Special REPORT

Chronic Fibrosing Interstitial Lung Disease With a Progressive Phenotype:

A Multidisciplinary Roundtable Discussion

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Introduction

Interstitial lung disease (ILD) refers to a diverse group of noncancerous, rarely occurring pulmonary disorders comprising greater than 200 individual disease entities with similar clinical, diagnostic, physiologic, or pathologic features.[1-3] These conditions include autoimmune diseases that involve the lung, drug-induced lung diseases, genetic disorders affecting the lung, and lung damage caused by occupational or environmental hazards.[1,2] Many ILDs have an etiology that is idiopathic in nature and are considered idiopathic interstitial pneumonias[4]; idiopathic pulmonary fibrosis (IPF) is the archetypal and most extensively studied ILD of this type. IPF occurs more commonly in men aged over 60 years and is characterized by progressive lung fibrosis, an irreversible decline in lung function, and high mortality.[5-8] Interstitial lung diseases other than IPF generally present at a younger age, occur at a more balanced ratio among men and women, and result in more heterogeneous and less severe patient outcomes.[6] However, several of these ILDs can evolve to a progressive fibrosing phenotype (Figure 1).[3,5]

In general, ILDs are associated with *restrictive* pulmonary effects compared with the *obstructive* pulmonary disorders (eg, asthma, emphysema, chronic obstructive pulmonary disease [COPD]) more commonly observed in clinical practice.[9] Although epidemiologic data on ILD occurrence in the general population are limited, the overall estimated prevalence in Europe is up to 76 cases per 100,000 people, and prevalence in the United States is 74.3 cases per 100,000.[6] The most commonly occurring fibrotic ILDs

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This special report was supported by Boehringer Ingelheim Pharmaceuticals, Inc.

include sarcoidosis, connective tissue disease (CTD)-associated ILDs, and IPF; their estimated crude prevalence is 30.2, 12.1, and 8.2 cases per 100,000 individuals, respectively.[10]

Of note, ILDs vary significantly with regard to prognosis, clinical course, monitoring strategy, and therapeutic management. Among ILDs that are reversible and self-limited, the treatment goal includes removing the inciting ILD etiology and observing the patient for 3 to 6 months to confirm that disease regression has not occurred. For progressive, irreversible disease that does not respond to therapeutic management, the goal is to slow progression and observe the patient long term to assess the disease course and need for lung transplantation or palliative care.[11] For example, respiratory bronchiolitis–associated interstitial pneumonia is often reversible and self-limiting, whereas IPF is commonly progressive and irreversible despite ongoing therapy.[11]

Overview of Diagnosis and Management Of ILDs

Patients who present with ILD often are misdiagnosed and may be administered various unproven therapies.[9] Diagnosis of an ILD can be complex and often requires extensive investigation to exclude other potential causes including asthma, COPD, or heart failure.[4,9] Once other potential conditions have been eliminated from the differential diagnosis, ILD should be considered in all patients with chronic dyspnea on exertion or those with a cough for more than several months.[9] Per the 2013 American Thoracic Society (ATS)/European Respiratory Society (ERS) statement, a diagnosis of ILD should be completed via a thorough review of clinical, pulmonary, radiological, and possibly histopathologic features.[11,12]

Clinical symptoms of ILDs (eg, dyspnea, cough) are often nonspecific; therefore, an ILD diagnosis may not occur until late in the disease process.[9] Marilyn Glassberg Csete, MD, a professor of medicine and the chief of the Division of Pulmonary Medicine, Critical Care, and Sleep Medicine at the University of Arizona in Phoenix, Arizona, noted that as a pulmonologist, she "often sees patients with ILD very late in the disease process, since often the primary disease manifestation is not pulmonary in nature. Generally, patients arrive symptomatic. They may or may not have gone to their primary care physician already, and ultimately, they are referred to our clinic. We also see patients referred by a rheumatologist who is concerned about progressive pulmonary symptoms. Our clinic sees a spectrum of ILD associated with autoimmune disease, including nonspecific interstitial pneumonitis, and progressing subtypes." Elana J. Bernstein, MD, MSc, an assistant professor of medicine at Columbia University Vagelos College of Physicians and Surgeons and the director of the Scleroderma Program at Columbia University Irving Medical Center, in New York, New York, concurred stating that many of her patients "are postponed in coming to our scleroderma program, and in those patients the ILD diagnosis is delayed. Typically, these patients are symptomatic; however, their physicians don't necessarily identify the presence of systemic sclerosis. Therefore, it may take a patient quite a while—sometimes years—to be seen by a rheumatologist, who will usually make the diagnosis, and then the patient may ultimately receive care at an expert scleroderma center. Unfortunately, many patients who receive a delayed diagnosis of systemic sclerosis also have ILD."

Patient History and Presentation

A complete medical history should be performed in patients with a suspected ILD diagnosis. This history includes a review

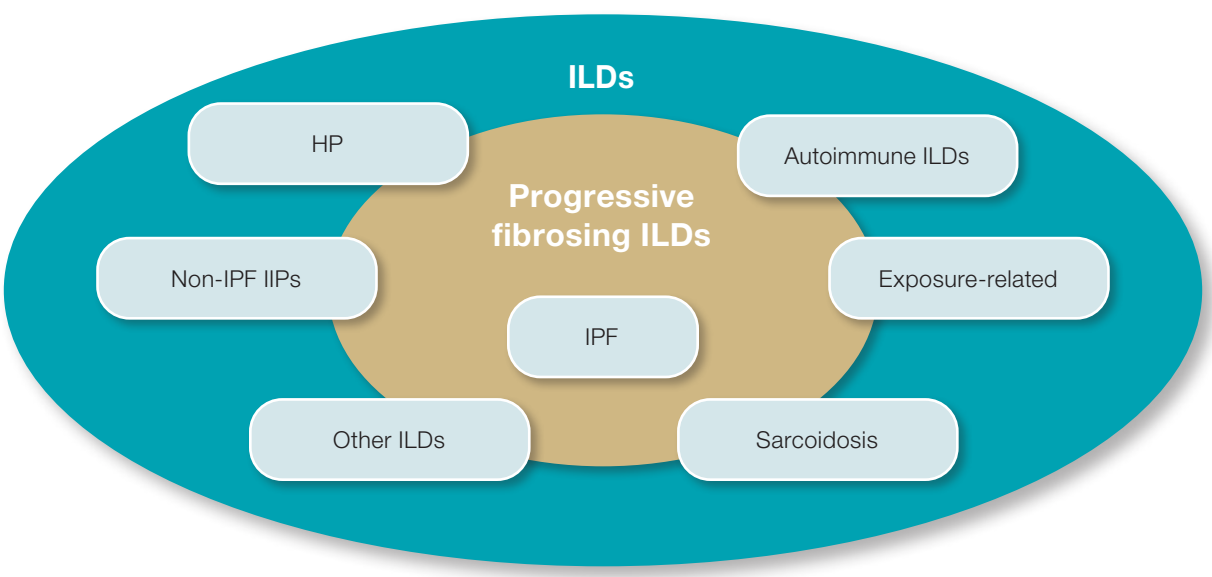

Figure 1. Types of ILD associated with a risk of developing a progressive fibrosing phenotype.

HP, hypersensitivity pneumonitis; **IIP,** idiopathic interstitial pneumonia; **ILD,** interstitial lung disease; **IPF,** idiopathic pulmonary fibrosis
Reprinted from Kolb M, Vasakova M. The natural history of progressive fibrosing interstitial lung diseases. *Respir Res.* 2019;20(1):57.

of smoking behavior, potential occupational exposures, locations frequently visited, medication use, and familial history; history may be extremely valuable in isolating a specific ILD type (Table 1).[13,14] The ATS advises that all clinicians use a standardized approach to gathering a detailed patient history when an ILD has been suspected.[15,16] Various published questionnaires are utilized for this purpose in clinical practice, including one from the American College of Chest Physicians.[17]

Beyond the extensive medical history, clinicians perform lung auscultation during the physical examination in order to listen for telltale *crackling* sounds upon inspiration.[9] A baseline chest radiograph also may be helpful in cases where findings from the physical exam are unclear and may be useful as a means to follow disease progression[1]; however, ILD should not be diagnosed by this imaging study alone, as it lacks specificity and sensitivity.[18] Geoffrey D. Rubin, MD, MBA, the chair of the Department of Medical Imaging and a professor of medical imaging at the University of Arizona College of Medicine in Tucson, Arizona, stated: "Radiographs always contain information so consequently there is utility; however, it is important to understand the limitations of a radiograph. In the setting of early ILD, the radiograph is frequently negative and may not show any abnormal findings. So, it is important to remember that a negative radiograph does not exclude the possibility of an ILD. I think the value of the radiograph principally in this setting is to identify other diseases that may, in fact, be causing the symptoms observed in the patient. For a person with a known ILD diagnosis, radiographs are probably most valuable in the setting of acute symptoms in order to assess if the patient has pneumonia or superimposed heart failure."

HRCT

A clinical picture suggestive of ILD should prompt the order of a high-resolution computed tomography (HRCT) scan. HRCT is the preferred imaging method for ILD diagnosis and monitoring.[1] Dr Rubin stated: "The assessment of ILD really is dependent upon having the correct HRCT technique, and attention to technique is really quite critical. For suspected ILD, patients routinely are positioned supine on the table, lying on their back. We want to be sure that we are acquiring scans with thin sections, ideally the thinnest sections that we can acquire. On modern scanners, that is going to be submillimeter section thickness, typically 0.5- or 0.6-mm section thickness. There are circumstances where acquiring at that thinnest section may work against the clinician, particularly in patients who are larger and for whom thin sections might suffer in image quality because of noise and an inability to sufficiently penetrate the chest wall.

Table 1. Key Areas of Questioning in a Comprehensive Medical History for ILD Diagnosis

Patient History	Risk Factor for ILD or ILD Complication
Environmental	Water intrusion/damage in home
	Water reservoirs inside or near home
	Exposure to mold
	Exposure to dusty environments
	Travel history
Hobbies/recreation	Exposure to birds or avian proteins
	Exposure to other animals
	Use of wind musical instruments
	Ceramics
Occupational	Exposure to birds or avian proteins
	Exposure to other animals
	Asbestos exposure
	Other dusts, gases, or fumes
	Use of respiratory protective gear
Smoking behavior	Cigars/cigarettes
	Marijuana
	Cocaine
	Other inhaled drugs
Medication use	Complete medication-use history
	Use of herbal medication
	History of medication for malignancy treatment
Family history	Incidence of ILD or ILD-related disease
	Inherited disease

ILD, interstitial lung disease

Based on reference 14.

Our guidelines recommend anything less than 2-mm section thickness. My advice would be to always try to get the thinnest sections, but if the patient is larger, going up to 1.0 or 1.5 mm may improve the overall quality of the image."

Dr Rubin noted, "When these images are acquired, we want them to be contiguous. There was a time in the past where diffuse lung disease was assessed with protocols, where we would sample various levels of the lungs, a 1-mm-thick section every 10 or 20 mm; however, this is no longer appropriate or standard of care for a high-quality ILD study. The reason is because we now appreciate the importance of assessing the lungs as 3-dimensional structures. Particularly when examining for findings, such as traction bronchiectasis or bronchiolectasis, and differentiating it from peripheral honeycomb cysts. Having the flexibility to evaluate the lungs through a variety of planes and perspectives allows for greater freedom to lay out the underlying anatomy and to be able to characterize it more effectively."

The HRCT scan "should be acquired in full inspiration and essentially total lung capacity. It's important that the technologists who are performing the scan communicate with the patient that goal up front, and ideally even practice with them by assisting them in taking some deep breaths in advance and preparing them for holding their breath. Again, on older scanners or in the past, when it would take 10 or 15 seconds to acquire the entirety of the lungs, it might be difficult for a person who has severe lung disease to suspend their ventilation and to hold their breath that long. But on modern scanners, it shouldn't take more than 2 to 3 seconds to cover the entirety of the lungs."

Dr Rubin added that "there are a couple of other techniques that get used with variable degrees of frequency in practice. One of them is the addition of prone imaging, which is where the patient rolls over and lies on their belly. Having a patient in the prone position and rescanning can help give a clearer evaluation of whether we're dealing with a fixed abnormality and early disease or whether what is observed on the scan is something that 'clears up.' Some practices with a high referral rate of ILD will routinely order prone exams as part of their protocol. The other technique is the use of expiratory imaging, which is where the scans are acquired not with total lung capacity but where we ask the patient to force the air out from their lungs as best as possible. The purpose here is to see if we can identify air trapping, which manifests as heterogeneity in the background lung attenuation. Air trapping occurs in regions that do not lighten on expiratory imaging. Expiratory scanning can particularly help to uncover regions where there is small airway disease that is preventing regions of the lung from adequately clearing gas during expiration."

Per the ATS/ERS/JRS/ALAT evidence-based guideline, HRCT is considered an essential part of the ILD diagnostic pathway and is critical for differentiating between the various ILDs.[15,16] This radiological imaging technique provides multiple benefits in the pulmonary setting: revealing alterations in lung structure, providing the opportunity for global anatomic assessment of the lung, and improving the sensitivity and specificity of the clinical diagnosis.[16,18] Dr Rubin noted that "a spectrum of findings" on HRCT may increase the suspicion of an ILD diagnosis (Figure 2).[14] This spectrum may include the "presence of reticulation, which is a term that applies to essentially a network of mesh-like or net-like lines. These lines, at their earliest stages, can occur in a very localized region in a diminutive quantity and then ultimately extend and expand involving larger portions of the lung. Certain types of ILD more commonly exhibit reticulation in the lower lungs, as opposed to presence in the upper and mid-lungs, which might indicate another disease. Honeycombing is another relevant finding on HRCT that is probably the most specific sign of pulmonary fibrosis. On HRCT, honeycombing appears as small clustered compartments or cysts that specifically align along the periphery of the lung. Early honeycombing may involve just 2 or 3 small peripheral cysts; however, its occurrence can extend to involve larger portions of the lung similar to reticulation."

Dr Rubin also stated that the presence of fibrosis is another characteristic finding of ILD,[14] and "fibrosis tends to disrupt the architecture or normal structure of the lungs and lead to pulmonary disorganization. Additionally, the presence of ground-glass opacity may be indicative of ILD. Ground-glass opacity refers to an increase in the general opacity or attenuation of the lungs. Its presence does not mean that there is a 'whiteout' of the lungs obscuring the underlying structures, but rather an increased opacity where underlying normal lung structures are still visible." Lastly, Dr Rubin noted that "the overall size of the lungs, particularly in the setting of later-stage disease, will be reduced on HRCT. This occurs since ILD is a restrictive process, and ongoing fibrosis tends to draw upon and essentially collapse the lungs or result in a reduction in lung expansion."

Serologic Testing

Serologic testing also plays a vital role in the evaluation of patients with ILD. In particular, for patients with suspected CTDs such as systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Sjögren's syndrome, and dermatomyositis/polymyositis, serologic testing may be useful as part of the overall constellation of symptoms and physical findings to confirm or eliminate a diagnosis.[16,19] Current guidelines note that there is generally disagreement regarding which specific serologic tests to perform. Routine serologic analysis may include C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor, anti–cyclic citrullinated peptide antibody, and antinuclear antibody titer and pattern.[16] However, several other serologic tests, including creatine kinase, antisynthetase antibodies, and scleroderma-associated antibodies, among many others, can further narrow the differential diagnosis in the appropriate clinical context.[15] Other clinical tests that may be appropriate for individual patients, depending on their symptoms, characteristics, and family history, include a baseline metabolic panel, a complete myositis panel, HIV testing, urinalysis for signs of renal failure, and screening for antiphospholipid antibodies.[12-14,16] With regard to serologic workup, Dr Glassberg said, "I try to tailor my serologic workup toward patient symptomatology; therefore, a classic presentation with dry eyes or dry mouth results in a patient undergoing a Sjögren's workup, and muscle complaints result in a myositis workup, etc. However, if overlapping symptoms exist, then the patient will generally receive a whole cadre of tests that are sent out to specialized testing centers." From Dr Bernstein's perspective, serologic testing is evaluated "in conjunction with symptoms and physical exam findings. Some of the autoantibodies, for example, are more associated with ILD than others. But none of the antibodies, in and of themselves, are diagnostic in isolation."

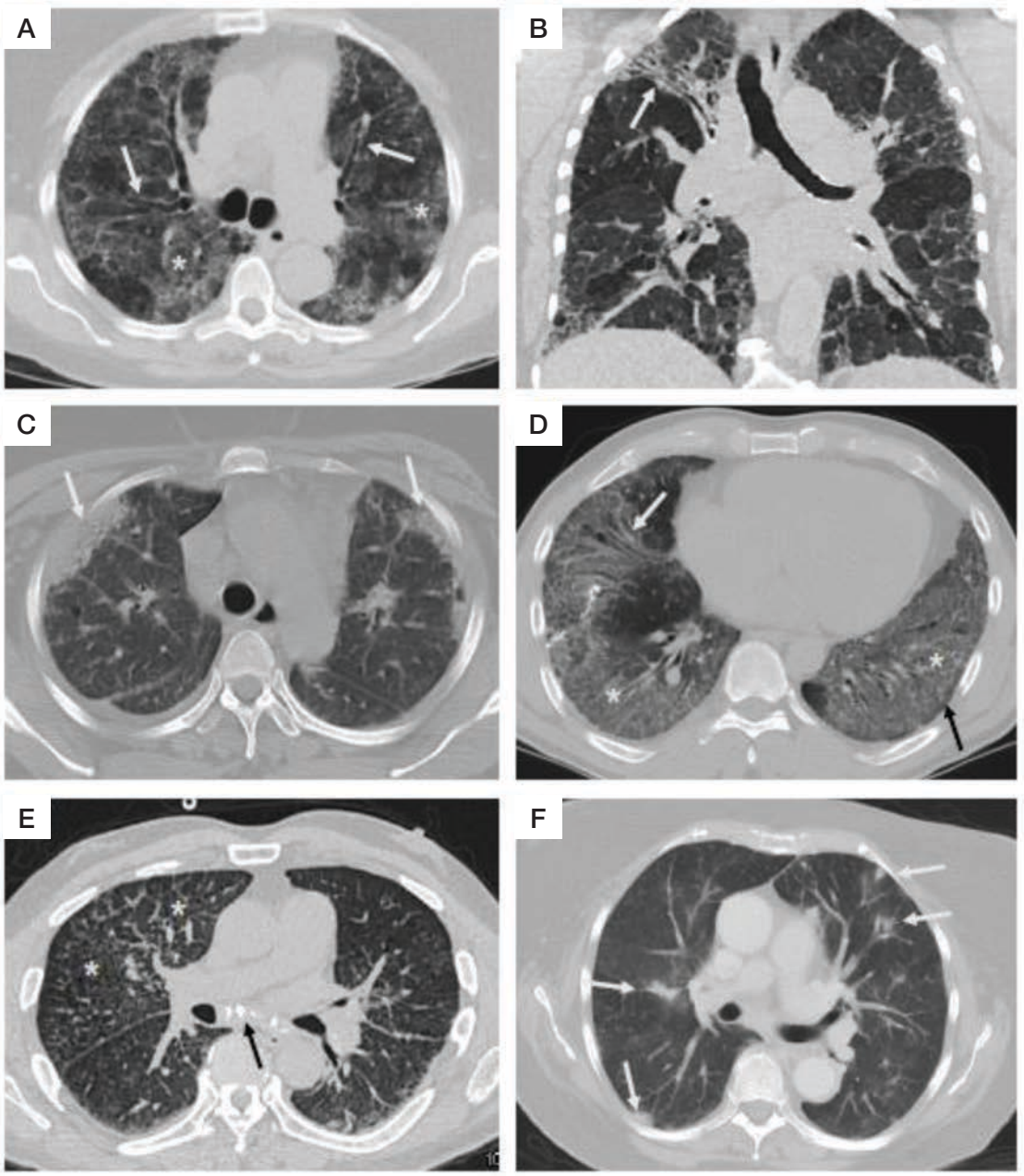

Figure 2. Common radiological patterns observed on HRCT imaging in various forms of ILD.

(A) Widespread GGO (asterisk) and accompanying traction bronchiectasis (arrows); overall clinical diagnosis was smoking-related ILD. **(B)** Findings of fibrosis in the right upper lobe with traction bronchiectasis and volume loss (arrow), and widespread areas of bilateral mosaic attenuation, defined as interspersed areas of hyperattenuated lung (gray) and hypoattenuated lung (black); overall clinical diagnosis was hypersensitivity pneumonitis. **(C)** Peripheral areas of consolidation (arrows); overall clinical diagnosis was ILD secondary to SLE. **(D)** Widespread areas of GGO (asterisk), mild sparing of the extreme periphery of the lung (black arrow), and mild traction bronchiectasis (white arrow); overall clinical diagnosis was ILD secondary to anti-synthetase syndrome. **(E)** Small nodules, reticular opacities, and prominent interlobular septa in the right upper lobe (asterisk) and to a lesser extent in the left lower lobe, along with calcified mediastinal adenopathy (arrow); overall clinical diagnosis was ILD secondary to chronic beryllium exposure. **(F)** Multiple ill-defined nodules (arrows) along with surrounding GGO; overall clinical diagnosis was ILD secondary to amiodarone.

GGO, ground-glass opacity; **ILD,** interstitial lung disease; **HRCT,** high-resolution computed tomography; **SLE,** systemic lupus erythematosus

Reprinted from Kalchiem-Dekel O, Galvin JR, Burke AP, et al. Interstitial lung disease and pulmonary fibrosis: a practical approach for general medicine physicians with focus on the medical history. *J Clin Med*. 2018;7(12):476.

6-Minute Walk Test

Patients with suspected ILD may also undergo a 6-minute walk test, whereby the patient's peripheral oxygen saturation (SpO_2) is measured before and after walking for 6 minutes, or a period of time sufficient to elicit exertional dyspnea.[20] A 3% drop in SpO_2 during the initial walk test indicates exertional desaturation and may dictate the prescription of supplemental oxygen therapy.[21] After the initial determination of desaturation, the patient walks again with oxygen titration in an attempt to determine the oxygen flow required to prevent desaturation below 86%. The patient's total distance walked is a key end point.[20] Dr Glassberg noted that "all patients with ILD have a walk test" during their appointments at her clinic. Before performing the 6-minute walk test, "These patients undergo a full exam and are asked functional questions, as it is important to be aware of the subtleties of what they're able to perform and their limitations," she said.

Pulmonary Function Testing

Pulmonary function testing (PFT) is another useful method for gauging the extent of disease and serially monitoring the disease course.[6] This testing is obtained in virtually all patients with ILD. Pulmonary function testing is most commonly done using spirometry, a procedure during which patients are asked to take a maximal inspiration and then forcefully expel air for as long and as quickly as possible. Measurements derived from this test include forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and the ratio of both (FEV_1/FVC).[22,23] Calculation of FEV_1/FVC allows identification of airway obstruction. Although spirometry is not diagnostic for ILD, it can be useful for eliminating the presence of obstruction and ruling out COPD.[6] Full PFT includes measuring the diffusing capacity of the lungs for carbon monoxide (DLCO), partial pressure of oxygen in arterial blood (PaO_2), and SpO2, which is useful, as reduction in DLCO often is one of the first lung function abnormalities to be noted in certain ILDs, such as IPF, and may adversely affect both PaO_2 and SpO_2, especially with exertion.[15] Dr Bernstein commented on the importance of PFTs in the various patient populations she commonly interacts with in clinical practice and the importance of comanagement with a pulmonologist. For her patients with systemic sclerosis, Dr Bernstein noted that all "receive full PFTs at baseline including spirometry, lung volumes, and DLCO." For patients with rheumatoid arthritis, Dr Bernstein stated that "screening guidelines are less clear; therefore, not all rheumatologists order screening PFTs in this setting." However, she does "routinely order PFTs in these patients, not just because of the possibility of ILD, but because patients with rheumatoid arthritis can also experience airway disease." Dr Bernstein also routinely orders PFTs in patients with dermatomyositis/polymyositis, but less routinely in patients with Sjögren's syndrome and systemic lupus erythematosus, unless there is a clinical indication.

Surgical Lung Biopsy

Historically, surgical lung biopsy was a major tool used for the diagnosis of ILD due to its diagnostic sensitivity. However, surgical lung biopsy can be associated with complications in high risk patients; thus, some clinicians are reluctant to subject patients to risks associated with the procedure.[1,3] Dr Glassberg noted that "from a pulmonary standpoint, we really stay away from lung biopsy in ILD unless there is the possibility of a malignancy, such as a suspicious nodule or an infiltrate that may look like bronchoalveolar cell carcinoma; we use the HRCT of the chest to guide us."

Management Approach in ILD

Once an ILD diagnosis has been established through a formal multidisciplinary discussion or input from the pulmonologist, radiologist, rheumatologist, and possibly pathologist in an informal setting, patient management should include ongoing education, support, and adequate control of symptoms and comorbidities.[24] The goals of relieving symptoms and improving quality of life may be more easily reached when patients are well informed about the natural history of their disease and seek care for complications. Management often is individualized due to the limited proven therapies, the heterogeneity in disease progression, and patient preferences regarding supportive care.[25] Symptom relief of comorbid conditions, including serious and life-threatening illnesses such as pulmonary hypertension and obstructive sleep apnea, and more frequently occurring diseases such as gastroesophageal reflux disease (GERD), should be included in a comprehensive management strategy that permits patients to maximize their participation in normal activities of daily living.[13,25]

Regarding GERD, patients with IPF and other ILDs experience an increased incidence, with some reviews suggesting an association between the treatment of GERD and increased survival and other reviews showing no benefit.[26-28] There has also been increasing evidence linking esophageal involvement with the development of ILD in certain patients, such as those with systemic sclerosis. Patients with active GERD may ultimately develop more progressive systemic sclerosis–related ILD, although data remain unclear on the relationship.[29] Appropriate GERD management in patients with ILD may include proton pump inhibitor administration in conjunction with nonpharmacologic approaches (eg, wedge pillow usage).[30]

Counseling patients about appropriate lifestyle changes also is essential. These changes may include improvements in nutrition, increased exercise, or weight loss.[13] An important lifestyle change for patients with ILD is smoking cessation. Although some studies have found an association between smoking and increased survival in patients with some forms of ILD, this relationship is unclear. For example, it is suspected that smokers who develop IPF have longer survival simply because these individuals are more likely to recognize disease symptoms and seek diagnosis and treatment earlier than their nonsmoking counterparts.[31,32] Beyond any potential direct impact on ILD, smoking is a risk factor for several comorbidities.[33] The care team also should help patients take steps to avoid other comorbidities. Because patients with ILD are at an increased risk for infection, they should receive seasonal influenza vaccines along with the pneumococcal and pertussis vaccines.[34] Patients also should be counseled to avoid contact with people who are sick and be proactive about reporting any signs of illness.

Oxygen supplementation is an example of a nonpharmacologic intervention that may improve quality of life in some patients with ILD, particularly those experiencing extreme hypoxia.[15] Research has demonstrated the benefits of oxygen

supplementation in other pulmonary diseases, including COPD.[35] Ambulatory oxygen is frequently used in ILD, as in some cases, it may be able to improve oxygen saturation and quality of life, potentially allowing the patient to participate in normal daily activities.[25,36]

Clinicians can improve the overall well-being of patients by recommending pulmonary rehabilitation. Several small studies over the past decade have demonstrated the efficacy of pulmonary rehabilitation in patients with ILD, such as those with IPF. Pulmonary rehabilitation provides significant short-term improvements in functional exercise capacity, quality of life, and perception of dyspnea. In addition, a continued program of exercise-based pulmonary rehabilitation results in increased oxygen uptake and improved physical conditioning, all of which can improve the overall health of patients with ILD.[37-40]

In some cases, a lung transplant may be the only acceptable option, especially for those patients whose disease progresses despite maximized medical therapy.[41,42] The optimal timing of this procedure, which is costly and limited by donor organ availability, is unclear.[41,42] As a result, many patients receive pharmacologic therapies aimed at reducing the decline in lung function.[1] Regarding lung transplant, Dr Glassberg stated: "The lesson in lung transplant is early referral. Don't wait until the FVC has declined below 50% and the patient is oxygen dependent. What we want to see is early referral of a patient who has a recent requirement for supplemental oxygen. A late referral is the patient who is on 6 to 8 L of oxygen, can no longer walk, and is not participating in a pulmonary rehabilitation program." Dr Bernstein added that there is "extensive testing and patient education that needs to happen before a patient is listed for a lung transplant, so that's another reason why it's critical to refer early. A lot of patient and family counseling needs to occur to assure that patients have strong support prior to transplant listing."

No formal guidelines exist recommending how often patients should undergo HRCT or serial PFT once an ILD diagnosis has been established. However, regular testing intervals are usually necessary even in relatively asymptomatic patients with mild disease. Some clinicians will engage in shared decision making with patients and engage in an approach of watchful waiting before initiating therapies that have side effects, which may affect quality of life.[1,3] Dr Bernstein stated that in her clinical practice, she certainly has "patients who are not in favor of medication who have normal PFT and no severe symptoms, where watching is acceptable. In that case, I present the risks of what could happen if their disease progresses, but ultimately, it's the patient's decision regarding treatment. I monitor these patients every 3 months typically and routinely ask about their dyspnea and cough, complete a physical exam, perform serial PFT as necessary, and review the patient with the pulmonologist."

Chronic Fibrosing ILD With Progressive Phenotype

Overview

The terminology "chronic fibrosing ILD with progressive phenotype" is newer to the lexicon and is used to describe IPF and other progressive fibrosing ILDs that share similar clinical, radiological, and pathologic presentations. These similarities suggest that fibrosing ILDs with a progressive phenotype may share common pathophysiology.[3] Most patients with this ILD type exhibit a combination of inflammation and fibrosis and experience varying therapeutic responses to immunomodulatory agents.[6,43] Figure 3 identifies the types of ILD (in boldface) that radiologists and pulmonologists associate with a progressive fibrosing phenotype.[3] Dr Bernstein acknowledged that she does "not use the term chronic fibrosing or chronic fibrosing progressive ILD currently in clinical practice," which may reflect its relatively recent uptake. However, she does "discuss with patients whether their ILD is progressive or not based on PFT, symptoms, and repeat HRCT imaging, and there does seem to be a final common pathway in many of these patients." Specifically, Dr Bernstein "feels like patients with rheumatoid arthritis are a bit more likely to develop chronic progressive fibrosing ILD" from what she has observed in practice.

Limited data have assessed the prevalence and associated mortality of this ILD subtype. In a 2017 multinational survey of pulmonologists, rheumatologists, and internists, respondents estimated that 18% to 32% of patients who have been diagnosed with a non-IPF ILD will develop a progressive fibrosing phenotype.[44] Results from this same publication demonstrated that these patients experience significant delays in diagnosis and detection of progressive fibrosis, and that the estimated time from symptom onset to death was 61 to 80 months.[44]

Overall, progressive fibrosing ILDs are associated with high mortality[5]; however, estimates of survival time vary depending on the population studied. For example, median post-diagnosis survival is 3.2 years in patients with IPF[45] and 11.2 years from the initial HRCT revealing ILD among patients with systemic sclerosis.[46] Various factors that predict mortality in patients with progressive fibrosing ILDs have been identified, including a decreased FVC and DLCO. In particular, a decline in FVC greater than 10% predicted is a well-established mortality predictor among these patients[47]; however, smaller annual declines in FVC also may become substantial when added up over years.[5] Of note, composite scoring systems (eg, the GAP model) have been developed as a means to predict mortality in patients with IPF, a common type of progressive fibrosing ILD[48]; however, these systems offer limited value in accurately predicting disease progression in an individual patient.[5]

Diagnosis

The diagnosis of ILD generally involves a multidisciplinary approach with pulmonologists, radiologists, pathologists, and other relevant health care providers giving input based on a comprehensive evaluation of a patient's medical history, physical examination, PFT, serology, and HRCT imaging as well as surgical lung biopsy results, if available.[24] Although there is no universally accepted approach to the diagnosis of fibrosing ILD with the progressive phenotype, Cottin et al have proposed a diagnostic algorithm (Figure 4) that can be used by clinicians reviewing cases suspected of having the progressive phenotype.[3]

Assessment of Progressive Disease

How to definitively assess disease progression in patients with chronic fibrosing ILD is unclear, and there is even debate in how the term *progression* should be defined.[3] Although there is no consistently accepted definition, researchers have proposed criteria based on changes in FVC, DLCO, patient symptoms, and radiological appearance (Table 2).[49,50]

As seen in the Cottin diagnostic algorithm (Figure 4),[3] monitoring of disease progression through clinical assessments, serial PFT, and follow-up HRCT is key to establishing a diagnosis of progressive disease (Figure 5).[5] Weekly or possibly even daily measurement of FVC using home spirometry may provide a more accurate picture of disease progression and facilitate rapid therapeutic decision making.[51,52] Regarding identifying progression of lung disease, Dr Glassberg stated that in her experience, "it does have a lot to do with patient symptoms, and that loss of FVC is a surrogate that correlates with decreased survival. Additionally, bronchiectasis, as assessed by HRCT and patient symptomatology, needs to be evaluated for frequency of exacerbation and overall patient quality of life. Worsening events or missed days of work is a good indicator of progression as is escalation of oxygen therapy. Exercise capacity is also important, and that's why involvement in pulmonary rehabilitation is recommended, so that patients maintain their physical activity."

HRCT is the preferred imaging method for ILD diagnosis and can also be used in monitoring for disease progression, differentiating between early versus advanced disease and identifying acute exacerbations.[1,18] The extent of honeycombing and reticulation and severity of traction bronchiectasis on HRCT have been used as predictors of mortality in patients with various forms of ILD. The extent of fibrosis may be indicative of a poor prognosis for patients with fibrosing ILDs, including those with little honeycombing.[53] However, overall data are conflicting with regard to the prognostic value of HRCT findings in ILD,

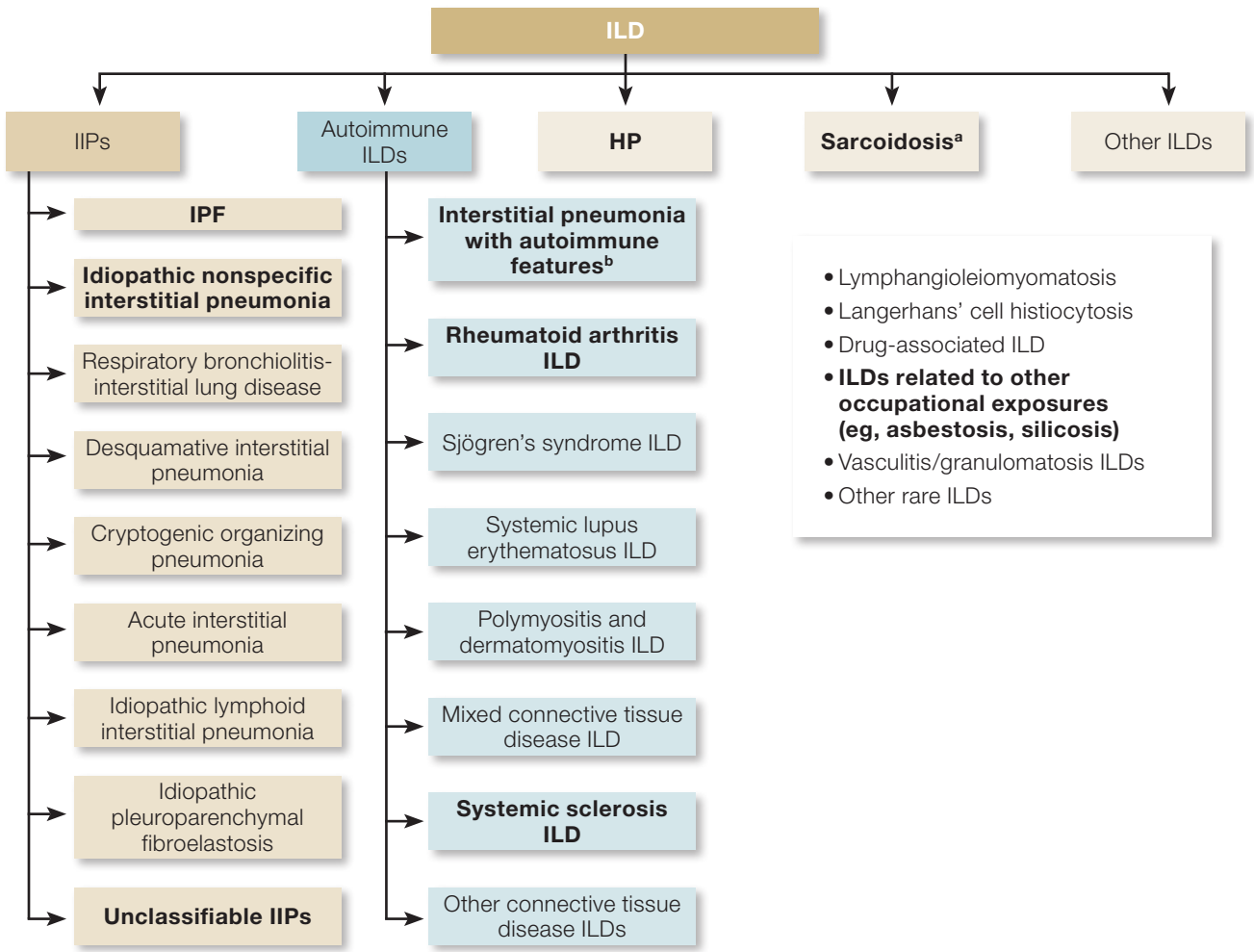

Figure 3. ILD types most likely to advance to a progressive fibrosing phenotype (indicated in bold).

[a] Stage 4 sarcoidosis only; [b] Not an established clinical diagnosis.

HP, hypersensitivity pneumonitis; **IIP,** idiopathic interstitial pneumonia; **ILD,** interstitial lung disease; **IPF,** idiopathic pulmonary fibrosis

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with some studies concluding that clinical, but not radiological, features are more predictive of survival.[18]

Regardless of any potential prognostic significance, serial HRCT imaging may be useful for assessing ILD progression through changes in the extent of honeycombing, reticulation, and fibrosis, although the ordering of serial scans is currently not routine practice.[18] Dr Bernstein noted that she "doesn't routinely order serial HRCTs; however, if a patient's symptoms progressed and their PFT has worsened, she would consider a repeat HRCT scan and discussion with the pulmonologist. In this situation, I'm interested in the degree of inflammation compared to fibrosis and whether or not that ratio has changed. Has the inflammation led to more fibrosis? What is the extent of their ILD?" Although there is a lack of consensus regarding the necessity of serial HRCT imaging, this approach may allow detection of interstitial changes associated with various fibrosing ILDs with a progressive phenotype. However, patients with a progressive fibrosing ILD may experience deterioration in clinical parameters with a stable HRCT scan and are referred for workup of other potential causes including cardiac disease.[18]

Another important consideration regarding HRCT is that interpretation depends largely on a visual analysis of the scan, which limits accuracy and generally restricts description to vague terminology such as mild, moderate, or severe. This can lead to difficulty in assessing subtle changes on serial HRCT scans.[54] In order to combat this issue, quantitative imaging techniques are increasingly being used to identify pulmonary abnormalities and diagnose specific ILDs.[18] These techniques include histogram and complex textural-based analyses coupled with machine learning. Results from clinical studies have shown that outcomes of computer-assisted imaging can be correlated with PFT and patient-centric measures of dyspnea and functional disability.[55-58] Although results from these studies are promising, quantitative tools have not solved all the perceptual tasks that radiologists find most complicated to

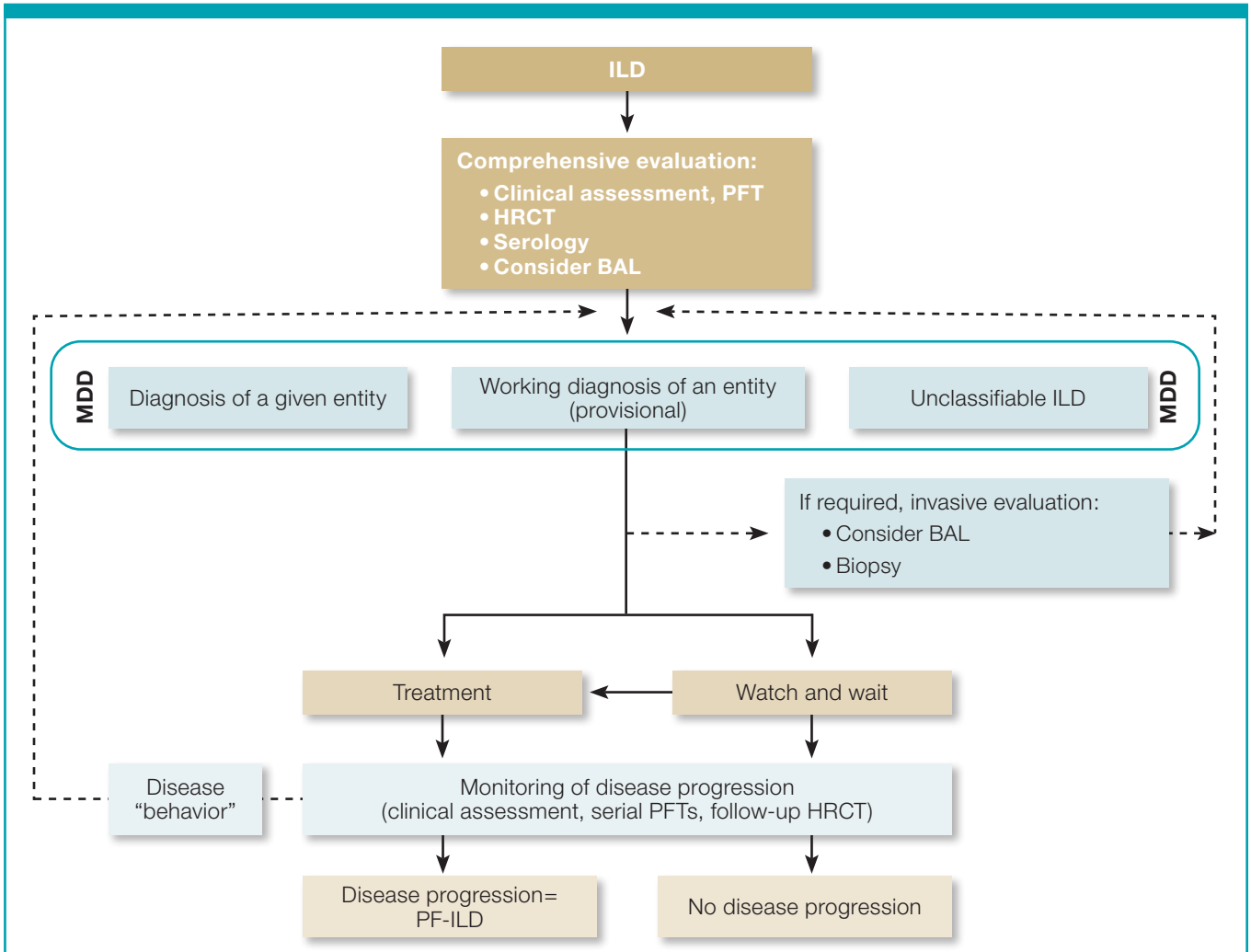

Figure 4. Proposed algorithm for the diagnosis of fibrosing ILD with a progressive phenotype.

BAL, bronchoalveolar lavage; **HRCT,** high-resolution computed tomography; **IIP,** idiopathic interstitial pneumonia; **ILD,** interstitial lung disease; **MDD,** multidisciplinary discussion; **PF,** pulmonary fibrosis; **PF-ILD,** progressive fibrosing interstitial lung disease; **PFT,** pulmonary function test

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perform, such as separating honeycombing from the occurrence of emphysema and traction bronchiectasis.[18] Dr Rubin commented on the ongoing advancement of imaging interpretation: "Artificial intelligence has been burgeoning in our world in general, even down to the level of interpreting CT scans. Artificial intelligence in this setting basically refers to using computer vision and analytical techniques to extract features within the lungs and display and quantify those features in a manner that the human brain isn't necessarily adept at doing. Regarding ILDs, there has been a strong interest in assessing whether or not computational neural networks can be trained to recognize reticulation or honeycombing, and even potentially identify specific patterns that we as human beings have not been able to recognize. These networks may be trained to patient outcomes or symptoms and observe whether associations can be identified in the CT images that are related to clinical circumstances such as progression.

"It is a really multidimensional question. At one level, the use of these analytical techniques can potentially be applied to uncover very early disease manifestations that might elude a radiologist, particularly those who don't evaluate ILD scans very frequently. There also is the possibility that use of these tools may result in better disease characterization. In other words, what may look like stable disease to the radiologist, to the computer may look like disease that is changing in a certain way or that may respond to a specific therapy. Another application for artifical intellengence and CT scans is to use the computer to quantify change, such as when a pulmonary region has increased in one dimension by 10% or reduced in another region by 5%."

Role of a Biomarker(s) in Progressive Fibrosing ILD

The World Health Organization defines a biomarker as "any substance, structure, or process that can be measured in the body or its products and influences or predicts the incidence of outcome or disease."[59] A variety of biomarkers are currently under evaluation in chronic fibrosing ILD with a progressive phenotype in order to potentially improve clinical classification of the various ILDs, predict prognosis, or monitor treatment response.[60] Table 3 presents biomarkers currently under investigation in chronic fibrosing ILD with a progressive phenotype and their mechanistic pathways.[61] Although most of the available data on biomarkers are in patients with IPF, there are ongoing studies in other chronic fibrosing ILDs with a progressive phenotype. However, no specific biomarker has been validated in a large, prospective, and adequately powered clinical study to date.[60]

Table 2. Proposed Criteria for ILD Progression

Patients have experienced disease progression if they meet any of the following criteria within a 24-mo period:
Relative decline of ≥10% in FVC
Relative decline of ≥15% in DLCO
Worsening symptoms or a worsening radiological appearance accompanied by a ≥5 to <10% relative decrease in FVC

DLCO, diffusing capacity of the lungs for carbon monoxide; **FVC,** forced vital capacity

Based on references 49 and 50.

Acute Exacerbations: Risk Factors and Management

Acute exacerbations in patients with chronic fibrosing ILD with a progressive phenotype may result in significant morbidity and signal disease progression. Exacerbations may occur at any time point in the ILD disease course and are characterized by rapid respiratory deterioration (eg, dyspnea, hypoxemia) with alveolar abnormality.[62] There is no uniformly accepted single definition of acute exacerbation for all fibrosing ILDs with a progressive phenotype.[62] However, per an international working group, acute exacerbation in the setting of IPF is defined as an acute clinically significant respiratory deterioration, typically less than 1 month in duration, characterized by evidence of new widespread alveolar abnormality not fully explained by cardiac failure or fluid overload.[63] On HRCT, an acute ILD exacerbation may present as a new diffuse, bilateral, ground-glass opacification superimposed on a background of chronic fibrotic changes; however, this may not consistently occur.[62]

Data on the incidence and prevalence of acute exacerbations among patients with fibrosing ILDs with a progressive phenotype are limited and vary widely between studies.[62] In IPF, the annual incidence of acute exacerbations has been reported between 8.5% and 14%, and potentially higher as acute exacerbations may not be reported due to diagnostic uncertainty.[64,65] In other ILDs where a segment of patients develop a progressive fibrosing phenotype, the highest acute exacerbation rates tend to be observed in patients with a radiological or histologic usual interstitial pneumonia pattern.[62] This includes patients with chronic hypersensitivity pneumonia, asbestosis, and CTD–associated ILD.[12]

Regarding risk factors for the potential development of acute exacerbations, data from retrospective studies in IPF suggest that exacerbations may be more commonly seen in patients with advanced disease.[63,65] For many patients with IPF who experience an acute exacerbation, no external triggers are identified.[63] However, limited evidence suggests that infection, lung biopsy, surgical resection, and various medications may precipitate an acute exacerbation of the disease process.[65] Acute exacerbations have been observed to occur more frequently during the spring and winter months when viral infections are more commonplace.[66]

The optimal management of acute exacerbations in ILDs is unclear, as no randomized controlled studies have been conducted in this setting.[62] For patients with IPF, guidelines recommend supportive care, symptom relief, and oxygen therapy as needed.[25] Corticosteroids are also often prescribed in the setting of an acute exacerbation in IPF due to the high observed mortality rate. Patients with idiopathic interstitial pneumonia, CTD–associated ILD, and selected cases of sarcoidosis and hypersensitivity pneumonitis also may be administered

corticosteroid therapy, although the benefit is questionable and the optimal regimen is undefined.[13,21] Clinicians should attempt to identify and eliminate any potential causative agents (eg, medications or exposures) if possible, particularly in patients with hypersensitivity pneumonitis.[13] Empirical antibiotic therapy may be considered to rule out or treat an infectious cause.[34] Immunosuppressives (eg, azathioprine, cyclophosphamide) also may be administered with corticosteroids; however, conclusive evidence supporting use of these agents is lacking.[13,44] An acute exacerbation in patients with IPF also may result in significant respiratory failure requiring mechanical ventilation; however, clinicians should weigh the risks and benefits of this intervention as the risk for mortality is high.[67] A minority of patients may require lung transplantation as a last resort after an acute worsening of ILD.[41,42] Extracorporeal membrane oxygenation (ECMO) has emerged as a potential treatment option for patients experiencing severe acute exacerbations. ECMO may minimize the risk for triggering underlying chronic processes that lead to fatal lung deterioration by providing pulmonary support, and may serve as a bridge to lung transplantation if needed.[42,62]

Management Approach

With regard to the overall management of patients with chronic fibrosing ILD with a progressive phenotype, the general approach is similar to that taken for patients with ILD. This includes ongoing patient education and support as well as adequate control of symptoms and comorbidities.[13,25] Pulmonary rehabilitation and supplemental oxygen therapy may improve quality of life.[25,36] Lung transplantation is an option in selected patients.[41,42] There are limited proven therapies for the treatment of chronic fibrosing ILD with a progressive phenotype[6]; immunomodulation with immunosuppressives and/or glucocorticoids is often administered despite weak published evidence for their use outside of sarcoidosis and systemic sclerosis–associated ILD.[6] However, several ongoing clinical trials are assessing the efficacy and safety of various nonpharmacologic and pharmacologic therapeutic options for patients with ILD.[68] Evidence-based treatment guidelines are lacking for the majority of ILDs except for IPF[69] and systemic sclerosis–associated ILD.[70] Overall, management decisions for patients with chronic fibrosing ILD with a progressive phenotype are hampered by a lack of high-quality evidence on the efficacy and safety of specific therapies.

Conclusion

Interstitial lung disease comprises hundreds of nonneoplastic pulmonary disorders with comparable clinical, diagnostic, physiologic, or pathologic features including those associated with autoimmune diseases, drug-induced lung diseases, genetic disorders, occupational-related lung damage, and lung disorders of unknown etiology.[1-3] Chronic fibrosing ILD

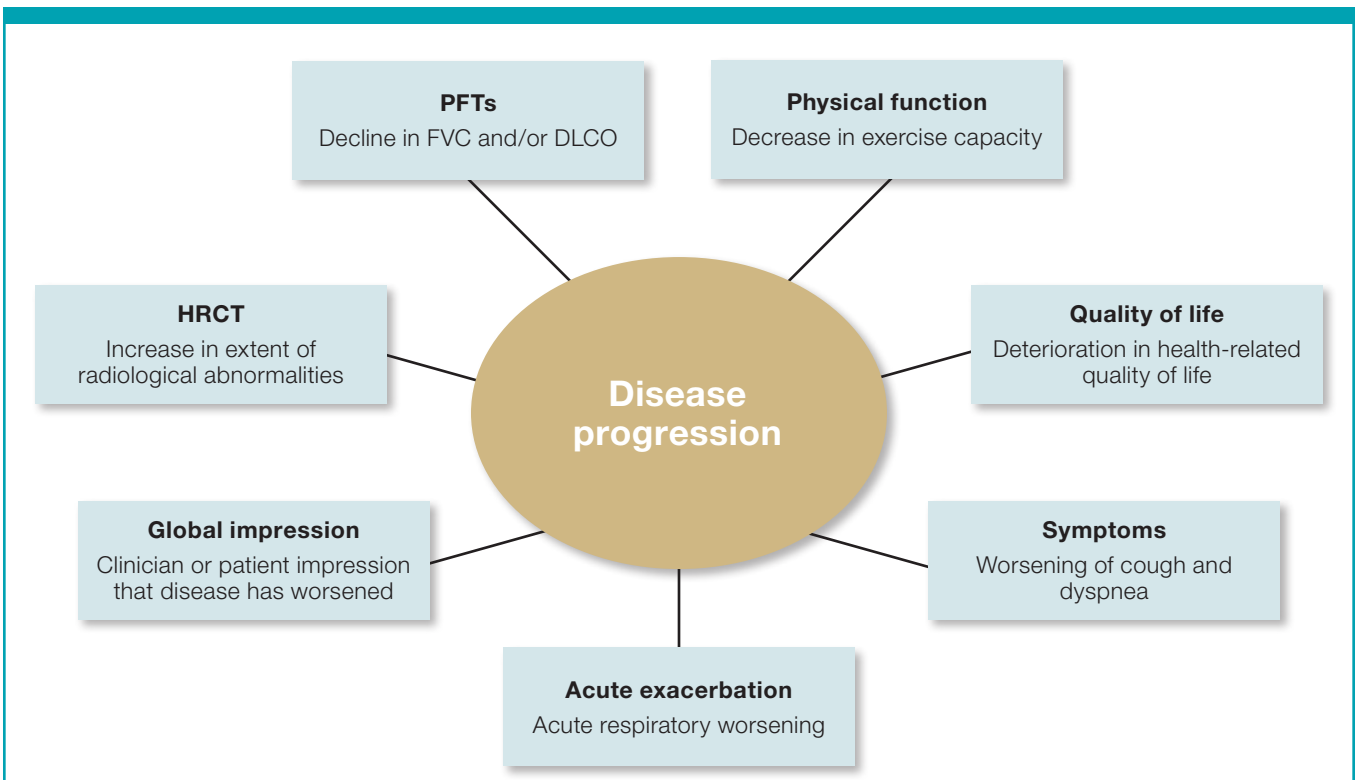

Figure 5. Factors that reflect progression of ILDs.

DLCO, diffusing capacity of the lungs for carbon monoxide; **FVC,** forced vital capacity; **HRCT,** high-resolution computed tomography; **PFTs,** pulmonary function tests

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Table 3. Biomarkers in Chronic Fibrosing ILDs With a Progressive Phenotype

Biomarker	Mechanistic Pathway	Disease
Risk and Predisposition Biomarkers		
MUCB5 **TERT** **TERC** **FAM13A** **RTEL1**	Epithelial cell dysfunction and ECM remodeling	IPF
TOLLIP **HLA**	Immune dysregulation	IPF
MUCB5	Epithelial cell dysfunction and ECM remodeling	Chronic fibrosing ILDs with a progressive phenotype • Rheumatoid arthritis-ILD
HLA	Immune dysregulation	Chronic fibrosing ILDs with a progressive phenotype • Sarcoidosis • Systemic sclerosis-ILD • Rheumatoid arthritis-ILD
Diagnostic Biomarkers		
MMP-1, MMP-7, other MMPs **IGFBP-2** **VEGF** **Periostin** **PAI-1**	Epithelial cell dysfunction and ECM remodeling	IPF
CXCL13 **S100A8, S100A9**	Immune dysregulation	IPF
KL-6 **SP-A, SP-D** **CC16** **MMP-1, MMP-7, MMP-12** **TIMP-1** **Periostin**	Epithelial cell dysfunction and ECM remodeling	Chronic fibrosing ILDs with a progressive phenotype • Idiopathic interstitial pneumonias • Hypersensitivity pneumonitis • Sarcoidosis • Asbestosis • Idiopathic nonspecific interstitial pneumonia • Systemic sclerosis-ILD • Rheumatoid arthritis-ILD • Cryptogenic organizing pneumonia
CCL18, CCL2 **CCL15, CCL18** **S100A8, S100A9** **CXCL10** **IL-4, IL-6, IL-7, IL-8** **IL-12, IL-18, sIL-2R** **Anti-topoisomerase I, anti-U1 RNP, anti-U3 RNP, anti-U11/U12 RNP, anti-endothelial cell antibodies** **CRP** **SAA** **Anti-MX1**	Immune dysregulation	Chronic fibrosing ILDs with a progressive phenotype • Systemic sclerosis-ILD • Rheumatoid arthritis-ILD • Sarcoidosis • Idiopathic nonspecific interstitial pneumonia

Biomarker	Mechanistic Pathway	Disease
Prognostic Biomarkers		
KL-6 **MMP-7** **SP-A, SP-D** **YKL-40** **ICAM-1, VCAM-1** **MUCB5, TOLLIP** **TERT, TERC** **CA 19-9** **CA-125** **Tenascin C**	Epithelial cell dysfunction and ECM remodeling	IPF
CCL18 **IL-6, IL-8** **LOXL2** **S100A12**	Immune dysregulation	IPF
KL-6 **SP-A, SP-D** **YKL-40** **MMP-7** **MMP-12, TIMP-1** **CC16** **Tenascin C** **CA 19-9** **CA-125** **VCAM-1**	Epithelial cell dysfunction and ECM remodeling	Chronic fibrosing ILDs with a progressive phenotype • Hypersensitivity pneumonitis • Sarcoidosis • Idiopathic nonspecific interstitial pneumonia • Systemic sclerosis-ILD
S100A9 **CCL2, CCL18** **IL-6, IL-2** **CRP** **IFN-γ** **CXCL4, CXCL10, CX3CL1** **CXCL13** **Anti-MX1** **Anti-citrullinated protein** **Chitotriosidase**	Immune dysregulation	Chronic fibrosing ILDs with a progressive phenotype • Hypersensitivity pneumonitis • Sarcoidosis • Idiopathic nonspecific interstitial pneumonia • Systemic sclerosis-ILD • Rheumatoid arthritis-ILD

CA, cancer antigen; **CC16,** 16-kDA Clara cell secretory protein; **CCL,** C-C motif chemokine ligand; **CRP,** C-reactive protein; **CX3CL1,** fractalkine; **CXCL,** C-X-C motif chemokine; **ECM,** extracellular matrix; **HLA,** human leukocyte antigen; **ICAM-1,** intercellular adhesion molecule 1; **IFN,** interferon; **IGFBP,** insulin-like growth factor–binding protein; **ILD,** interstitial lung disease; **IPF,** idiopathic pulmonary fibrosis; **KL-6,** Krebs von den Lungen-6; **LOXL2,** lysyl oxidase–like 2; **MMP,** matrix metalloproteinase; **MX1,** myxovirus resistance protein 1; **PAI-1,** plasminogen activator inhibitor-1; **RNP,** ribonucleoprotein; **S100,** S100 calcium-binding protein; **SAA,** serum amyloid A; **sIL-2,** soluble IL-2 receptor; **SP-A,** surfactant protein A; **SP-D,** surfactant protein D; **TIMP-1,** tissue inhibitor of metalloproteinase-1; **VCAM-1,** vascular cell adhesion molecule 1; **VEGF,** vascular endothelial growth factor; **YKL-40,** chitinase-3–like protein

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with a progressive phenotype refers to IPF and other progressive fibrosing ILDs that share similar clinical, radiological, and pathologic presentations, suggesting a common pathophysiology.[3] There is no universally accepted approach to the diagnosis of fibrosing ILD with a progressive phenotype; however, ongoing monitoring of disease progression through clinical assessments, serial PFT, and follow-up HRCT is key to establishing the presence of progressive disease.[3] Several biomarkers are under evaluation in patients with chronic fibrosing ILD with a progressive phenotype and may play a significant role in improving clinical classification of the various ILDs, predicting prognosis, or monitoring treatment response. However, no specific biomarker has been validated in a clinical trial setting to date.[60]

Acute exacerbations in the setting of chronic fibrosing ILD with a progressive phenotype can occur at any time, may cause rapid respiratory deterioration, result in significant morbidity and mortality, and indicate disease progression.[62] Management of acute exacerbations involves supportive care, symptom relief, oxygen therapy, and medication use as needed.[13,21,25]

The overall management of patients with chronic fibrosing ILD with a progressive phenotype is similar to the approach taken for patients with ILD. This approach includes ongoing patient education and support, adequate control of symptoms and comorbidities, enrollment in a pulmonary rehabilitation program, and supplemental oxygen therapy, as indicated.[25] For patients who have maximized medical treatment, lung transplantation may be an option.[41,42] Regarding pharmacologic therapies for this patient population, there are limited proven therapies; off-label immunomodulation with immunosuppressives and/or glucocorticoids is frequently prescribed even in the absence of high-quality published evidence supporting their use for the majority of progressive fibrosing ILDs.[6] Ongoing clinical trials are assessing the efficacy and safety of various nonpharmacologic and pharmacologic therapeutic options for patients with chronic fibrosing ILD with a progressive phenotype.

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Disclosures: Dr Bernstein reported that she has received honoraria from Boehringer Ingelheim, and has received grant/research support from Boehringer Ingelheim and Pfizer.

Dr Glassberg reported that she is a consultant to Bellerophon Therapeutics, Boehringer Ingelheim, and Genentech, and has received grant/research support from Roche/Genentech.

Dr Rubin reported that he is a consultant to Boehringer Ingelheim, Fovia, HeartFlow, and Nanox.

PC-US-119765

SR202 MAY 2021