Approach to the Diagnosis of Interstitial Lung Disease

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KEYWORDS

• Interstitial lung disease • Idiopathic interstitial pneumonia
• Diagnosis

Interstitial lung diseases (ILDs) are a heterogeneous group of more than 150 disease entities that differ significantly with respect to prevention, therapy, and prognosis. The current classification scheme of ILDs is shown in **Fig. 1**.[1]

The diagnostic strategy in a patient with ILD is based on considerations regarding the dynamic time course (acute, subacute, chronic), the cause (known or unknown), and the context of the disease at presentation (presence of extrapulmonary/systemic disease manifestations). **Fig. 2** summarizes the main disease categories that have to be differentiated during the diagnostic process.[1–3]

Once an interstitial disease process has been recognized in a patient, there are 3 crucial questions that have to be addressed in the diagnostic workup:

1. Is there a discernible cause for the disease?
2. If no cause is identifiable, is it idiopathic pulmonary fibrosis (IPF)?
3. If there is no cause of the disease and if it is not IPF, should surgical lung biopsy be recommended?

After a diagnosis has been established, the severity and dynamics of the disease have to be assessed and monitored, with or without therapy. Diagnosis and disease severity/dynamics are fundamental for treatment decisions and to predict prognosis. The diagnostic approach to ILD may have to be adapted to different clinical scenarios that eventually lead to presentation of a patient:

1. Patient presents with clinical symptoms (eg, dry cough, dyspnea).
2. Patient is at risk of ILD due to known exposures (eg, amiodarone, asbestos).
3. Patient is at risk of ILD due to family history.
4. Patient is asymptomatic but presents with chance finding on chest radiography or computed tomography.
5. Patient is asymptomatic but presents with chance finding on pulmonary functioning test (eg, restrictive pattern, reduced gas transfer).

This article deals with diagnostic approaches suitable for patients presenting with clinical symptoms of ILD in the first place.

CLINICAL EVALUATION

History Taking

A comprehensive patient history taking is of crucial importance for the diagnosis of ILD. There are 4 main questions to be answered: (1) when did respiratory symptoms start, (2) how did the disease develop over time to the present, (3) are there or have there been any exposures to

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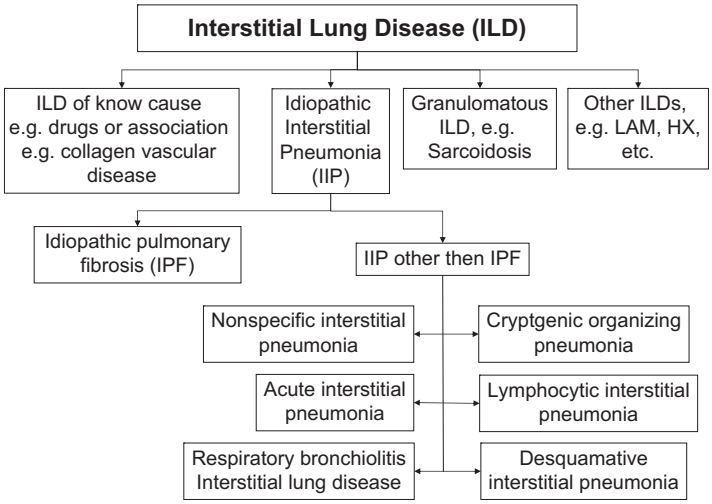

Fig. 1. Classification of ILDs. HX, histiocytosis X; LAM, lymphangiomyomatosis. (*Adopted from* American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002;165:279; with permission.)

etiologic agents known to cause ILD, and (4) what is the severity of symptoms at presentation.[1]

The disease chronology can be subdivided into 4 categories: (1) acute, days up to a few weeks; (2) subacute, 4 to 12 weeks; (3) chronic, longer than 12 weeks; and (4) episodic, ie, symptomatic phases that are followed by asymptomatic phases. In addition, all available radiographs of the lung should be reviewed to characterize the nature and development of the radiologic pattern. Flitting opacities on chest imaging studies may drive the differential diagnosis to focus on eosinophilic pneumonia,

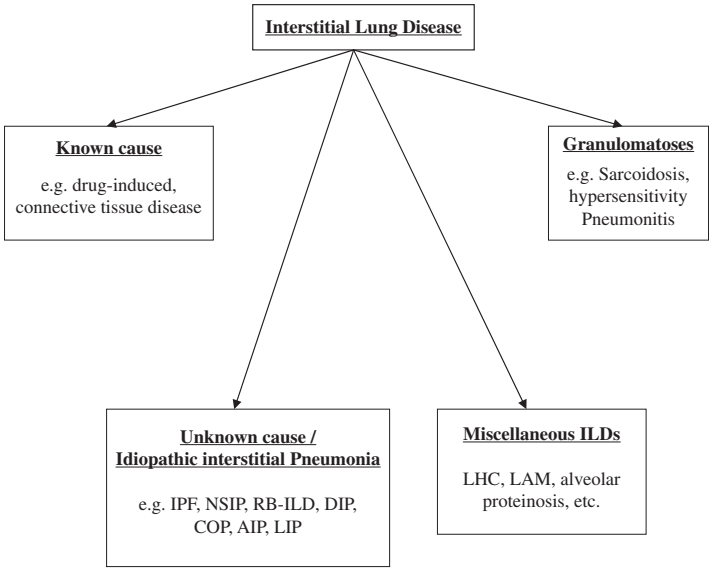

Fig. 2. Overview of different ILD disease categories. AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleiomyomatosis; LCH, Langerhans cell histiocytosis; LIP, lymphoid interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; RB-ILD, respiratory bronchiolitis and interstitial lung disease. (*Data from* American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002;165:279; with permission.)

hypersensitivity pneumonitis (HP), vasculitis, or organizing pneumonia.[1,3,4]

Assessment of Symptoms

Dyspnea with exertion or at rest is the predominant symptom in most ILDs.[5,6] It is of importance to accurately assess the degree of exercise limitation and dyspnea in a reproducible manner by asking specific questions: after what distance, after how many steps, or after how many stairs or floors does dyspnea occur and for how long has the patient experienced this degree of dyspnea and how fast did it develop or when was the most recent change. The degree of dyspnea is linked to disease severity and prognosis.[5] It is also necessary to exclude nonrespiratory symptoms as a cause of the exercise limitation, for example, joint pains, muscle pains, or weakness.

Cough is the second most frequent symptom in patients with ILD and sometimes becomes really bothersome. Although a dry cough is common in IPF, cough is generally an airway symptom and therefore more indicative of airway-centered diseases such as sarcoidosis, HP, or organizing pneumonia. Increased secretions from ILD-associated bronchitis or bronchiectasis cause productive cough. Wheeze is another airway-associated symptom that is infrequent in ILD but may occur in certain entities such as Churg-Strauss syndrome, HP (eg, pigeon breeder's lung), or airway-stenotic sarcoidosis.[7]

Pleural pain and effusion in the context of an ILD indicate connective tissue disease (eg, systemic lupus erythematosus or rheumatoid arthritis) or drug-induced or asbestos-related disease. Differential diagnoses include complications such as infections or pulmonary embolism. Hemoptysis is always an alarming signal and may indicate manifestation of pulmonary hemorrhagic syndromes, for example, Goodpasture syndrome or granulomatosis with polyangiitis (GPA, previously called Wegener disease). Alternatively, infections, lung cancer, or pulmonary embolism have to be considered.[3] Gastroesophageal reflux is another common symptom in patients with ILD that is suspected of causing or at least exacerbating ILD. A history of acid reflux should, therefore, be taken in all patients with ILD.[8]

Extrapulmonary features of associated diseases may provide important hints to the correct diagnosis. Therefore, joint pain and swelling (rheumatoid arthritis), cutaneous thickening, Raynaud phenomenon and dysphagia (systemic sclerosis), oculocutaneous albinism and colitis (Hermansky-Pudlak syndrome), chronic granulomatous sinusitis (GPA and Churg-Strauss syndrome), renal failure (Goodpasture syndrome), renal angiomyolipoma (lymphangioleiomyomatosis), and Crohn disease should be carefully asked and sought for.[2,3,7]

Next Step is a Comprehensive Investigation of Possible Causes for ILDs

Causative agents

A comprehensive history taking of all respiratory risk factors and exposures in the past and present is of utmost importance. Because history taking is a very complex and time-consuming task, it is often helpful to use a standardized questionnaire, as that available from the American College of Chest Physicians.[9] The following items have to be checked: (1) smoking history, (2) hobbies, (3) travel, (4) occupations, and (5) drug history and treatments (eg, radiation therapy).[3,10,11] Of special interest in this context is the family history as it becomes more and more clear that a considerable subset of patients and diseases do have hereditary traits.[2,3,12]

Comorbid diseases

There are several diseases that mimic or that are associated with ILDs: (1) Infectious agents such as mycobacteria, cytomegalovirus, *Pneumocystis jiroveci*, and human immunodeficiency virus (HIV) and parasite infestations are able to cause an ILD-like condition. (2) Connective tissue diseases are frequently associated with ILDs. This is especially the case for systemic sclerosis and rheumatoid arthritis. (3) Vasculitides, for example, GPA, Churg-Strauss syndrome, and microscopic polyangiitis, are able to manifest in the lungs as ILD.[3,7]

PHYSICAL EXAMINATION

On physical examination, inspection of the integument may reveal valuable findings: skin thickening and acral necrosis (scleroderma), oculocutaneous albinism (Hermansky-Pudlak syndrome), clubbing (up to 40% in all ILDs, up to 66% in IPF), livedo racemosa (systemic lupus erythematosus), cutaneous vasculitis (Churg-Strauss syndrome), and edematous-cyanotic skin (dermatomyositis, "disease lilac").[2,3,7] Palpation may reveal lymphadenopathy, hepatosplenomegaly pointing at sarcoidosis, HIV infection, or connective tissue disease.

On auscultation of the lungs, symmetric fine "Velcro-like" inspiratory crackles are found in more than 90% of patients with IPF and in about 60% of patients with connective tissue disease–associated ILD. Crackles are less frequent in HP and rare in sarcoidosis. Wheezing and inspiratory squeaks reflect bronchiolitis and/or bronchial obstruction and are associated with

Churg-Strauss syndrome, HP, and rarely nonspecific interstitial pneumonia.[1–3] Cyanosis may be present and should be confirmed by pulse oximetry, which can be easily performed in clinic.[2,3,7]

LABORATORY TESTING

There are no specific laboratory tests that allow for the diagnosis of an ILD, but, in an appropriate clinical setting, laboratory test results may be strongly supportive of a specific diagnosis. Routine laboratory testing should include a complete blood cell count; leukocyte differential; platelet count; erythrocyte sedimentation rate; determination of serum electrolyte levels, including calcium, serum urea nitrogen, and creatinine; liver function tests; and urinary sediment.[7] These laboratory values allow the exclusion or suggestion of an associated hematologic, liver, or kidney disease in a potential context of systemic disease (eg, sarcoidosis, vasculitis, amyloidosis), malignancy (eg, lymphoma), or infection (eg, tuberculosis, HIV). To further evaluate the presence of connective tissue disease, systemic disease (eg, sarcoidosis, connective tissue disease) or HP additional measures may be appropriate as summarized in **Table 1**.

There have been multiple attempts to find biomarkers to monitor disease activity or to predict prognosis in different ILDs. Intraindividual changes of serum angiotensin-converting enzyme activity or of serum concentration of the soluble interleukin 2 receptor are to some extent helpful in monitoring disease activity in sarcoidosis.[13] The serum lactate dehydrogenase activity is to some extent predictive of prognosis in IPF. Limited data are available for serum levels of Krebs von der Lungen 6, a high-molecular-weight glycoprotein representing human MUC1 mucin, surfactant proteins A and D, matrix metalloproteinases, and CCL-18.[3,14] However, none of these biomarkers have been validated sufficiently to be recommended for the routine use in the monitoring and follow-up of patients with ILD.

PULMONARY FUNCTION TESTING

Patients with ILD should undergo comprehensive pulmonary function testing, which includes arterial

Table 1
Useful laboratory tests for patients with ILD, beyond routine laboratory testing

Laboratory Test	Indication	Interpretation
ANA; rheumatoid factor; ANA differentiation, including Jo-1 or ScL-70 antibodies	Suspected CTD or idiopathic ILD for which CTD cannot be excluded	Low titers occur in up to 20% of patients with IPF, high titers suggest underlying CTD
Creatine kinase activity, myoglobin, aldolase	Suspected myositis	Elevated values support a diagnosis of dermatomyositis
Immunoglobulins	Suspicion of immunodeficiency	Decreased serum immunoglobulins suggest common variable immunodeficiency syndrome or LIP
c-ANCA, p-ANCA	Suspected vasculitis	c-ANCA suggestive of GPA (Wegener syndrome), microscopic polyangiitis p-ANCA suggestive of CSS or MPA
Antiglomerular basement membrane antibody	Hemoptysis due to DAH, renal failure	Positive result is diagnostic of Goodpasture syndrome
Serum angiotensin-converting enzyme activity, serum-soluble interleukin 2 receptor	Sarcoidosis	Low sensitivity and specificity
Specific serum IgG antibodies	Exposure to antigens that cause HP	Valid only within an appropriate clinical context

Abbreviations: ANA, antinuclear antibody; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody (antiproteinase 3); CSS, Churg-Strauss syndrome; CTD, connective tissue disease; DAH, diffuse alveolar hemorrhage; LIP, lymphocytic interstitial pneumonia; MPA, microscopic polyangiitis; p-ANCA, perinuclear antineutrophil cytoplasmic antibody (antimyeloperoxidase).

or capillary blood gas analysis at rest and eventually under exertion, spirometry and body plethysmography, as well as measurement of the diffusion capacity using carbon monoxide as a tracer in the single-breath method (DLco).[1,3,4,15] In addition, measurement of compliance may be helpful in objectifying the elevated stiffness of the lung.[15] Pulmonary function tests are in general not able to support a specific ILD diagnosis, but they are necessary to assess the respiratory limitations and to monitor the disease during follow-up.[2,3]

Lung function abnormalities generally reflect the effects of interstitial inflammation and scarring resulting in a restrictive ventilatory deficit and impaired gas exchange as well as reduced compliance. Airway obstruction and emphysema are not features of ILD, however, may be present when bronchial asthma or chronic obstructive pulmonary disease coexist in the patient. Moreover, some diseases such as lymphangioleiomyomatosis, Langerhans cell histiocytosis, sarcoidosis, and HP may present with airway obstruction and/or hyperinflation as part of the underlying disease process or associated bronchiolitis.[3,7] A disproportionate decrease of the DLco in comparison with the restrictive ventilatory deficit should prompt suspicion of emphysema or pulmonary hypertension (PH).[16]

During follow-up, changes in lung function parameters are widely used and helpful for disease monitoring.[2,3,15] Especially in IPF, a small decrease of only 5% to 10% of forced vital capacity during an observation period of 6 months is already indicative of increased mortality.[17] Less well established are changes of DLco and blood gases as prognostic predictors, but these parameters may well be used to support the clinical relevance of marginal changes in forced vital capacity. Calculated lung function indices may also be helpful to objectify the course and prognosis of the disease. The composite physiologic index (CPI) is such a calculated index that reflects the extent of fibrosis on high-resolution computed tomography (HRCT) and corrects for coexisting emphysema.[18] An increase in CPI indicates progression of fibrosis and is associated with increased mortality.[18–20]

RADIOLOGIC ASSESSMENT

An abnormal chest radiograph is often the initial finding in patients with ILD. A diffuse reticulonodular pattern, ground-glass opacities, or both are the most common findings on a chest radiograph in patients with ILD. The pattern and distribution of radiologic appearances contribute to initial diagnostic considerations as summarized in **Table 2**.[1–3,7]

For a more subtle diagnosis, HRCT is the key diagnostic procedure and is sufficient for diagnosis in a significant number of patients with IPF.[2] The criteria that aid in making a confident diagnosis of IPF are presented in **Table 3**.[3] HRCT findings suggestive of an alternative diagnosis other than IPF are shown in**Tables 4** and **5**.

Interpretation of chest radiographs and HRCTs should always include a complete review of all images available for a specific patient and should be done in direct communication between the pulmonologist and the radiologist to optimize the diagnostic yield.

BRONCHOSCOPY

In patients with ILD, bronchoscopy can be performed to obtain materials for microbiological, cytologic, and histologic analyses. The applied techniques encompass bronchoalveolar lavage (BAL), transbronchial lung biopsy (TBLB), and transbronchial needle aspiration (TBNA) for cytologic or histologic (Wang needle) analyses. However, bronchoscopy is associated with some morbidity and even a very low rate of mortality and therefore is not an obligatory diagnostic procedure for all patients with ILD.[2,3] Moreover, to make bronchoscopy and BAL/TBLB a valuable tool in the workup of patients with ILD, each clinical site must establish routine methods for handling and analysis of the materials.[2] Best use of this BAL/TBLB requires that the clinician identify very clear questions that are to be addressed with the biological materials obtained and that it is reasonable these questions can be answered with these materials before the procedure is performed. If these obligatory prerequisites are fulfilled, bronchoscopy and BAL with or without TBLB are valuable tools in the diagnostic workup of patients with ILD.[21]

With the use of BAL, TBLB, and/or TBNA (eventually endobronchial ultrasonography guided), a diagnosis of sarcoidosis, lymphangitis carcinomatosa, eosinophilic pneumonia, alveolar proteinosis, Langerhans cell histiocytosis, lymphoid interstitial pneumonia, and several bacterial, viral, and fungal infections can be confirmed, thus avoiding more invasive procedures such as mediastinoscopy, video-assisted thoracoscopic (VATS) biopsy, or open surgical lung biopsy. In several patients with probable or possible IPF, bronchoscopic techniques may be used to rule out alternative diagnoses, such as HP in selected patients,[21] especially if VATS biopsy seems too risky or has to be performed in elderly patients.

Table 2
Diagnostic considerations based on a chest radiograph

Low lung volumes	IPF; CTD-related ILD; chronic HP; asbestosis; chronic drug-induced fibrosis; chronic COP, CEP, or DIP
Preserved/increased lung volumes	RB-ILD, IPF plus emphysema, LCH, LAM, sarcoidosis, tuberous sclerosis, neurofibromatosis, bronchiolitis
Upper zone predominance	Sarcoidosis, silicosis, coal workers' pneumoconiosis, HP, LCH, berylliosis, CEP, Caplan syndrome, nodular rheumatoid arthritis
Lower zone predominance	IPF, CTD-associated ILD, asbestosis, DIP, chronic HP
Peripheral predominance	IPF, COP, CEP
Micronodular	Infection, sarcoidosis, HP, malignancy
Septa thickening	Malignancy, chronic left heart failure, infection, pulmonary veno-occlusive disease
Honeycombing	IPF, asbestosis, CTD-associated ILD, chronic HP, sarcoidosis
Migratory opacities	Löffler disease, COP, HP, ABPA
Kerley B lines	Chronic left heart failure, lymphangitic carcinomatosa
Pleural disease	CTD-associated ILD, asbestosis, malignancy, radiation-induced ILD, sarcoidosis
Pneumothorax	LCH, LAM, tuberous sclerosis, neurofibromatosis
Mediastinal/hilar lymphadenopathy	Sarcoidosis, malignancy, silicosis, berylliosis, CTD-associated ILD, infection
Normal (about 10%)	HP, NSIP, CTD-associated ILD, RB-ILD, bronchiolitis, sarcoidosis

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; CEP, chronic eosinophilic pneumonia; COP, cryptogenic organizing pneumonia; CTD, connective tissue disease; DIP, desquamative interstitial pneumonia; LAM, lymphangioleiomyomatosis; LCH, Langerhans cell histiocytosis; NSIP, nonspecific interstitial pneumonia; RB-ILD, respiratory bronchiolitis and ILD.

Table 3
Criteria diagnostic for IPF

UIP Pattern (All 4 Features)	Possible UIP Pattern (All 3 Features)	Inconsistent with UIP Pattern (Any of the 7 Features)
• Subpleural basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis • Absence of features listed as inconsistent with UIP pattern (see third column)	• Subpleural basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP pattern (see third column)	• Upper lung or midlung predominance • Peribronchovascular predominance • Extensive ground-glass abnormality (extent>reticular abnormality) • Profuse micronodules (bilateral, predominantly upper lobes) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/air trapping (bilateral, in $\geq$3 lobes) • Consolidation in bronchopulmonary segments/lobes

From Raghu G, Collard HR, Egan JJ, et al. An Official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:794; with permission.

Table 4
HRCT findings suggesting specific alternative diagnoses other than IPF

HRCT Features Atypical for IPF	Probable Diagnosis
Centrilobular nodules, air trapping, ground-glass opacities, relative sparing of bases	HP
Pleural effusion, pleural thickening, esophageal dilation	Collagen vascular disease
Pleural plaques, pleural thickening	Asbestosis
Focal abnormality	Localized scar

However, especially in patients with IPF, bronchoscopy and BAL have the potential of triggering acute exacerbation of IPF, so that the indication for bronchoscopic evaluation should be discussed critically in every individual patient.[2]

SURGICAL LUNG BIOPSY

Surgical lung biopsy, nowadays preferentially performed during VATS, is the most invasive diagnostic procedure used for diagnosis of ILD. It is associated with significant morbidity and mortality and should be reserved for those patients in whom the management and treatment could change depending on the result of biopsy.[2,3,22,23] In IPF, histologic analysis from a surgical lung biopsy is no longer the gold standard of diagnosis because it has become clear that because of sampling error and uniformity of disease pattern in patients with advanced disease, histologic examination will not provide the diagnostic clue in many patients.[2] Consequently, in IPF, the multidisciplinary discussion (MDD) involving the pulmonologist, radiologist, and pathologist has become the gold standard for diagnosis. This also seems the appropriate approach to diagnosis for the vast majority of patients with ILD. Because IPF is one if not the most important differential diagnosis in most patients with ILD, an MDD seems to be the most promising approach to reach a confident diagnosis.[2,24]

ASSESSMENT OF PH

PH is frequently associated with ILD. Among patients with advanced disease on the waiting list for lung transplantation, 40% to 80% have PH. In patients with less-advanced disease, still 10% have significant PH. Moreover, PH in ILD is clinically relevant because it is associated with an excess exercise intolerance and mortality. Consequently, this condition is of clinical relevance

Table 5
Diagnostic considerations based on HRCT patterns

Specific Computed Tomographic Findings	Entity
Cysts	Langerhans cell histiocytosis Lymphangioleiomyomatosis Lymphoid interstitial pneumonia Birt-Hogg-Dube syndrome
Perilymphatic nodules	Sarcoidosis Chronic beryllium disease Lymphangitic carcinoma Lymphoma
Centrilobular nodules	HP Respiratory bronchiolitis
Tree-in-bud pattern	Infection Aspiration Other forms of bronchiolitis
Mosaic attenuation	HP Obliterative bronchiolitis Pulmonary thromboembolism

for the general management of patients with ILD to diagnose PH, even though no targeted therapy is yet approved for this condition. In patients with ILD, the diagnosis of associated PH may avoid overtreatment with immunosuppressive agents and provide early indication for the initiation of long-term oxygen therapy or listing for lung transplantation. In addition, identification of PH may support the diagnosis of other treatable conditions, such as left heart disease.[16,25]

To find PH in patients with ILD, clinical symptoms are rather unspecific. Lung function showing a disproportionate reduction in DLco and very low oxygen partial pressures in arterial or capillary blood at rest and/or during mild exercise may indicate the presence of PH. Doppler echocardiography is suitable as a screening tool to support a clinical suspicion of PH, but about one-third of the patients will have a technically insufficient result. Brain natriuretic peptide may be used as a biomarker but is per se not sufficient to prove or exclude PH.[16,25–27] In patients with signs and symptoms of PH associated with ILD, in whom a therapeutic consequence is feasible, a right

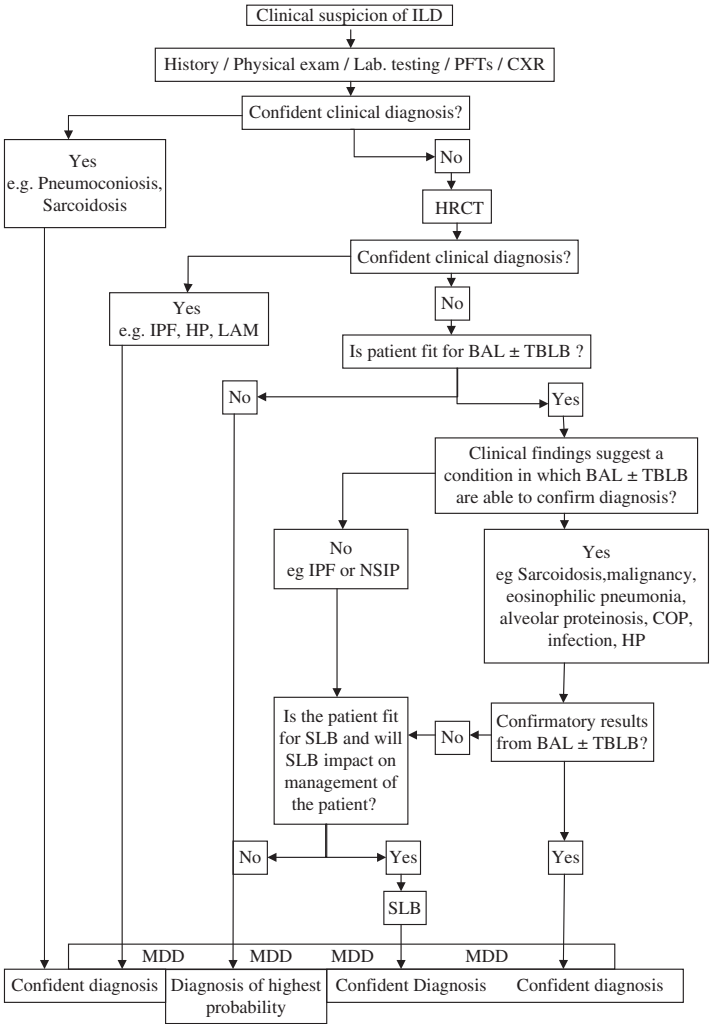

Fig. 3. Algorithm for the diagnosis of ILD. COP, cryptogenic organizing pneumonia; CXR, chest radiography; HP, hypersensitivity pneumonitis; LAM, lymphangioleiomyomatosis; MDD, multidisciplinary discussion; NSIP, nonspecific interstitial pneumonia; PFT, pulmonary function testing; SLB, surgical lung biopsy. (*Data from* Raghu G, Mageto YN, Lockhart D, et al. The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease: a prospective study. Chest 1999;116:1168–74; with permission; and Bradley B, Branley HM, Egan JJ, et al. British Thoracic Society Interstitial Lung Disease Guideline Group, British Thoracic Society Standard of Care Committee; Thoracic Society of Australia; New Zealand Thoracic Society; Irish Thoracic Society. Interstitial lung disease guideline. Thorax 2008;63(Suppl 5):v57.)

Table 6
Characterization of different disease patterns as a guide to treatment approach and monitoring strategy

Pattern of Disease	Broad Treatment Approach	Monitoring Strategy
Self-limited inflammation	Remove cause/observe or treat (usually with steroid therapy) in short term	Short-term monitoring to confirm disease regression
Major inflammation with risk of progression to fibrosis	Antiinflammatory therapy (eventually high dose) for a response, then rationalize lower-dose therapy to maintain response	Monitor in short term to quantify the response to high-dose treatment. Monitor less frequently in long term to ensure that gains are preserved
Stable fibrosis	Observation alone (in treatment-naive patients, a treatment trial may be considered)	Long-term monitoring to ensure ongoing stability
Progressive fibrosis with stabilization realistic	Treat with steroid or immunosuppressive therapy, high dose if necessary to stabilize; consider antifibrotic drugs	Long-term monitoring to confirm absence of progression
Inexorably progressive fibrosis	Consider therapy to slow progression but avoid toxic agents	Long-term monitoring to quantify rapidity of progression with a view to transplant or for effective palliation

Data from Wells AU. Diffuse parenchymal lung disease: an introduction. In: Warrell DA, Cox TM, Firth JD, editors. Oxford textbook of medicine. Vol 2. 5th edition. Oxford (United Kingdom): Oxford University Press; 2010. p. 3365–75.

heart catheterization should be performed to make a firm diagnosis of PH and to differentiate precapillary and postcapillary PH.[16] Right heart catheterization may prompt the performance of left heart catheterization and coronary angiography in addition to show or rule out treatable left heart disease.

DIAGNOSTIC ALGORITHM

A diagnostic algorithm for patients with ILD is shown in **Fig. 3**. After differentiating ILDs with known causes from those with unknown causes, HRCT is the crucial diagnostic procedure that leads to a final diagnosis, for example, IPF, or that prompts further diagnostic steps, which eventually include bronchoscopic techniques such as BAL and TBLB or VATS lung biopsy. The evolution of the prognostic process may vary depending on the clinical presentation or setting, that is, symptomatic patients or asymptomatic patients with risk factors for ILD or chance findings of ILD. In all cases, a multidisciplinary discussion involving pulmonologists, radiologists, and pathologists should be used to establish a confident diagnosis.[2]

CLASSIFICATION OF DISEASE BEHAVIOR

In addition to a diagnosis based on nosology, it is of critical importance to also stratify a particular patient with ILD according to the disease behavior, which may have a more profound impact on management and therapy of an individual patient than the specific ILD diagnosis by itself. In **Table 6**, a classification scheme for the disease behavior is proposed that will guide the choice of treatment options. Obviously, there is an interaction between the underlying diagnosis and the prevalence of one or another pattern of disease behavior. Nonetheless, it seems very helpful to select the broad treatment approach in an individual patient by applying the patterns of disease behavior characterized in **Table 6**.

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