

Interstitial lung disease: clinical evaluation and keys to an accurate diagnosis

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A wide range of acute and chronic pulmonary disorders is capable of diffusely affecting the lung parenchyma with variable amounts of inflammation, fibrosis, and architectural distortion. As a group, they commonly are referred to as the interstitial lung diseases (ILD). Using strict terminology, the pulmonary interstitium is confined to the microscopic anatomic space that is bounded by the basement membranes of epithelial and endothelial cells. The pathologic features of these diseases, even if originating in the interstitium, regularly include structures that are well beyond it, including the alveolar space, small airways, vessels, and even the pleura. Although a more appropriate descriptive term for this heterogeneous group of lung diseases may be needed, because of the diffuse involvement of the parenchyma and overlapping clinical presentations, ILD remains an appropriate term if the wide scope of these diseases is appreciated.

In approaching the patient who has ILD, the conscientious physician is confronted with a heterogeneous group of disorders that includes at least 150 distinct clinical entities. The physician who evaluates ILD has to amass specific knowledge that relates to a large number of potential diagnoses. Because of the extent of the differential diagnostic possibilities that are involved, it often is useful to categorize ILD broadly into seven main groups (Fig. 1). Because there can be dramatic prognostic and therapeutic

differences among these disorders, an accurate diagnosis is essential to the appropriate management of the patient.

In essence, without a medical history, all ILDs are of unknown cause. For an accurate diagnosis there is no substitute for a complete clinical evaluation. This should be considered the key diagnostic step in the evaluation of the patient who has ILD. This includes a thorough history elicitation, with complete evaluation of the chief complaint; a comprehensive review of multiple systems; identification of all medications or drugs, including over-the-counter and naturopathic medications; and an exhaustive review of past medical, social, family, and occupational histories with an exploration of all potential environmental exposures. A careful physical examination is absolutely essential [1,2]. The clues that surface during this evaluation help clinicians to narrow the broad differential diagnosis to a few possible disorders.

Although the presence of diffuse lung disease in the immunocompetent host poses a significant challenge, clinicians recognize some general findings that are common to most patients who have ILD. These include: (1) exertional dyspnea or cough; (2) bilateral diffuse interstitial infiltrates on chest radiographs; (3) physiologic and gas exchange abnormalities, including a decreased DLCO and an abnormal alveolar-arteriolar PO₂ difference [P(A-a)O₂] at rest or with exertion; and (4) histopathologic abnormalities of the pulmonary parenchyma that are characterized by varying degrees of inflammation, fibrosis, and remodeling. If a diagnosis or risk factors for immunoincompetency, such as HIV infection or other acquired

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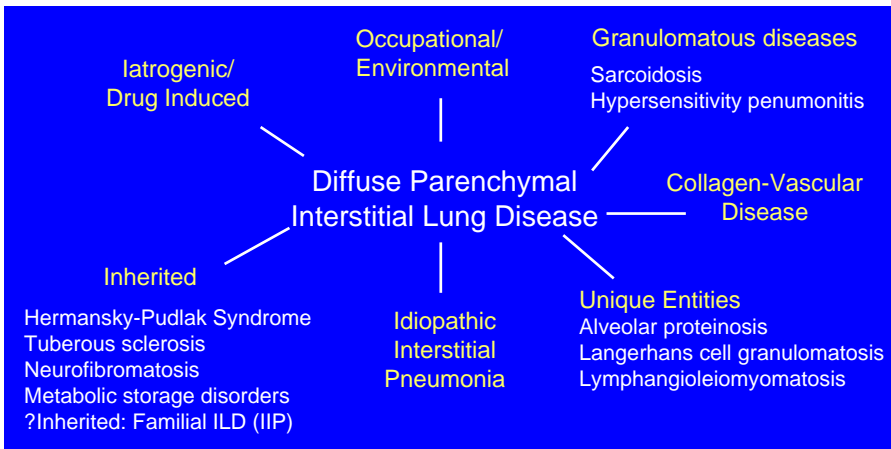


Fig. 1. Interstitial lung diseases in the immunocompetent host can be categorized into seven main groups.

or innate immunosuppressive disorder are identified from the history, the opportunistic infectious and noninfectious processes that complicate these disorders need to be evaluated appropriately and added to the differential diagnosis.

Because a pathologic host response to specific exposures are a common and potentially reversible cause of ILD, the clinician's index of suspicion for the diagnosis should be raised by the elicitation of a history of clinically significant exposures to agents that are known to cause lung disease. Avocations that are associated with the development of hypersensitivity pneumonitis (eg, exposure to birds), specific occupational exposures (eg, sand blasting), and multiple drugs or medications [3] are capable of causing diffuse lung disease. If a potential etiologic factor surfaces from the history and if the patient is affected minimally, a simple follow-up after avoidance of further exposure might resolve the problem. In instances when a temporal cause-and-effect relationship is not clear, tissue diagnosis may be the only way to ascertain the diagnosis. Several systemic disorders also may affect the lung adversely, particularly the autoimmune connective tissue diseases. When presented with a patient who has a systemic disorder, direct complications of the disease and potential complications of any previous or ongoing therapy must be considered as a possible cause of ILD.

Diffuse neoplasia (eg, lymphangitic carcinomatosis, bronchoalveolar cell carcinoma), a variety of pulmonary infections, pulmonary vascular disorders, and even congestive heart failure must be suspected in appropriate clinical settings. Even when appropriate evaluation has taken place, the clinician must be aware that it often fails to provide a definitive

diagnosis; a surgical lung biopsy may be necessary. In one large series of 1234 patients who had ILD, 502 (41%) underwent open lung biopsy [4]. Idiopathic pulmonary fibrosis (IPF), as then defined, was the diagnosis in more than one third of biopsied patients. Neoplasia, infection, congestive heart failure, pneumoconiosis, and pulmonary vascular disease were noted often enough to make them important considerations during the initial evaluation.

History of onset of illness

The presenting respiratory system complaints of a patient who has ILD should be characterized fully with a focus on the onset and duration of symptoms, rate of progression, and any associated extrathoracic symptoms, such as fever or joint discomfort. Acute symptoms (days to a few weeks) of cough, dyspnea, and fever necessitate evaluation for infection (viral, bacterial [particularly the atypical organisms], pneumocystis). In the absence of infection, cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), acute eosinophilic pneumonia (AEP), drug-induced pulmonary injury, and hypersensitivity pneumonitis (HP) should be considered. This acute presentation is atypical in IPF; pulmonary Langerhans cell granulomatosis (LCG); and ILD that is associated with collagen vascular disease (CVD), other than systemic lupus erythematosus and, rarely, polymyositis. Patients who have sarcoidosis also may present with a brief illness and fever. They often have accompanying erythema nodosum and arthritis (Löfgren's syndrome). Acute symptoms that rapidly progress to respiratory failure raise the possibility of AIP

and AEP. Subacute (weeks to months) presentations include COP, subacute HP, drug-induced ILD and CVD. Chronic symptoms (months to years) generally indicate IPF, nonspecific interstitial pneumonia (NSIP), fibrotic or chronic HP, chronic occupation-related lung disease (eg, asbestosis), and CVD.

Respiratory symptoms other than dyspnea

Besides exertional dyspnea, other specific coexisting respiratory symptoms, such as cough, hemoptysis, and chest pain, may occur. Although cough is nonspecific, it can be the initial manifestation of ILD. Its presence raises the possibility of superimposed/coexisting airways disease that is associated with respiratory bronchiolitis–interstitial lung disease (RB-ILD), sarcoidosis, HP, and acid gastroesophageal reflux (GER). A chronic irritable cough has been associated with lymphangitic carcinomatosis; mucoid or “salty” sputum is suggestive of bronchoalveolar cell carcinoma. In long-standing and advanced pulmonary fibrosis that is associated with traction bronchiectasis, cough may become productive and unresponsive to conventional treatment and remedies. Hemoptysis may suggest a diffuse alveolar hemorrhage syndrome (DAH); pulmonary capillaritis; or other vasculitis; such as Wegener’s granulomatosis or Goodpasture syndrome; and catamenial hemoptysis, although its absence does not exclude DAH or other underlying conditions that are associated with microscopic hemorrhage (eg, systematic lupus erythematosus [SLE]). In patients who have known IPF, new onset hemoptysis should raise the concern for superimposed malignancy, pulmonary embolus, or infection. Pleuritic chest pain raises the possibility of a pneumothorax—this is seen in patients who have lymphangiomyomatosis (LAM), tuberous sclerosis (TS), pulmonary LCG, neurofibromatosis, and catamenial syndrome—or pleuritis that can be seen in the CVD, such as SLE. Wheezing suggests ILD that is associated with airways disease, such as allergic bronchopulmonary aspergillosis (ABPA), Churg-Strauss syndrome, chronic eosinophilic pneumonia (CEP), and parasitic manifestation. Rarely, endobronchial lesions may result in wheezing (eg, sarcoidosis, Wegener’s granulomatosis, amyloidosis, inflammatory bowel disease, endobronchial metastases).

Extrapulmonary symptoms

Several extrapulmonary symptoms provide useful clues. A history of dyspepsia and gastroesophageal

reflux disease (GERD) may suggest IPF or scleroderma-related ILD. Most patients who have IPF do not have symptoms of GERD, although 90% have physiologic evidence of acid GER [5]. Overt aspiration or dysphagia suggests aspiration pneumonia, scleroderma, or mixed connective tissue disease; frank inflammatory arthritis suggests a CVD or sarcoidosis; ocular symptoms suggest sarcoidosis, CVD, or HLA-B27–related disease; recurrent sinusitis suggests Wegener’s granulomatosis; combined muscle and skin symptoms suggest polydermatomyositis; dry and gritty eyes and dry mouth (sicca syndrome) suggest Sjögren’s syndrome, or other CVD; and other skin lesions, such as lupus pernio suggest sarcoidosis. Lower gastrointestinal symptoms may suggest inflammatory bowel disease. Neurologic symptoms (cranial nerve involvement, Bell’s palsy) suggest the possibility of vasculitis or sarcoidosis, whereas the polyuria and polydipsia of diabetes insipidus suggest sarcoidosis or pulmonary LCG. Hematuria raises the possibility of pulmonary-renal syndromes. A history of epilepsy or mental retardation may be seen in TS. When present, specific systemic symptoms will direct the clinician to appropriate laboratory testing that may lead to a particular diagnosis.

Demographics and family medical history

The patient’s age, cigarette-smoking status, and gender may provide important clues. IPF is almost always an adult disorder and typically occurs in patients who are older than 60 years of age. Patients who have NSIP usually are younger than 60. Although pulmonary sarcoidosis can manifest in the elderly patient, it is more common in the young and middle-aged. Pulmonary LCG typically occurs in young, cigarette-smoking men. RB-ILD and desquamative interstitial pneumonia (DIP) are seen almost exclusively in cigarette smokers, but can occur in men and women of all ages. LAM is a rare disorder that occurs exclusively in women, most often in those of childbearing age. Although ILD associated with TS seems to be virtually identical to LAM, in this rare genetic disorder the lung disease also can occur in men. ILD also occurs in a subgroup of patients who have known inherited disease, including neurofibromatosis, TS, Hermansky-Pudlak syndrome and metabolic storage disorders [5]. History of a documented ILD among first-degree biologic relatives (siblings, parents, children) raises the strong possibility of the ILD being heritable (ie, familial pulmonary fibrosis) [6]. Ongoing molecular genetic studies in affected families hope to discover the putative pulmonary

fibrosis (PF) gene and allow us to conduct genetic screening to predict susceptibility of manifesting PF in a given individual.

Environmental/occupation/medication history: identifying exposures

An exhaustive environmental and occupational exposure history is essential because it may lead to identification of a specific cause for ILD. At-risk occupations for ILD include miners (pneumoconiosis); sandblasters and granite workers (silicosis); dental workers (dental workers' pneumoconiosis); welders, shipyard workers, pipe fitters, electricians, automotive mechanics (asbestosis); farm workers (hypersensitivity pneumonitis); poultry workers, bird fanciers, bird breeders (hypersensitivity pneumonitis); and workers in aerospace, nuclear, computer, and electronic industries (berylliosis). History of existing, persistent environmental 'fibrogenic' factors at home; in the workplace; in automobiles; in frequently visited facilities/homes; associated with hobbies, such as exposure to birds, molds, woodworking; or the use of saunas and hot tubs often are ignored but are equally important and may provide the useful clue for specific diagnosis and management of hypersensitivity pneumonitis [7].

Several drugs are well-known causes of ILD [3]. These include chemotherapeutic and cytotoxic agents, anti-inflammatory agents (nonsteroidal), antibiotics (particularly macrolidantins), narcotic analgesics, antiarrhythmics (amiodarone), hydralazine, tricyclic antidepressants, methotrexate, and penicillamine (see elsewhere in this issue). The list continues to increase; thus, any new medication that the patient may have taken before the onset of ILD must be considered as a potential cause. Use of over-the-counter medications and "alternative medicines" ("herbal" medicines, naturopathics, and vitamins and mineral supplements) must not be overlooked (Table 1).

Physical examination

Pulmonary signs

Auscultated crackles, typically described as "dry," "Velcro," end-inspiratory, and predominantly basilar, are detected in more than 80% of patients who have IPF [8]. Occasionally, crackles that are due to ILD may be detected on physical examination, even in the setting of a normal chest radiograph. Although

crackles are reported in many different ILDs, they are detected less commonly in granulomatous ILDs (eg, sarcoidosis). Midinspiratory high-pitched squeaks are reported in the primary bronchiolitis and other diseases with airway-centered pathology (eg, HP). Clubbing may be seen in patients who have IPF [8], but also is seen in patients who have asbestosis, chronic HP, and DIP; it is rare in RB-ILD and uncommon in collagen vascular disease-associated ILD, sarcoidosis, COP, lymphocytic interstitial pneumonitis (LIP), acute ILD, and other ILDs. Signs of pulmonary hypertension may be encountered in the later stages of all chronic ILDs as a result of progressive interstitial fibrosis and alveolar hypoxemia, but have been identified more specifically as part of the pathogenesis in CVD-associated ILD and pulmonary veno-occlusive disease. In IPF, pulmonary hypertension at rest can be expected when the vital capacity decreases to less than 50% of the predicted normal value or the DLCO decreases to less than 30% of the predicted normal. In a recent study, only one-third of patients who had IPF had evidence of pulmonary hypertension at the time of listing for lung transplantation [9]. Physical findings that are suggestive of pulmonary hypertension include an increased intensity of the pulmonary component of the second heart sound, the holosystolic murmur of tricuspid regurgitation, a right-sided S3, and elevated jugular venous pressure.

Extrapulmonary signs

Although examination of the respiratory system is seldom helpful because an abnormal physical examination is nonspecific and patients who have ILD may have normal findings, additional insight often is gained from the presence or absence of extrathoracic findings. For example, skin abnormalities, peripheral lymphadenopathy, and hepatosplenomegaly are associated commonly with sarcoidosis. Characteristic skin rashes and lesions also occur in CVD, amyloidosis, pulmonary LCG, TS, and neurofibromatosis. Subcutaneous nodules (especially around elbow and metacarpophalangeal joints) are suggestive of rheumatoid arthritis. Muscle tenderness and proximal muscle weakness raise the possibility of coexisting polymyositis. Signs of arthritis may be associated with sarcoidosis or CVD. Fever, erythema nodosum, and arthritis raise the likelihood of Lofgren's syndrome. Often, patients who have IPF also have arthralgias but do not have active synovitis on physical examination; however, if they do, the ILD and arthritis usually are secondary to an occult CVD. Sclerodactyly, Raynaud's phenomenon,

Table 1
Clues from history and physical examination for patients who have interstitial lung disease

Finding	Relative frequency of condition/finding	Possible clinical conditions/diagnosis
History		
Age	~2/3 of patients who have IPF are >60 y old at diagnosis	IPF predominates >60 y old. CVD, sarcoidosis, pulmonary LCG, LAM, metabolic ILDs (eg, Gaucher's disease), and familial IPF are more common among 20–40-y-old patients
Gender	LAM - 100% female	LAM and TS-associated ILD are seen almost exclusively in women
Smoking history	RB-ILD (100%) DIP (~90%) Pulmonary LCG (~90%) Goodpasture's syndrome	RB-ILD, DIP, pulmonary LCG, and pulmonary involvement in Goodpasture's syndrome are unlikely in the never-smoker. HP and sarcoidosis are less likely in smokers. HP; occupational ILD
Exposures (eg, asbestos, birds, humidifiers, cooling systems)	Exposure is presumed in all cases of HP	
Acute symptoms (days to weeks), fever	Fever is variable	Infection, AIP, AEP, AHP, COP, a DAH syndrome (eg, Goodpasture's syndrome), drug-induced ILD, or CVD (eg, acute lupus pneumonitis). Suggests CVD-associated ILD
Arthralgias, myalgias, rash, dysphagia, sicca symptoms, Raynaud's syndrome	Up to 20% of patients who have CVD may present initially with ILD alone	
Hemoptysis	Absent in 33% of initial DAH presentations	Alveolar hemorrhage syndromes, LAM, pulmonary venoocclusive disease, pulmonary capillaritis, D-penicillamine, pulmonary hypertension due to mitral stenosis, catamenial syndrome. In patients who have known IPF, may suggest cancer, PE, or pneumonia.
Physical examination		
Pulmonary		
Crackles	IPF (>80%)	Common in many chronic ILDs. Less common in sarcoidosis.
Midinspiratory "squeaks"	Variable	Suggestive of bronchiolitis
Clubbing	IPF (50%), DIP (nearly 50%)	Common in IPF; uncommon/rare in RB-ILD, CVD, COP, sarcoidosis.
Elevated P2, RV lift, TR murmur	Expected in advanced IPF when VC <50% predicted, DLCO <45% predicted. Secondary pulmonary hypertension	Suggests pulmonary hypertension secondary to progressive fibrosis or as more specific feature of pathogenesis (eg, CVD, pulmonary LCG)
Extrapulmonary		
Erythema nodosum	Variable	Sarcoidosis, IBD, Behcet's syndrome
Maculopapular rash	Variable	Sarcoidosis, amyloidosis, Behcet's syndrome
Other characteristic skin lesions/rash	Variable in extent	Sarcoidosis, pulmonary LCG, TS, neurofibromatosis, Churg-Strauss syndrome, drug-induced.
Arthritis	Variable	CVD, IBD, sarcoidosis, Behcet's syndrome, AS
Uveitis/conjunctivitis	Variable	Sarcoidosis, Behcet's syndrome, IBD, AS

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Table 1 (continued)

Finding	Relative frequency of condition/finding	Possible clinical conditions/diagnosis
Lacrimal/salivary gland/parotid enlargement	Variable	Sarcoidosis, SS
Adenopathy, hepatosplenomegaly	Variable	Sarcoidosis, amyloidosis
Muscle weakness or tenderness	Variable	Polymyositis/dermatomyositis
Neurologic abnormalities	Variable	Sarcoidosis (cranial nerve deficits), TS (mental retardation), lymphomatoid granulomatosis

Abbreviations: AHP, acute hypersensitivity pneumonitis; AS, ankylosing spondylitis; IBD, inflammatory bowel disease; PE, pulmonary embolus; P2, pulmonary component of second heart sound; RV, right ventricle; SS, Sjögren's syndrome; TR, tricuspid regurgitation.

Adapted from Fessler M, Brown K. Approach to patient with Interstitial Lung Disease. In: Lillington GA, editor. Best Practice of Medicine. Available at: http://www.praxis.md/index.asp?page=bmp_1st=gi. Accessed July 16, 2004.

and telangiectatic lesions are characteristic features of scleroderma and CREST syndrome. Iridocyclitis, uveitis, or conjunctivitis may be associated with sarcoidosis, Behcet's disease, inflammatory bowel disease, and autoimmune syndromes. Oculocutaneous albinism raises the possibility of ILD that is associated with Hermansky-Pudlak syndrome. Abnormalities of the central nervous system suggest the diagnosis of sarcoidosis (cranial nerves abnormalities, diabetes insipidus, anterior pituitary dysfunction), pulmonary LCG (diabetes insipidus), or TS (epilepsy, mental retardation).

Diagnostic tests

Laboratory testing

Laboratory blood testing alone rarely permits one to either rule in or rule out a specific diagnosis, but may be strongly supportive in the appropriate clinical setting. Routine laboratory tests should be obtained and include a complete blood count with leukocyte differential, erythrocyte sedimentation rate (ESR), chemistry profile (serum electrolytes, serum urea nitrogen, creatinine, liver tests, and calcium). Chronic anemia (microcytic) may suggest occult pulmonary hemorrhage; abnormal liver or kidney function tests may suggest pulmonary-renal syndromes, CVD, or sarcoidosis. Antinuclear antibody (ANA), rheumatoid factor (RF), and ESR should be obtained, especially in the setting of history or physical findings that are suggestive of CVD. Low titers of ANA (<1:160) and RF occur in 10% to 20% of patients who have IPF. Slightly elevated ESR, C-reactive protein, and hypergammaglobulinemia are common and nonspecific findings. An elevated level of angiotensin-converting enzyme may be seen with sarcoidosis, but is insen-

sitive and nonspecific because it also is abnormal in other disorders (eg, silicosis, HP, LIP, acute respiratory distress syndrome). Serum precipitins that are focused on known exposures may be considered if the environmental history suggests HP; however, false negative results may be encountered, and similarly, the presence of precipitating antibody may represent sensitization to an environmental antigen and not disease. Random "HP panels" are almost never helpful in the absence of a specific exposure and should rarely, if ever, be performed. If pulmonary vasculitis (pulmonary nodules, hemoptysis, arthritis, rash, sinusitis) or DAH (hemoptysis) is suspected, antineutrophil cytoplasmic antibody (C-, P-ANCA), antiglomerular basement membrane antibody, ANA, and urine sediment should be checked. Proximal muscle weakness or tenderness should prompt measurement of aldolase, creatine kinase, anti Jo-1 antibody, and possibly an electromyogram and muscle biopsy to rule out polymyositis. A clinically suspected or histopathologic diagnosis of LIP should prompt measurement of serologies (to rule out a CVD, particularly Sjögren's syndrome) and immunoglobulin levels (to evaluate for associated common variable immunodeficiency) and an HIV test. Peripheral blood lymphocyte proliferation that is stimulated by the antigen that may be causing the ILD (eg, beryllium—the beryllium lymphocyte proliferation test) has high sensitivity for chronic berylliosis. This test is available at only a few research laboratories and the *in vitro* lymphocyte proliferation test to specific antigen has not been validated (Table 2).

Chest radiograph: useful diagnostic patterns

A diffusely abnormal chest radiograph often is the initial finding that alerts the physician to the possi-

Table 2
Clues from blood and urine tests for patients who have interstitial lung disease

Laboratory test	Indications	Interpretation
CBC count, LFTs, Cr, SUN	All patients who have suspected ILD	Eosinophilia (CEP, drugs), normocytic anemia (CVD), Fe-deficiency anemia (DAH), leucopenia/thrombocytopenia (CVD, sarcoidosis, lymphoma), liver disease (sarcoidosis, amyloidosis), renal disease (CVD, amyloidosis, WG, Goodpasture's syndrome) Elevated values are supportive of PM
Aldolase, creatine kinase, Jo-1 antibody	Muscle pain, weakness	
Immunoglobulins	Clinically suspected or histopathologic diagnosis of LIP.	Low levels of immunoglobulins may indicate an underlying diagnosis of CVID.
Urinary sediment	Suspected vasculitis (CVD, WG, MPA, Goodpasture's syndrome)	RBC casts or dysmorphic RBCs suggest systematic vasculitis
ANA, RF	Suspected IIP, IPF, CVD or ILD for which CVD cannot be ruled out	Low titers of ANA (< 1:160) and RF occur in 10–20% of patients who have IPF.
C-, P-ANCA	Suspected WG or MPA (lung nodules, sinusitis, DAH)	Positive C-ANCA or antiproteinase 3 is most suggestive of WG; P-ANCA may be seen in WG, but suggests MPA.
Anti-GBM antibody	Suspected Goodpasture's syndrome (ie, DAH)	Positive result in patient who has DAH is diagnostic of Goodpasture's syndrome.
Specific serum precipitins	Exposure history appropriate for HP	Interpret within clinical context. A negative result does not rule out HP; a positive result is not diagnostic of HP.

Abbreviations: BAL, bronchoalveolar lavage; CA, bronchogenic carcinoma; CBC, complete blood cell; Cr, creatinine; CVID, common variable immunodeficiency; GBM, glomerular basement membrane; HRCT, high-resolution computed tomography; IIPs, idiopathic interstitial pneumonias; LFTs, liver function tests; MPA, microscopic polyangiitis; PAP, pulmonary alveolar proteinosis; RBC, red blood cell; SUN, serum urea nitrogen; WG, Wegener's granulomatosis.

Adapted from Fessler M, Brown K. Approach to patient with Interstitial Lung Disease. In: Lillington GA, editor. Best Practice of Medicine. Available at: http://www.praxis.md/index.asp?page=bpm&bpm_1st=gi. Accessed July 16, 2004.

bility of ILD. The clinician should make every effort to obtain previous chest radiographs for review. This may allow one to ascertain the onset, chronicity, rate of progression, or stability of the patient's disease. A rare patient who has dyspnea and restrictive pulmonary function test abnormalities will have a normal chest radiograph and high-resolution CT (HRCT), despite clinically significant ILD. Although HRCT scanning is more sensitive, classification of abnormalities on routine chest radiograph that are based on distribution, location, and overall appearance are useful in narrowing the differential diagnosis [10]. For example, a pattern of upper lobe/zone predominance in ILD, suggests sarcoidosis, berylliosis, pulmonary LCG (especially with preserved lung volumes), HP, silicosis, and ankylosing spondylitis (Table 3). Conversely, lower lobe predominance with decreased lung volumes is seen characteristically in IPF, chronic HP, fibrotic NSIP, polymyositis, systemic sclerosis, and asbestosis. Normal (preserved lung volume) and increased lung volumes on the chest radiograph in the context of ILD suggest the coexis-

tence of an obstructive airflow defect and a few specific disease entities. Prominent in this regard are LAM, pulmonary LCG, HP, TS, and sarcoidosis. Associated pneumothorax raises the possibility of LAM or pulmonary LCG.

The presence of pleural plaques or localized pleural thickening with parenchymal opacities that affect the lower lobes suggest asbestosis. Unilateral or bilateral pleural thickening can result from asbestos pleurisy, rheumatoid arthritis, scleroderma, or malignancy. In the absence of left ventricular failure and transudative pleural effusion, the coexistence of exudative pleural effusion raises the possibility of rheumatoid arthritis, SLE, a drug reaction, asbestos-related lung diseases, amyloidosis, LAM (chylothorax), or lymphangitic carcinomatosis. Associated mediastinal adenopathy raises the possibility of sarcoidosis, CVD, and malignancy.

Thus, recognition of these straightforward abnormalities may provide useful clues and is a good starting point in narrowing the differential diagnoses. In interpreting these findings, the chest radiograph

Table 3
Useful chest radiographic patterns

Pattern	Suggested diagnoses
Decreased lung volumes	IPF, CVD-related, chronic hypersensitivity pneumonitis, asbestosis, NSIP, chronic drug-induced, subgroup of chronic COP, CEP, DIP
Increased or preserved lung volumes	RB-ILD, IPF with coexisting emphysema, sarcoidosis, acute hypersensitivity pneumonitis, LAM, TS, pulmonary LCG, neurofibromatosis, bronchiolitis, IPF coexisting with emphysema, cigarette smoking
Mid-upper zone predominance	Sarcoidosis, silicosis, coal workers' pneumoconiosis, hypersensitivity pneumonitis, pulmonary LCG, berylliosis, AS, CEP, Caplan syndrome, nodular rheumatoid arthritis
Lower zone predominance	IPF, CVD-related, asbestosis, DIP
Peripheral zone	COP, CEP
Micronodules	Infection, sarcoidosis, hypersensitivity pneumonitis
Septal thickening	Malignancy, chronic congestive heart failure, infection, pulmonary veno-occlusive disease
Honeycombing	IPF, asbestosis, CVD-related, sarcoidosis, chronic hypersensitivity pneumonitis, NSIP fibrotic
Migratory or remitting infiltrates	COP, hypersensitivity pneumonitis, APBA, Löffler's syndrome
Pleural disease	CVD-related, asbestosis, malignancy, radiation-induced sarcoidosis
Pneumothorax	LAM, pulmonary LCG, TS, neurofibromatosis, catamenial syndrome
Mediastinal/Hilar lymphadenopathy	Sarcoidosis, malignancy, silicosis, infection, chronic beryllium disease, CVD
Normal (rare)	Hypersensitivity pneumonitis, NSIP (cellular), CVD-related, bronchiolitis, RB-ILD, sarcoidosis
Location of radiographic abnormality	Common clinical disorders/syndromes
Mid-upper lung zone	Hypersensitivity pneumonitis, sarcoidosis, pulmonary LCG, chronic beryllium disease
Lower lung zone	CVD-related, IPF, asbestosis, chronic HP
Peripheral	COP, IPF, CEP
Along bronchovascular sheath	Sarcoidosis
Along Kerley B lines	Lymphangitic carcinomatosis

Data from Schwarz M, King TE, Raghu G. Approach to the evaluation and diagnosis of interstitial lung disease. In: Schwarz MI, King TE, editors. Interstitial lung disease. Hamilton (Ontario): BC Decker, Inc.; 2003; with permission and Lynch D. Imaging of diffuse parenchymal lung disease. In: Schwarz MI, King TEJ, editors. Interstitial lung disease. 4th edition. Hamilton (Ontario): BC Decker Inc; 2003; with permission.

provides only a semiquantitative assessment of lung volume and often correlates poorly with estimates of histologic and functional impairment.

High-resolution CT

HRCT should be considered a standard procedure during the initial evaluation of almost all patients who have ILD. It is more sensitive than the plain radiograph in identifying ILD (with a sensitivity greater than 90%) and the image pattern of parenchymal abnormalities on HRCT often suggests a particular set of diagnostic possibilities (Table 4) [11]. HRCT also identifies "mixed" patterns of disease (eg, ILD plus emphysema) or additional pleural, hilar, or mediastinal abnormalities. It has a better correlation with physiologic impairment and is especially useful to guide selection of appropriate sites of bronchoal-

veolar lavage (BAL) or lung biopsy. Ground glass changes are nonspecific; a completely normal HRCT scan of the chest essentially rules out IPF but does not rule out microscopic inflammation and granulomatous changes. Further details of HRCT findings are discussed elsewhere in this issue.

Pulmonary function testing

Initial pulmonary function tests (PFTs) should include a spirometry (with and without bronchodilator), plethysmographic lung volumes, and DLCO (corrected to hemoglobin). PFTs cannot diagnose a specific ILD and cannot distinguish between active lung inflammation versus fibrosis, but are critically important in the objective assessment of respiratory symptoms as well as in paring the differential diagnosis, grading the severity of disease, and monitoring

Table 4
Useful high-resolution CT patterns in interstitial lung disease

Finding	Common clinical disorders/syndromes
Reticular lines, honeycombing, traction bronchiectasis	CVD-related, IPF, asbestosis, sarcoidosis, CEP
Airspace opacity, “ground-glass”	COP, CEP, AIP, AEP, PAP, consolidation, lymphoma, sarcoidosis
Nodules	Granulomatous diseases, pneumoconiosis, malignancy, rheumatoid arthritis
Septal thickening	Infection, edema, malignancy, drug reaction, pulmonary veno-occlusive disease
Cystic changes	LAM, LIP, pulmonary LCG (emphysema must be distinguished)
Mosaic patterns	Air-trapping (constrictive bronchiolitis)

Data from Schwarz M, King TE, Raghu G. Approach to the evaluation and diagnosis of interstitial lung disease. In: Schwarz MI, King TE, editors. Interstitial lung disease. Hamilton (Ontario): BC Decker, Inc.; 2003; with permission and Lynch D. Imaging of diffuse parenchymal lung disease. In: Schwarz MI, King TEJ, editors. Interstitial lung disease. 4th edition. Hamilton (Ontario): BC Decker Inc; 2003; with permission.

response to therapy or progression. PFT abnormalities in ILD generally reflect the effects of elevated elastic recoil (restrictive lung defect) and alveolo-capillary dysfunction (decreased diffusion capacity when corrected to hemoglobin), although increased lung volumes (eg, LAM) or an increased diffusing capacity (eg, DAH) can be seen. A typical PFT pattern in ILD is a restrictive lung defect with symmetrically decreased lung volumes (total lung capacity [TLC], functional residual capacity [FRC], and residual volume [RV] <80% of predicted); forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) decreased in parallel with a normal or elevated FEV₁/FVC ratio; and a decreased DLCO corrected for hemoglobin. The DLCO generally normalizes or moves toward normal when corrected for alveolar volume (DLCO/VA); however, not all of these abnormalities are detected in every patient and all PFT values may be normal in some patients.

Coexisting obstructive airflow defect, when present, can help significantly with diagnosis. A mixed pattern of restriction (decreased TLC, FRC) and obstruction (decreased FEV₁/FVC, elevated RV, lack of supranormal airflows on a flow-volume loop, or significant response to bronchodilator) in the patient without coexisting emphysema may suggest sarcoidosis, HP, RB-ILD, pulmonary LCG, LAM among others, and ILD associated with asthma (chronic eosinophilic pneumonia, Churg-Strauss syndrome). Obstructive airflow defect without significant restriction may reflect obliterative bronchiolitis (constrictive bronchiolitis). A DLCO that is decreased out of proportion to other tests also may indicate concomitant pulmonary vascular disease as in scleroderma, CREST syndrome, pulmonary veno-occlusive disease, and chronic pulmonary emboli, and can be seen occasionally in pulmonary alveolar proteinosis, pulmonary LCG, and LAM. Because TLC and FVC are effort- and muscle strength-dependent maneuvers,

occasionally a restrictive pattern (TLC <80% predicted) may be partly or wholly due to respiratory muscle weakness (eg, polymyositis), as revealed by decreased maximal inspiratory pressure (MIP), maximal inspiratory pressure (MEP), and decreased maximum minute ventilation (MVV), and elevated RV without a decrease in FEV₁/FVC ratio. Thus, addition of MVV, MIP, and MEP maneuvers to the PFTs may clarify respiratory muscle weakness/strength in the appropriate clinical setting.

Gas exchange evaluation at rest and with ambulation using pulse oximetry (ie, a formal 6-minute or modified walk test) should be performed because they guide prompt diagnostic and therapeutic interventions besides directing early oxygen therapy based on physiologic needs. A decrease of 4 or 5 absolute percentage points (eg, from 94% to 89%) or greater with exertion generally is considered to be significant. Pulse oximetry may be an unreliable indicator of oxygenation, especially if patients have poor peripheral circulation, Raynaud's phenomenon, or arrhythmia. Because respiratory alkalosis can shift the hemoglobin saturation curve leftward and falsely increase (normalize) the oxygen saturation, arterial blood gas analysis should be considered as part of the initial evaluation; mild respiratory alkalosis and mildly elevated P(A-a)O₂ difference may be the only abnormality seen. Occasionally, PFTs and resting arterial blood gas analysis may be entirely normal in patients who have ILD; the physiologic abnormality is discovered only with direct arterial blood sampling that is obtained during exercise (ie, decreased PaO₂, widening alveolar-arterial oxygen gradient). Consequently, formal cardiopulmonary exercise testing that allows measurement of peak oxygen consumption, exercise gas exchange, and dead space ventilation may be helpful, especially in patients who do not demonstrate significant oxygen desaturation while walking in the clinic (ie, formal-

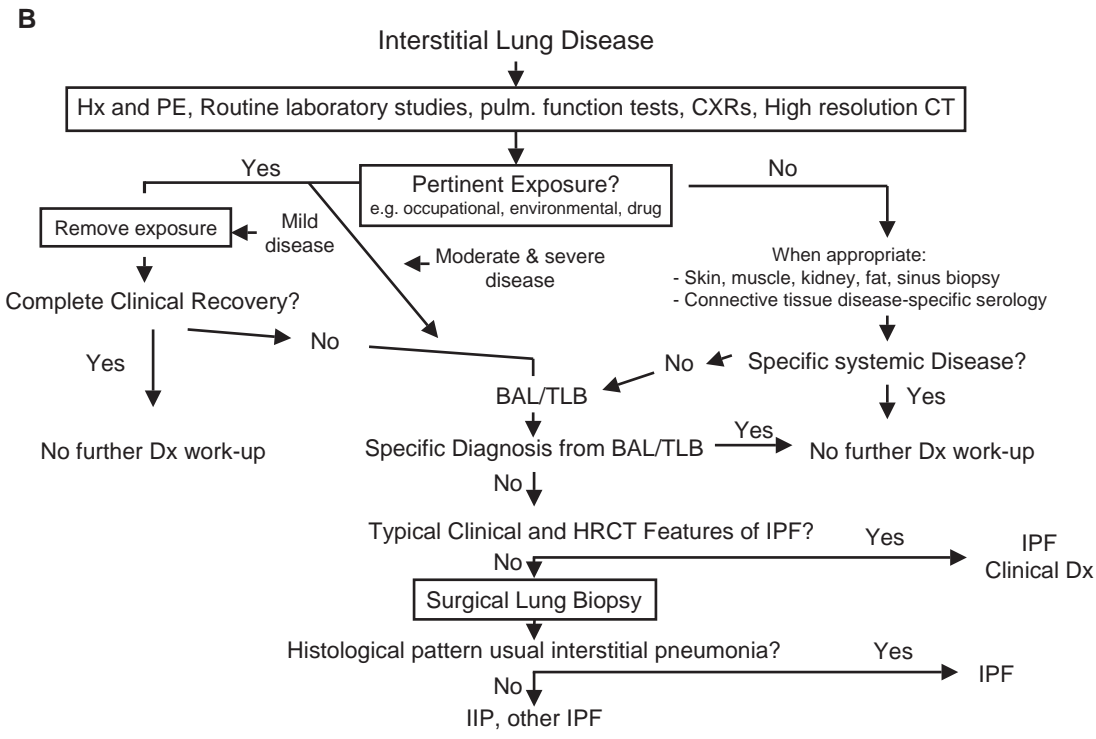
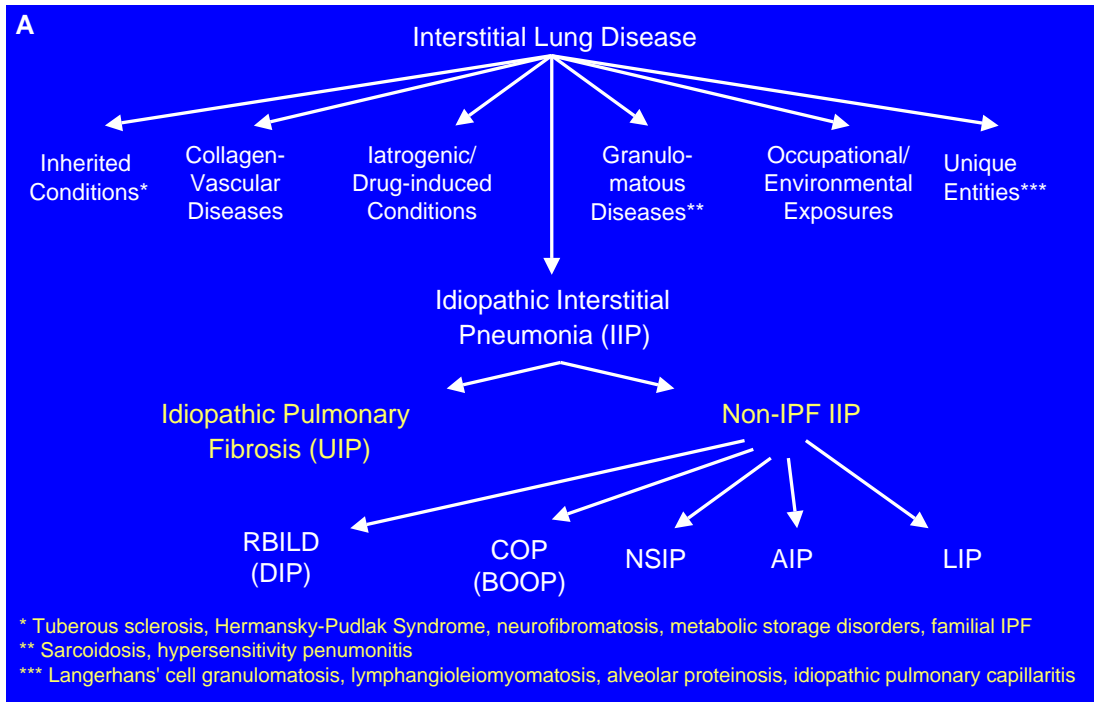


Fig. 2. A suggested algorithm for narrowing the differential diagnosis of ILD (A) and the diagnostic evaluation for ILD (B). BOOP, bronchiolitis obliterans organizing pneumonia; RBILD, respiratory bronchiolitis ILD. (Modified from Raghu G. Interstitial lung disease: a diagnostic approach. Are CT scan and lung biopsy indicated in every patient? Am J Respir Crit Care Med 1995;151:909–14; with permission.)

ized 6-minute walk test or a modified walk test), for further diagnostic intervention of otherwise unexplained dyspnea, grading disease severity, and for prompt initiation of treatment and monitoring response to therapy. Resting and exercise physiologic pulmonary abnormalities are discussed in detail elsewhere in this issue.

Summary

The clinician who is confronted with a patient who has ILD needs to amass specific knowledge of several heterogeneous acute and chronic diffuse lung disorders. The history must be detailed with leading questions asked to provoke occult, forgotten, or otherwise considered irrelevant information from the patient's social, family, occupational, environmental, and medical histories that might lead to the identification of the specific cause of the patient's ILD. With specific symptoms, signs, and further knowledge that is gained by recognition of chest radiograph/HRCT, pulmonary, physiologic, and gas exchange patterns, and supported by specific blood and urine diagnostic procedures, the clinician is able to narrow the broad differential diagnoses to a few specific diagnoses. Only after eliminating CVD; granulomatous diseases; drug-induced, inhalation (occupation, domestic), and inherited causes; and other specific entities (eg, LAM), can the diagnosis of an idiopathic interstitial pneumonia (IIP) be entertained. Because most patients who have IIP have IPF and the prognosis and therapeutic interventions of IPF are significantly worse than in IIP and other non-IIP ILDs, it is critical for the clinician to make an accurate diagnosis of IPF. The prudent clinician can make an accurate diagnosis of IPF without a surgical lung biopsy and with a high specificity (>90%) following a thorough, detailed clinical assessment [12,13]. Although time consuming, the accumulated clinical assessment (detailed history elicitation, thorough physical examination, laboratory findings, chest radiograph, HRCT, physiologic and gas exchange patterns) should be considered as the key diagnostic procedure, without which the additional information that is derived from bronchoscopy (BAL and transbronchial lung biopsy) and the histologic knowledge that is gained by invasive and multiple lung biopsy specimens may be meaningless. An algorithm for narrowing the differential diagnosis of ILD and a diagnostic scheme is suggested in Fig. 2.

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