years after transplantation and only 53% survive for more than 5 years.[59] Common complications include primary graft dysfunction, acute and chronic forms of allograft rejection, cytomegaloviral and other infections, and cancer.[59] IPF has not been shown to recur in the allograft. Referral to a transplantation center should be made at the time of diagnosis, since the evaluation process and waiting time can last for months to years.[62] Common contraindications include recent cancer, advanced nonpulmonary organ failure, and lack of a reliable social support system.[62]

PHARMACOLOGIC MANAGEMENT

During the past 5 years, notable advances have been made in pharmacotherapeutic approaches to IPF.[63] Two medications, nintedanib and pirfenidone, have been shown to be safe and effective in the treatment of IPF; both are recommended for use in patients with IPF (Table 3).[63] In placebo-controlled, randomized trials, each drug has been shown to slow the rate of FVC decline by approximately 50% over the course of 1 year.[64,65] Both have shown some efficacy in reducing severe respiratory events, such as acute exacerbations, and hospitalization for respiratory events.[66,67] Pooled data and meta-analyses suggest that these agents may reduce mortality.[68,69] The cost of each medication is estimated to exceed $100,000 annually.

Nintedanib is a tyrosine kinase inhibitor that targets growth factor pathways, including those downstream from vascular endothelial growth factor receptors 1, 2, and 3, fibroblast growth factor receptors 1, 2, and 3, and platelet-derived growth factor receptor (Fig. 2). Patients should initially be prescribed 150 mg of nintedanib, to be taken by mouth twice daily. The medication should be taken with food and can be continued indefinitely. Patients taking nintedanib commonly have diarrhea, which can often be managed with antidiarrheal agents.[64] The dose can be decreased to 100 mg twice daily if unmanageable side effects occur. Cases of drug-induced liver injury have been reported. Liver function should be tested at baseline, monitored monthly for the first 3 months, and then monitored as clinically indicated. Since nintedanib is associated with a small increase in the risk of bleeding, this agent should be used with great caution, if at all, in patients receiving full-dose anticoagulant therapy. Atheroembolic events, including myocardial infarction, have also been reported with nintedanib.[64] Caution should be used when treating patients with cardiovascular risk factors, including those who have coronary artery disease.

Pirfenidone has a number of antiinflammatory and antifibrotic effects, including inhibition of collagen synthesis, down-regulation of TGF-β and tumor necrosis factor alpha, and a reduction in fibroblast proliferation.[70] Pirfenidone is prescribed in an escalating-dose fashion over a 14-day period: 267 mg (one capsule) by mouth three times daily for 1 week, 534 mg (two capsules) three times daily for 1 week, and 801 mg (three capsules) three times daily thereafter. Patients can subsequently be transitioned to an 801-mg tablet three times daily. Pirfenidone must be taken with food and can be continued indefinitely. Common side effects, such as anorexia, nausea, and vomiting,[65] can often be ameliorated by judicious use of antacids and antiemetic agents. In some cases, side effects are severe enough to require a lower total daily dose (six to eight capsules daily). A photosensitive rash can also occur. Liver function should be monitored periodically.

It is difficult to recommend one agent over the other, since there have been no head-to-head comparisons. A network meta-analysis concluded that pirfenidone and nintedanib provide similar benefits.[71,72] No data are available to guide clinicians regarding the timing of initiation of therapy, how a response should be defined, and when the therapy should be discontinued.[73] Recent data on treatment that combines these agents

suggest clinically significant gastrointestinal side effects.[74]

Treatment guidelines for IPF include a strong recommendation against the use of prednisone in combination with azathioprine and oral *N*-acetylcysteine, a regimen associated with an increase in mortality by a factor of 9, as compared with placebo.[10] A clinical trial showed no effect of *N*-acetylcysteine monotherapy on lung function.[75,76] Interferon-γ,[77] endothelin antagonists,[78] and warfarin[79] are ineffective or harmful in patients with IPF. The Food and Drug Administration has appropriately warned consumers against various unapproved stem-cell "therapies" advertised for the treatment of IPF.[80]

Although current guidelines recommend the use of antacid therapy to treat IPF,[63] there are no data from clinical trials to support this recommendation. In two studies, antacid use was associated with a slower decline in lung function and a lower mortality rate.[81,82] These observational studies of treatment effect are, by nature, confounded by indication and should not be used to inform clinical practice.[83] More recent data suggest that antacid therapy may increase the risk of respiratory infections in patients with IPF.[84]

Growing knowledge of the biologic underpinnings of fibroproliferation has opened new therapeutic avenues. A phase 2 trial of pamrevlumab, an intravenously administered antibody targeting connective-tissue growth factor, slowed the decline in FVC, as compared with placebo, over a period of 48 weeks.[85] PBI-4050, which targets multiple profibrotic cytokines and alters fibroblast function,[70] may improve FVC when administered in combination with nintedanib.[86] TD139, an inhaled galectin-3 inhibitor, has been shown to lower galectin-3 expression on alveolar macrophages in IPF.[87] GLPG1690, which targets autotaxin, an enzyme responsible for LPA production, may reduce circulating LPA levels while influencing lung function and findings on functional respiratory imaging. Trials of BMS-986020 (ClinicalTrials.gov number, NCT01766817), an oral LPA antagonist, and BG00011 (NCT01371305), a monoclonal antibody targeting the αVβ6 integrin, have been completed, and the results are pending. A phase 1 study has shown that PRM-151 (recombinant pentraxin-2) is safe in patients with IPF[88]; a phase 2 study (NCT02550873) has been completed. Two clinical trials of antimicrobial therapy potentially targeting the lung microbiome in IPF are ongoing (NCT02759120; and EudraCT number, 2014-004058-32).

There are several possible approaches for the management of cough in IPF, though none are universally effective. A trial of thalidomide confirmed that it could be used to ameliorate cough in patients with IPF.[89] An observational study suggests that pirfenidone may attenuate cough.[90] The P2X3 antagonist AF-219/MK-7264 (gefapixant) suppresses idiopathic cough[91]; a trial of this agent in patients with IPF has been completed (NCT02502097). Finally, an inhaled cromolyn preparation was shown to ameliorate cough in patients with IPF.[92]

COMPLICATIONS AND MORTALITY

IPF carries a poor prognosis, with a median survival of 3.8 years among adults 65 years of age or older in the United States.[6] Although this statistic is disappointing, in practice it is not uncommon for patients to live 5 years or more after receiving the diagnosis. Many patients die from progressive, chronic hypoxemic respiratory failure. Palliative care is rarely instituted in patients with IPF before the end of life.[93]

Each year, approximately 10 to 20% of patients with IPF have an acute exacerbation, characterized by worsened hypoxemic respiratory failure, with bilateral ground-glass opacities, consolidation, or both on high-resolution CT imaging that are not fully explained by volume overload.[94] Exacerbations may be triggered by a clinical event (e.g., infection, aspiration, or drug toxicity) but are frequently idiopathic.[94] Most patients with an acute exacerbation die from acute respiratory failure. Available guidelines make weak recommendations for the use of glucocorticoids and do not recommend the use of mechanical ventilation in patients with an acute exacerbation, emphasizing the need to establish physician orders regarding life-sustaining treatment before the onset of a life-threatening event.[2]

Patients with IPF are at increased risk for venous thromboembolism,[95] lung cancer,[96] and pulmonary hypertension.[97] A high index of suspicion should be maintained for pulmonary embolism as the cause of any acute respiratory deterioration. Incidental pulmonary nodules should be managed according to established guidelines for high-risk patients.[98] Annual low-dose CT scanning should be considered for patients meeting

the U.S. Preventive Services Task Force criteria for lung-cancer screening.[99] Although pulmonary hypertension occurs in some patients with IPF, management in the outpatient setting should consist solely of supplemental oxygen, without pulmonary vasodilator therapy. Until further data are available, targeted therapies approved for pulmonary arterial hypertension should be avoided in patients with IPF unless they are enrolled in a clinical trial investigating such therapies.[100]

FUTURE DIRECTIONS

In light of the rising prevalence of IPF and the increase in associated mortality, we hope that the next 5 years will be marked by greater recognition of the disease on the part of primary care providers, leading to earlier involvement of a multidisciplinary team to aid in diagnosis and management. Novel preventive interventions, evolving use of screening biomarkers, and the eventual ability to target newly discovered risk factors for IPF could lead to a decline in the incidence of this disease as well as other fibrotic interstitial lung diseases in coming years. Advances in therapeutics, including individualized approaches and interventions to halt collagen deposition, may one day eliminate the need for lung transplantation and turn IPF into a lifelong chronic disease.

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