Spectrum of Fibrotic Lung Diseases

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DIFFUSE PARENCHYMAL LUNG DISEASES ENCOMPASS A LARGE NUMBER of conditions, with a wide range of causes, clinical manifestations, and imaging and pathological features, as well as variable outcomes. Despite the intrinsic heterogeneity of this group of diseases, in most of them, the pulmonary alveolar walls are infiltrated by various combinations of inflammatory cells, fibrosis, and proliferation of certain cells that make up the normal alveolar wall. Since these pathologic abnormalities predominate in the lung interstitium, the disorders are termed interstitial lung diseases (ILDs).

Idiopathic pulmonary fibrosis (IPF) is the archetypal and most common fibrotic ILD. IPF is characterized by an imaging and pathological pattern of usual interstitial pneumonia (UIP) without an identifiable cause or association with a disease known to be associated with pulmonary fibrosis. It occurs more commonly in men than in women (sex ratio, 7:3) and is more common in people older than 60 years of age than in younger people.[1,2] IPF is a chronic and irreversible disease, usually progressing to respiratory failure and death (median interval between diagnosis and death, 3 years).[3] In contrast to IPF, other ILDs are generally characterized by a younger mean age at presentation (20 to 60 years) and a more balanced sex ratio. The variable underlying pathological features of other ILDs, with fibrosis generally less prominent than inflammatory infiltration, also translate into more heterogeneous and often less severe outcomes, as compared with IPF. However, a number of these other ILDs are also characterized by progressive fibrosis.[4] As in any other organ, fibrosis in the lungs can be a manifestation of several clinical entities, and if the fibrosis is progressive, it will ultimately result in organ failure,[5] causing respiratory symptoms, limited exercise capacity, an impaired quality of life, and an increased risk of death.[6]

ILDs are typically assigned to many disease categories for classification and management purposes, roughly on the basis of a known underlying disease (e.g., pulmonary fibrosis associated with rheumatoid arthritis), an inciting agent (e.g., pneumoconiosis), or the absence of a known cause (e.g., IPF).[4,7] In this review, we address pulmonary fibrosis in various contexts and disease entities, emphasizing the commonalities in pathophysiological features, clinical manifestations, and diagnostic features, as well as the similarly progressive nature of many of these diseases.

EPIDEMIOLOGY

Although each of the individual fibrosing ILDs is rare, collectively they affect a considerable number of patients, representing a substantial burden of disease. The overall prevalence of ILD is estimated to be up to 76.0 cases per 100,000 people in Europe and 74.3 cases per 100,000 in the United States. Sarcoidosis, connective-tissue disease (CTD)–associated ILDs, and IPF are the most common fibrotic ILDs, with an estimated prevalence of 30.2, 12.1, and 8.2 cases per 100,000, respectively[8] (Table 1). Among all patients with fibrotic ILDs other than IPF, 13 to 40%

have a progressive fibrosing phenotype,[18] representing up to 20 patients per 100,000 people in Europe and up to 28 patients per 100,000 in the United States (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[19]

Pulmonary fibrosis occurs throughout the world, with geographic variation.[19] The prevalence of IPF, estimated to be 8 to 60 cases per 100,000 population,[8,20] is higher in North America and Europe than in the rest of the world, whereas the prevalence of sarcoidosis is higher in northern Europe and among Black persons and is lower in Japan.[21]

PATHOPHYSIOLOGY

The formation of fibrosis is an essential response of the body against pathogens and in normal wound healing.[22] In pulmonary fibrosis, various and often disease-specific triggers set off exaggerated cascades of inflammatory and fibrotic responses, leading to downstream fibrotic tissue remodeling and extracellular-matrix deposition,[23] which in turn perpetuate fibrosis formation (Fig. 1). Much is still unknown about the pathophysiology of specific disease entities and the factors that differentiate normal wound repair from progression to fibrosis. Although triggers, susceptibility, and initial inflammatory responses vary among diseases, the current assumption is that in later phases, common mechanisms play a role.[23]

A variety of genetic studies have identified both common and rare variants that are associated with enhanced susceptibility to pulmonary fibrosis, with remarkable similarities between familial IPF and other fibrotic ILDs.[24] For example, a frequent polymorphism in the promoter of *MUC5B*, which is involved in airway clearance and bacterial host defense, is associated with increased risks of IPF, rheumatoid arthritis with ILD[25] (RA–ILD), and chronic hypersensitivity pneumonitis (CHP)[26] but not systemic sclerosis with ILD (SSc–ILD), sarcoidosis, or antisynthetase syndrome. Telomere shortening and telomere-related gene mutations (*TERT, TERC, RTEL1,* and *PARN*) are found in IPF, RA–ILD, and CHP.[24,26] Some rare genetic variants, such as telomere-related gene mutations, are clearly associated with progressive disease.[24]

Besides shared genetic risk factors, different ILDs have heterogeneous, overlapping initial pathways[7] (Fig. 1). In IPF, an as yet undefined insult to alveolar epithelial-cell integrity may initiate disease through the interaction between epithelial cells and myofibroblasts.[5] Granulomatous inflammation in response to a putative, persistent, unknown trigger progresses to fibrosis in only a small percentage of patients with sarcoidosis.[13] In SSc–ILD, a combination of inflammation, endothelial dysfunction, and vasculopathy leads to pulmonary fibrosis in a majority of patients, driving the prognosis.[23] Studies investigating specific conditions suggest that various inflammatory responses may lead to a profibrotic environment and cytokine milieu (including, especially, transforming growth factor β, connective-tissue growth factor, platelet-derived growth factor, and WNT and hedgehog signaling). Shared downstream pathways may activate and sustain a complex interplay leading to fibroblast activation and differentiation into myofibroblasts, which further orchestrate fibrogenesis.[23] Once established, structural tissue changes and the profibrotic milieu form a feed-forward loop, leading to self-perpetuating fibrosis.

DISEASE ENTITIES WITH PULMONARY FIBROSIS

ILDs can be divided into five broad clinical categories: ILDs related to distinct primary diseases (e.g., sarcoidosis, Langerhans-cell granulomatosis, eosinophilic pneumonia, lymphangioleiomyomatosis, and pulmonary alveolar proteinosis); ILDs related to environmental exposures, including pneumoconiosis due to inhalation of inorganic substances and hypersensitivity pneumonitis mostly related to inhalation of organic particles (e.g., domestic or occupational exposure to mold or birds or other exposures); ILDs induced by drugs, illicit drugs, or irradiation; ILDs associated with CTDs, including RA–ILD and SSc–ILD, idiopathic inflammatory myopathy, and primary Sjögren's disease; and idiopathic interstitial pneumonias,[27] which include IPF, idiopathic nonspecific interstitial pneumonia, and other, less common entities.

Pulmonary fibrosis can occur in the context of many of these ILDs (Table 1 and Table S1). A separation can be made between pulmonary fibrosis in the context of underlying systemic diseases, such as CTDs and sarcoidosis, and conditions that are restricted to the lung, such as CHP, drug-induced pulmonary fibrosis, idiopathic non-

Table 1. Clinical Characteristics of Selected Broad Categories of Pulmonary Fibrosis.*

Condition	Main Clinical Features	Findings on Chest Imaging	Other Features Not Characteristic of IPF	Management	Prognosis	Risk Factors for Progressive Fibrosis or Death	Relative Prevalence†	Progressive Fibrosing Phenotype
							% of patients	
IPF[3]	Velcro-like crackles; finger clubbing (30–50% of patients); male: female ratio, 3:1; age >50 yr	Definite or probable UIP pattern, indeterminate pattern for UIP (and biopsy findings or clinical course suggestive of IPF)	NA	Antifibrotic therapy (pirfenidone, nintedanib)	Median survival, 3–4 yr; potential for slowing progression	Older age, male sex, honeycombing or UIP pattern on CT, FVC <70%	12	90–100
SSc–ILD[9,10]	Raynaud's phenomenon, skin thickening, fingertip lesions, telangiectasia, gastroesophageal reflux, vasculopathy	More common fibrotic NSIP than UIP pattern	Younger age, more women than men affected, multisystemic involvement, autoimmune serologic findings (anti–Scl-70, anticentromere, and anti–RNA polymerase III antibodies), abnormal nailfold capillaroscopy	Immunosuppressive therapy: mycophenolate; alternatively, IV cyclophosphamide, azathioprine, rituximab, tocilizumab Antifibrotic therapy (nintedanib) Stem-cell transplantation or lung transplantation in select patients	10-Yr mortality, 40%; 35% of SSc-related deaths due to ILD; possible stabilization with treatment	Diffuse cutaneous SSc, <7 yr since diagnosis, male sex, Black race, anti–Scl-70 antibodies, disease extent on CT >20%, reduced FVC and DLco	9	40
Rheumatoid arthritis–ILD[11,12]	Morning stiffness, symmetric arthritis, synovitis, joint erosions, rheumatoid nodules	Predominance of UIP pattern over NSIP or indeterminate pattern, multicompartment involvement (association of airways or pleural involvement)	Autoimmune serologic features (ACPAs, but rheumatoid factor less specific)	Lack of evidence for immunosuppressive therapy; rituximab, abatacept, or mycophenolate occasionally used; antifibrotic therapy (nintedanib) used in cases of progressive fibrosis; pirfenidone is under investigation‡	Median survival, 3 yr (UIP pattern) or longer (other patterns); effect of treatment on lung disease unknown	Older age, male sex, disease extent on CT >20%, honeycombing or UIP pattern on CT, FVC < 70%	8	32
Sarcoidosis, fibrotic (stage IV)[13]	Multisystem disease in any organ, especially skin, eye, heart, liver, and lymph nodes; pulmonary involvement in 90% of cases; wide range of clinical phenotypes	Upper-lobe, peribronchovascular, and lymphatic distribution; dense perihilar fibrotic or cavitated masses; bronchial distortion, reticular opacities, and traction bronchiectasis; UIP-like pattern rare	Younger age; Female: male ratio, 1:1; multiorgan involvement; absence of bibasilar crackles and clubbing; noncaseating epithelioid-cell granulomas with giant cells on pathological evaluation	Monitoring alone or treatment with glucocorticoids; methotrexate or azathioprine as glucocorticoid-sparing agent or second-line therapy; infliximab or adalimumab as third-line therapy; lack of evidence for leflunomide and hydroxychloroquine for lung disease; benefit of antifibrotic therapy unclear	10-Yr mortality, about 10%; 75% of sarcoidosis-related deaths due to lung disease; generally responsive to immunomodulation	Black race, disease extent on CT >20%, pulmonary hypertension, female sex	45	13

Disease	Clinical features	Imaging features	Diagnosis	Treatment	Prognosis	Indicators of progression		
Chronic fibrotic hypersensitivity pneumonitis[14,15]	Prolonged exposure to inhaled particles, predominantly organic antigens; onset of symptoms over a period of 6 mo or more§	Reticulation and honeycombing, with peribronchovascular, upper- and middle-zone distribution; ground-glass attenuation with mosaicism and air trapping	Offending inhaled antigen not always identified; recurrent episodes of symptoms; BAL lymphocytosis (>20% of cases); positive precipitins; biopsy, if performed showing airway-centric lymphocytic infiltration, loose granulomas, and giant cells	Exposure avoidance; limited evidence for glucocorticoids and immunosuppressive therapy (mycophenolate or azathioprine); antifibrotic therapy (nintedanib) for progressive fibrosis; lung transplantation in rare cases	5-Yr survival, 50–80%; potential for improvement or stabilization with treatment	Persistent exposure to offending antigen, honeycombing or UIP pattern on CT	3	21
Unclassifiable fibrotic ILD[16,17]	Demographic features vary; median age, 60–65 yr; nonspecific symptoms with dyspnea and cough; no first-choice diagnosis; often subtle autoimmune features	Nonspecific features generally not meeting criteria for main patterns	Major discrepancy among clinical, imaging, and histologic features; nondiagnostic CT findings and no biopsy performed or biopsy results noncontributory	Limited evidence for glucocorticoids; immunosuppressive therapy often first-line; antifibrotic therapy (pirfenidone or nintedanib) in progressive fibrosis	5-Yr survival, 45–70%; variable disease course	Honeycombing on imaging, progressive decline in lung function	8	53

* More comprehensive information is provided in Table S1. ACPAs denotes anti–citrullinated protein antibodies, BAL bronchoalveolar lavage, DLco diffusing capacity of the lung for carbon monoxide, FVC forced vital capacity, ILD interstitial lung disease, IPF idiopathic pulmonary fibrosis, IV intravenous, NA not applicable, NSIP nonspecific interstitial pneumonia, SSc systemic sclerosis, and UIP usual interstitial pneumonia.

† Relative prevalence is the estimated prevalence among all patients with ILD.

‡ The trial is ongoing (ClinicalTrials.gov number, NCT02999178).

§ A list of inhaled organic antigens that can cause fibrotic hypersensitivity pneumonitis is available at www.hplung.com.
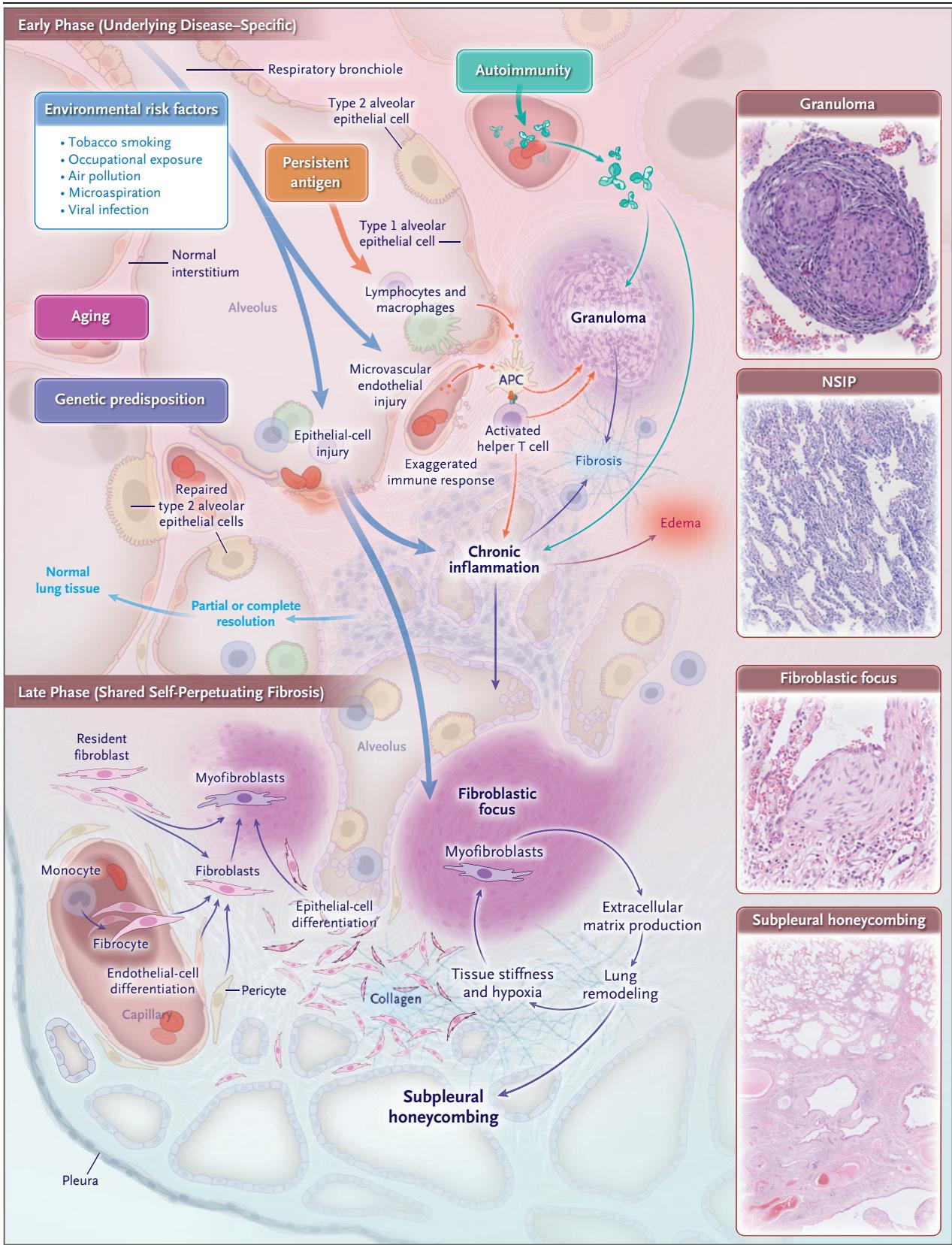
Early Phase (Underlying Disease–Specific)

Respiratory bronchiole

Autoimmunity

Type 2 alveolar
epithelial cell

Environmental risk factors
- Tobacco smoking
- Occupational exposure
- Air pollution
- Microaspiration
- Viral infection

Persistent
antigen

Type 1 alveolar
epithelial cell

Normal
interstitium

Lymphocytes and
macrophages

Granuloma

Alveolus

Aging

Microvascular
endothelial
injury

APC

Genetic predisposition

Epithelial-cell
injury

Activated
helper T cell

Fibrosis

Repaired
type 2 alveolar
epithelial cells

Exaggerated
immune response

Edema

**Normal
lung tissue**

**Partial or complete
resolution**

**Chronic
inflammation**

Late Phase (Shared Self-Perpetuating Fibrosis)

Resident
fibroblast

Myofibroblasts

Alveolus

**Fibroblastic
focus**

Monocyte

Fibroblasts

Myofibroblasts

Fibrocyte

Epithelial-cell
differentiation

Extracellular
matrix production

Endothelial-cell
differentiation

Pericyte

Tissue stiffness
and hypoxia

Lung
remodeling

Capillary

Collagen

**Subpleural
honeycombing**

Pleura

Granuloma

NSIP

Fibroblastic focus

Subpleural honeycombing

ology and burden of fibrosis within each diagnostic category, clinicians most often see patients with CTD–ILD, IPF, CHP, sarcoidosis, or unclassifiable fibrotic ILD.

Currently, there is a specific interest in the potential development of fibrosis after coronavirus disease 2019 (Covid-19). Although infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a range of pulmonary symptoms, male sex, older age, obesity, and coexisting conditions appear to be risk factors for the development of SARS.[28] Pulmonary fibrosis is a known complication of acute respiratory distress syndrome (ARDS), and there are similarities in the fibroproliferative response and risk factors between lung fibrosis in the context of ARDS and lung fibrosis in the context of other diseases.[29] Nevertheless, analysis of long-term follow-up data after ARDS[29] or infection with another strain of SARS-CoV in 2003[30] showed fibrotic changes that remained mostly stable over time and had little clinical relevance.[29] The long-term effect and the disease course of pulmonary fibrosis caused by Covid-19 are currently under investigation in prospective studies.

DIAGNOSTIC APPROACH

Other than disease-specific symptoms, cough, progressive exertional dyspnea, and exercise limitation are the main presenting symptoms. The diagnosis is often delayed by several months or even years. A thorough history, including environmental exposures, medication use, and extrapulmonary signs, should be taken.[2] On chest auscultation, fine crackles (also called Velcro rales or crepitations) are indicative of fibrosis,[31] although squeaks may be heard in patients with hypersensitivity pneumonitis. Premature graying of hair and hematologic abnormalities may be a sign of telomeropathy-related fibrosis. In CTDs, pulmonary fibrosis may develop either after the underlying condition is diagnosed or before the extrapulmonary manifestations are observed.[32] Hands, joints, and skin should be thoroughly examined.[32] Serologic testing is recommended, including for antinuclear antibodies and anti–citrullinated peptide antibodies.[2] If there is a clinical suspicion of an autoimmune condition, consultation with a rheumatologist and more extensive serologic testing are recommended.

High-resolution computed tomographic (CT)

specific interstitial pneumonia, and IPF.[3,27] There is also overlap between groups (e.g., drug-induced pulmonary fibrosis in CTD and a genetic predisposition in various ILDs). Owing to the epidemi-

scanning of the chest establishes the diagnosis of pulmonary fibrosis by revealing reticulation, architectural distortion, and lung volume loss and may identify patterns suggestive of specific causes (Table 1, Table S1, and Fig. S2).[2,3] The UIP pattern is the hallmark of pulmonary fibrosis, observed frequently in IPF, in RA–ILD, and in advanced disease irrespective of the underlying condition.[3,33] In contrast, the most common pattern in SSc–ILD is that of nonspecific interstitial pneumonia, which consists of mixed reticulation and ground-glass attenuation to a varying extent, often with traction bronchiectasis, central axial distribution, and sparing of the subpleural area. Expiratory imaging may be useful, especially in CHP.[34] Pulmonary-function testing assesses the level of disease impairment and is the most frequently used measure for monitoring the course of disease and response to therapy. In patients with pulmonary fibrosis, testing typically shows a restrictive lung-function pattern (decreased forced vital capacity [FVC], normal or increased ratio of forced expiratory volume in 1 second to FVC, decreased total lung capacity, and low residual volume), together with a decreased diffusing capacity of the lung for carbon monoxide. However, normal lung function does not rule out the presence of pulmonary fibrosis.

If the combination of clinical findings and imaging is not diagnostic, more invasive diagnostic procedures may be needed. Bronchoalveolar lavage contributes to the diagnosis of hypersensitivity pneumonitis and sarcoidosis. Bronchial mucosa and lymph-node biopsies are performed when sarcoidosis is suspected. It is recommended that all collected information be synthesized by a multidisciplinary team experienced in ILD (Fig. 2), which may either establish a diagnosis or discuss the indication for further diagnostic procedures such as thoracoscopic lung biopsy or transbronchial cryobiopsy. Weighing diagnostic yield and therapeutic consequences against potential risks associated with each procedure is crucial for discussion among the members of the multidisciplinary team and with the patient.[35] Consideration of the course of the disease in a given patient is important in guiding diagnosis and management and may reduce the need for invasive diagnostic procedures. Although a first-choice diagnosis can be made with sufficient confidence in the majority of cases,[36] a subgroup of ILD cases remains unclassifiable even after thorough assessment.[16]

PROGRESSIVE PULMONARY FIBROSIS

The natural course of untreated IPF is characterized by progression to respiratory failure in virtually every patient with a secure diagnosis.[3] In contrast, more than half of all patients with a diagnosis of pulmonary fibrosis other than IPF have stable, chronic disease or improvement with immunomodulatory therapy.[6] Despite treatment that is considered appropriate, however, a proportion of patients will have progressive pulmonary fibrosis associated with worsening respiratory symptoms, a decline in lung function, a decreased quality of life, and a risk of early death, independent of the classification of the ILD.[6,37] Outcomes may be similar to those of IPF, especially in patients with a UIP pattern, such as those with RA–ILD and some patients with CHP (Fig. S3).

The risk of progressive disease and the prognosis depend on the underlying entity (Table 1 and Table S1). However, the longitudinal disease course[4,27] varies and needs to be identified individually, since it has implications for management decisions and occasionally may lead to a reconsideration of the diagnosis. No serum biomarker has been validated for monitoring disease progression or assessing the respective components of inflammation and fibrosis in pathogenesis. Scores, especially those based on sex, age, FVC, and diffusing capacity of the lung for carbon monoxide, have been developed to assess the prognosis.[38] In case series, predictors of disease progression, despite immunomodulatory therapy, include demographic characteristics (e.g., persons of African descent with SSc–ILD or sarcoidosis), more extensive disease on CT imaging, greater impairment in lung function, presence of honeycombing[33] and a UIP pattern on CT, and persistence of the agent causing the disease (Table 1).

There is no standard definition of disease progression in patients with pulmonary fibrosis. Because a decline in FVC is predictive of death in patients with IPF,[39] it has been used as an end point in pivotal studies of antifibrotic drugs.[40] In a clinical trial evaluating the efficacy of antifibrotic therapy in patients with progressive fibrosing ILD,[41] patients were required to meet at least one of the following criteria for disease progression within the 24 months before screening: a relative decline in the FVC of 10% or more of the predicted value, a composite of a relative
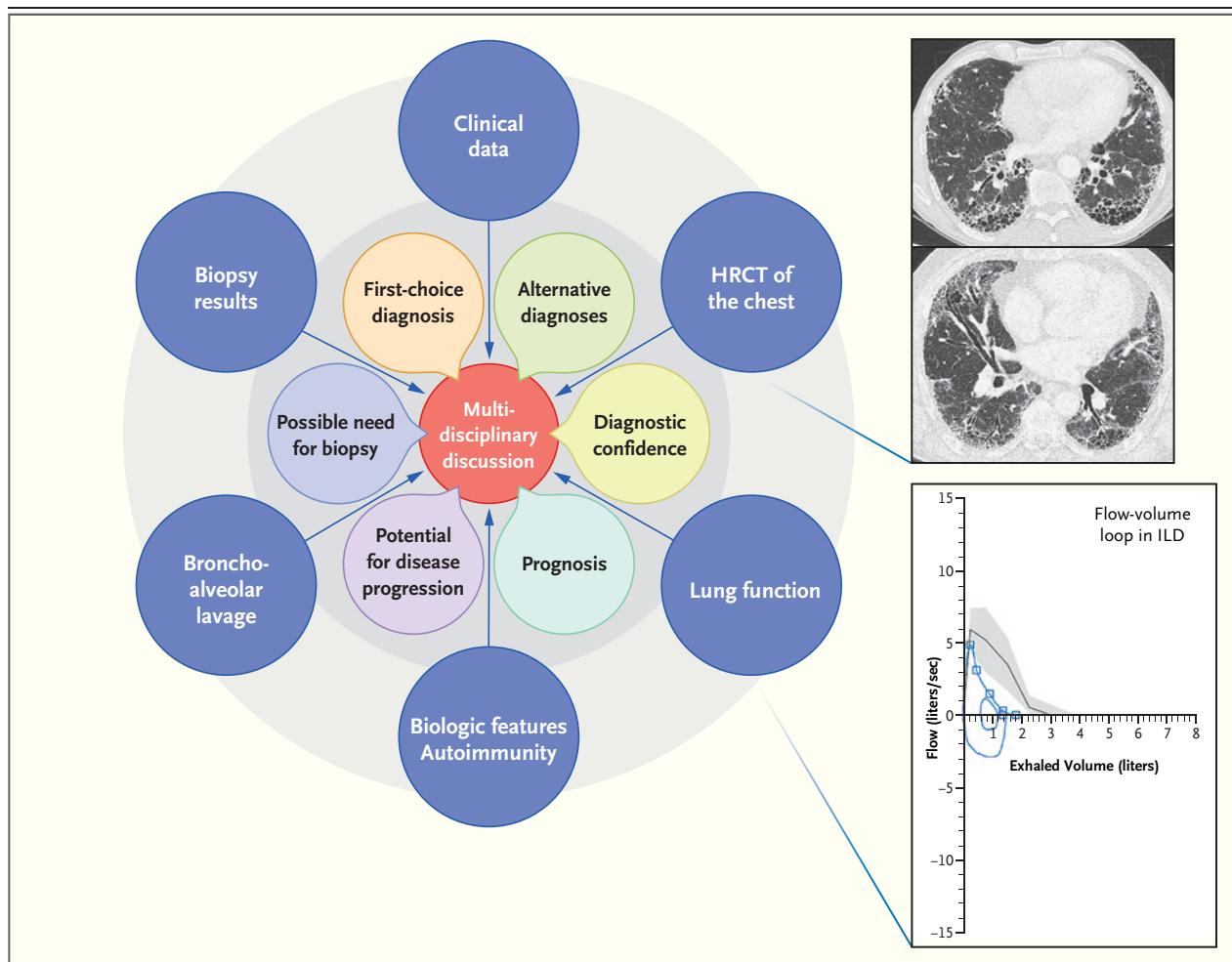
Figure 2. Algorithm for the Diagnosis of Pulmonary Fibrosis.

A multidisciplinary team can play a central role in the diagnosis and management of ILD. Key results of the diagnostic approach are discussed by members of the team, which includes clinicians, radiologists, pathologists, and other health care providers. The participants consider all data available and propose a first-choice diagnosis, assess the need for biopsy and confidence in the diagnosis, and consider possible alternative diagnoses, the potential for disease progression, and the prognosis. On the basis of this discussion, a management decision is made. However, not everyone in the world has equal access to a multidisciplinary team, and even when a multidisciplinary team is available, resources and time may not permit a team discussion of all cases. If a case cannot be addressed by a multidisciplinary team, it is important for the treating clinician to realize that many factors (outermost purple circles) need to be considered before diagnostic or therapeutic decisions can be made. The high-resolution CT (HRCT) scans at the upper right show a usual interstitial pneumonia pattern (top) and an NSIP pattern (bottom). The flow-volume loop shows a typical restrictive pattern (a decrease in forced vital capacity [FVC]) that is often seen in pulmonary fibrosis. The black line represents a predicted normal flow-volume loop for a patient of similar age, sex, height, and race, and the gray zone around it represents the 95% confidence interval. The FVC is shown on the horizontal axis as the volume from the origin to the intersection of the loop with that axis.

decline in the FVC of 5 to 10% of the predicted value and worsening symptoms or an increase in disease extent on chest CT, or worsening symptoms and an increase in disease extent on chest CT. Other criteria have also been used.[37,42-44] In clinical practice, no threshold or rate of decline has been formally accepted; however, assessment of the progression of fibrosis is usually based on serial lung-function tests performed at 3-to-6-month intervals. Since small variations in FVC may be confounded by measurement errors, multimodal assessment of disease progression also includes worsening of symptoms and exercise capacity, increased fibrosis on imaging, decreased diffusing capacity of the lung for carbon monoxide, need for oxygen supplementation, and clinical events predicting early death (acute exacerbation of fibrosis or nonelective hospitalization) (Fig. 3).[43]
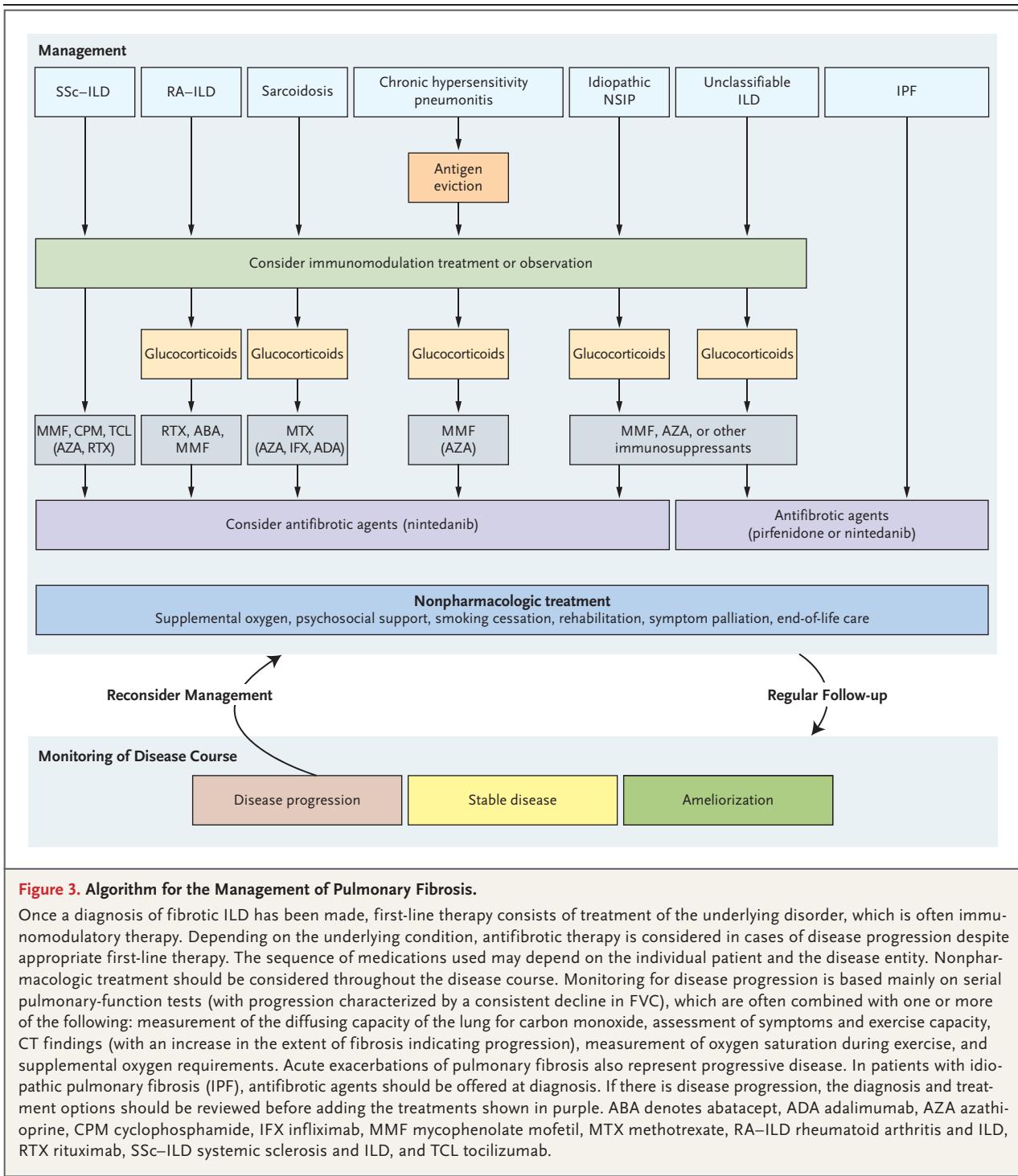
Figure 3. Algorithm for the Management of Pulmonary Fibrosis.

Once a diagnosis of fibrotic ILD has been made, first-line therapy consists of treatment of the underlying disorder, which is often immu-nomodulatory therapy. Depending on the underlying condition, antifibrotic therapy is considered in cases of disease progression despite appropriate first-line therapy. The sequence of medications used may depend on the individual patient and the disease entity. Nonphar-macologic treatment should be considered throughout the disease course. Monitoring for disease progression is based mainly on serial pulmonary-function tests (with progression characterized by a consistent decline in FVC), which are often combined with one or more of the following: measurement of the diffusing capacity of the lung for carbon monoxide, assessment of symptoms and exercise capacity, CT findings (with an increase in the extent of fibrosis indicating progression), measurement of oxygen saturation during exercise, and supplemental oxygen requirements. Acute exacerbations of pulmonary fibrosis also represent progressive disease. In patients with idio-pathic pulmonary fibrosis (IPF), antifibrotic agents should be offered at diagnosis. If there is disease progression, the diagnosis and treat-ment options should be reviewed before adding the treatments shown in purple. ABA denotes abatacept, ADA adalimumab, AZA azathi-oprine, CPM cyclophosphamide, IFX infliximab, MMF mycophenolate mofetil, MTX methotrexate, RA–ILD rheumatoid arthritis and ILD, RTX rituximab, SSc–ILD systemic sclerosis and ILD, and TCL tocilizumab.

MANAGEMENT

For most patients, a diagnosis of pulmonary fi-brosis is a life-altering verdict. The uncertainty about prognosis in combination with an increas-ing symptom burden has a major effect on the quality of life of patients and their family mem-bers. According to the underlying condition, treatment can be aimed at ameliorating the dis-ease or slowing down disease progression while improving or maintaining quality of life[45] (Fig. 3).

Educating patients and sharing decisions are

important, especially since there are many off-label treatment options with potentially serious side effects. Preventing exposures and events that may drive further disease progression is essential. Avoidance of the offending antigen in patients with CHP and cessation of tobacco smoking are priorities. Pneumococcal and influenza vaccinations are recommended. On the basis of expert opinion, supplemental oxygen is indicated in patients with resting hypoxemia (partial pressure of arterial oxygen [Pao_2] of <55 mm Hg, oxygen saturation as measured by pulse oximetry of <89%, or Pao_2 of <60 mm Hg and cor pulmonale or polycythemia).[46] Pulmonary rehabilitation[45] and use of ambulatory oxygen in patients with isolated exertional hypoxemia[47] improve the quality of life, reduce breathlessness, and increase walking ability. Identification and accurate treatment of coexisting conditions are essential. Lung transplantation is an option in select patients, although extrapulmonary disease or severe coexisting conditions may disqualify some patients, especially those with CTDs, from consideration as candidates for transplantation.[48] For many patients, the focus is on palliative care.[49]

Decisions about pharmacologic treatment are guided by the underlying diagnosis and by the disease course. For patients with IPF, treatment with antifibrotic drugs (pirfenidone or nintedanib) is recommended.[50] In most cases of fibrosing ILD other than IPF, immunomodulation with the use of glucocorticoids, immunosuppressive therapy, or both is indicated and is generally used as first-line therapy if there is a suspicion of inflammation-driven disease.[18,37,51] Except for SSc–ILD and sarcoidosis, however, the evidence in support of this approach is very weak.[51] In patients with a UIP pattern, there is theoretical concern that immunosuppression may not be beneficial or might even be harmful, as was previously shown in IPF.[52]

Nintedanib has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for patients with SSc–ILD and for patients with chronic fibrosing ILDs with a progressive phenotype. This agent is not associated with an improvement in function but reduces the decline in FVC by about half,[41] supporting the notion that progressive pulmonary fibrosis may be amenable to antifibrotic therapy regardless of the underlying specific disease. Pirfenidone reduces disease progression in patients with progressive, unclassifiable, fibrotic ILD.[44] In considering pharmacologic treatment, the benefit of long-term preservation of lung function should be balanced against the risk of side effects. Many questions remain, however, about appropriate timing and sequence of these treatments.

FUTURE DIRECTIONS

Pulmonary fibrosis is a pathologic process that stems from multiple underlying causes. Monitoring disease progression has become a priority in guiding treatment decisions. We hope that, in the coming years, different biomarkers and novel techniques such as molecular classifiers[53] will provide more insights into assessing and monitoring fibrosis-driven as compared with inflammation-driven disease activity, resulting in more individualized targeted treatments, since it is clear that a "one size fits all" approach does not apply to the broad spectrum of fibrosing diseases. Current research efforts may lead to earlier diagnosis and interventions to prevent, halt, and potentially reverse the development of life-limiting lung fibrosis.

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