REVIEW

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# Diagnosing interstitial lung disease: A practical approach to a difficult problem

## ABSTRACT

Interstitial lung disease has a variety of causes: environmental, infectious, autoimmune, and drug-related. Accurate diagnosis is essential because the prognosis and treatment of the disease varies widely depending on the cause. However, the respiratory symptoms and pulmonary radiographic picture of these various causes of interstitial lung disease are often similar, making the diagnosis of its cause confusing and frustrating. The practical, algorithmic approach to diagnosis outlined here identifies key diagnostic clues in the patient's history, physical exam, and radiographic findings.

## KEY POINTS

Interstitial lung disease is characterized by cough, progressive dyspnea, restrictive pulmonary physiology, and abnormalities on chest radiography.

A standardized, logical evaluation yields a diagnosis in the majority of patients with interstitial lung disease.

Although laboratory studies, radiography, and bronchoscopic procedures may provide useful information, they often do not provide the diagnosis, and surgical lung biopsy remains the standard for definitive diagnosis.

RECOGNIZING INTERSTITIAL lung disease (ILD) and identifying its cause can be difficult for several reasons:

- Many diseases can cause the cough, progressive dyspnea, and pulmonary fibrosis that are the chief features of ILD
- Symptoms are often mild and slowly progressive
- Patients wait long before reporting symptoms
- No underlying cause may be found (idiopathic pulmonary fibrosis).[1]

The prognosis and treatments for interstitial lung disease vary widely depending on the cause, so accurate diagnosis is essential. Whenever ILD is suspected, a disciplined evaluation using an algorithmic approach is the key to diagnosis of the causative disease, if there is one. In this article we outline such a practical approach and review key historical, physical, and radiographic features that help to narrow the differential diagnosis. Treatment options are discussed.

## THE CAUSES

The pathogenesis of ILD is thought to center around an injury to the lung—environmental, infectious, autoimmune, or drug-induced—followed by an attempt to heal the injury.[2] Whether this injury represents an ongoing insult, a series of multiple events, or an abnormal response to a single event that is no longer present is unknown. Whatever the scenario, it is believed that the attempt to control the injury eventually leads to inflammation and fibrosis, with subsequent destruction of lung

**TABLE 1**

**Causes and categories of interstitial lung disease**

**Inhaled agents**
Inorganic: asbestos, beryllium, silica
Organic: animal and bird antigens, farm antigens

**Drug-induced**
Antiarrhythmics
Antibiotics
Antidepressants
Anti-inflammatory agents
Chemotherapeutic agents
Oxygen
Radiation

**Connective tissue disease**
Ankylosing spondylitis
Behçet syndrome
Mixed connective tissue disease
Polymyositis/dermatomyositis
Rheumatoid arthritis
Scleroderma
Sjögren syndrome (primary)
Systemic lupus erythematosus

**Infectious**
Atypical pneumonias
*Pneumocystis carinii* pneumonia
Tuberculosis

**Other**
Acute interstitial pneumonia
Bronchiolitis obliterans organizing pneumonia
Desquamative interstitial pneumonia
Eosinophilic granuloma
Idiopathic
Lymphangioleiomyomatosis
Lymphocytic interstitial pneumonia
Nonspecific interstitial pneumonia
Respiratory bronchiolitis with interstitial lung disease
Sarcoidosis
Usual interstitial pneumonia

**Malignant**
Bronchoalveolar cell carcinoma
Lymphangitic carcinomatosis

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**Patients often realize the true duration of cough and dyspnea only in retrospect**

architecture and disruption of pulmonary function. An abbreviated list of causes of ILD is presented in TABLE 1.

## FEATURES OF INTERSTITIAL LUNG DISEASE

Patients with ILD typically present with cough and progressive dyspnea, but these symptoms are often subtle, nonspecific, and slowly progressive; it is common for patients to realize the true duration of symptoms only in retrospect. Therefore, the physician needs to maintain a suspicion of ILD to facilitate diagnostic testing.

Patients can also present with abnormalities on chest radiography, with a systemic illness that includes pulmonary symptoms such as cough and dyspnea, or with abnormalities on pulmonary function testing, such as a restrictive ventilatory defect or a gas exchange abnormality.

Other chest symptoms are unusual but may provide clues to the cause of ILD. For example, hemoptysis can be seen in patients with alveolar hemorrhage syndromes, pulmonary vascular disease, lymphangioleiomyomatosis, tuberous sclerosis, and chronic mitral valve disease. Acute chest pain may represent pleurisy in patients with collagen vascular illness or pneumothorax in patients with lymphangioleiomyomatosis, tuberous sclerosis, or eosinophilic granuloma.

### Symptom onset

The time over which symptoms develop can be important to the differential diagnosis. Acute onset is often seen in atypical infections, eosinophilic pneumonia, pulmonary hemorrhage, Wegener granulomatosis, acute interstitial pneumonia, and initial hypersensitivity reactions. An insidious onset is seen in patients with idiopathic pulmonary fibrosis, silicosis, asbestosis, long-standing hypersensitivity pneumonitis, and drug-induced lung diseases. Because dyspnea and cough are often subtle, nonspecific, and slowly progressive, patients often realize the true duration of symptoms only in retrospect.

Frequently, patients with ILD first present with abnormalities on a chest radiograph or pulmonary function testing that indicates a restrictive ventilatory defect or abnormal gas exchange. Keeping ILD in mind facilitates appropriate diagnostic testing.

### Clues from the medical history

A careful medical history is an essential part of the evaluation of patients with suspected ILD. Important features include the patient's age and sex: ILD caused by sarcoidosis, eosinophilic granuloma, familial idiopathic pulmonary fibrosis, and Gaucher disease is more common in younger patients, while other conditions are more likely to cause ILD in older patients. ILD caused by lymphangioleiomyomatosis and pulmonary involvement in tuberous sclerosis is seen exclusively in premenopausal women.

The medical history can also uncover a previous diagnosis of collagen vascular disease, a common cause of ILD. Evaluation of risk for human immunodeficiency virus (HIV) infection is also important because patients with HIV can have ILD due to infection, neoplasm, or other causes related to immune deficiency.[3]

### History of occupational and environmental exposures

A thorough history of occupational and environmental exposures aids the diagnosis and may also help to direct therapy. The range of exposures associated with the development of ILD is vast and includes avian, animal, and fish proteins, fungal spores, asbestos, silica, cobalt, beryllium, aluminum, isocyanates, and copper sulfate.[3] Because the latency period between disease onset and the development of symptoms can be years, a detailed assessment of all previous occupations and potential environmental exposures is also necessary.

Information about the patient's home environment is also important. A recent move or home remodeling can expose people to new antigens, and exposure-related conditions such as hypersensitivity pneumonitis can cause ILD. Similarly, information about pets, especially birds, narrows the differential diagnosis and directs therapy, such as removal or avoidance of the offending antigen.

The occupations of family members should also be ascertained, as contaminated clothing can also be a source of exposure.[4–6]

### Current and previous medications

A detailed account of current and previous medications should be obtained: many prescription and over-the-counter drugs have been associated with the development of ILD (TABLE 1). The history should also include the use of recreational drugs such as cocaine.[7,8]

### Smoking history

Several forms of ILD are seen almost exclusively in smokers: eg, respiratory bronchiolitis/ILD, desquamative interstitial pneumonia, and eosinophilic granuloma.[9] Cigarette smoking has also been implicated in the development of idiopathic pulmonary fibrosis.[10–13]

Paradoxically, smoking may reduce the incidence of sarcoidosis and hypersensitivity pneumonitis. However, when hypersensitivity pneumonitis is present in smokers, it follows a more chronic course with a worse clinical outcome.[14]

### Family medical history

Familial types of pulmonary fibrosis have been reported,[15,16] so obtaining a family medical history is advised. This may be helpful not only in narrowing the differential diagnosis but also in possibly identifying other family members with an earlier stage of disease.

## FINDINGS IN THE PHYSICAL EXAMINATION

**Ask about occupational, environmental exposures—past and present**

Physical findings related to ILD are nonspecific. The characteristic finding is dry bibasilar crackles, although inspiratory high-pitched rhonchi ("squeaks") can be heard with bronchiolitis. Clubbing (most common in idiopathic pulmonary fibrosis) and signs of right heart failure can also be seen in patients with advanced disease.

The physical examination is particularly helpful when it uncovers signs of an underlying connective tissue disorder. The presence of a rash (malar, heliotropic, vasculitic, or due to erythema nodosum), Raynaud phenomenon, joint deformity, synovial swelling, or muscle weakness should prompt a more complete evaluation for an underlying rheumatologic disorder.

## LABORATORY TESTING

Laboratory testing can be useful in the diagnosis and management of patients with ILD. A list of various laboratory findings and disease associations is shown in TABLE 2.

TABLE 2

## Laboratory findings in interstitial lung disease

| ABNORMALITY | ASSOCIATED CONDITION |
|---|---|
| Elevated angiotensin-converting enzyme (serum) | Sarcoidosis, hypersensitivity silicosis, Gaucher disease |
| Elevated antibasement membrane antibody | Goodpasture syndrome |
| Elevated antineutrophil cytoplasmic antibody | Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis |
| Eosinophilia | Eosinophilic pneumonia, sarcoidosis, systemic vasculitis, drug-induced (sulfa, methotrexate) |
| Hemolytic anemia | Connective tissue disease, sarcoidosis, lymphoma, drug-induced |
| Hypergammaglobulinemia | Connective tissue disease, sarcoidosis, systemic vasculitis, lymphocytic interstitial pneumonia, lymphoma |
| Hypogammaglobulinemia | Lymphocytic interstitial pneumonitis |
| Immune complexes | Idiopathic pulmonary fibrosis, lymphocytic interstitial pneumonitis, systemic vasculitis, connective tissue disease, eosinophilic granuloma |
| Lactate dehydrogenase elevation | Alveolar proteinosis, idiopathic pulmonary fibrosis |
| Leukopenia | Sarcoidosis, connective tissue disease, lymphoma, drug-induced |
| Lymphocyte transformation test | Chronic beryllium disease, aluminum potroom positive worker's disease, gold-induced pneumonitis |
| Normocytic anemia | Diffuse alveolar hemorrhage syndromes, connective tissue disease, lymphangitic carcinomatosis |
| Serum precipitating antibodies | Hypersensitivity pneumonitis |
| Thrombocytopenia | Sarcoidosis, connective tissue disease, drug- induced, Gaucher disease |
| Urinary sediment abnormalities | Connective tissue disease, systemic vasculitis, drug-induced |

ADAPTED FROM SCHWARZ MI, KING JR TE, CHERNIACK RM. GENERAL PRINCIPLES AND DIAGNOSTIC APPROACH TO THE INTERSTITIAL LUNGS DISEASES. IN: J. MURRAY AND J. NADEL, EDITORS. TEXTBOOK OF RESPIRATORY MEDICINE, 2ND EDITION. PHILADELPHIA: WB SAUNDERS, 1994: 1803–1826.

**The time over which symptoms develop is an important diagnostic clue**

A minimum panel of initial laboratory tests includes a complete blood count with differential, electrolytes, renal function studies, liver function studies, antinuclear antibodies, rheumatoid factor, and urinalysis.[3] If chronic beryllium disease is suspected, a lymphocyte transformation test should be performed.

### TESTING FOR ABNORMAL PULMONARY PHYSIOLOGY

Physiologically, a restrictive ventilatory defect that reflects reduced lung volumes is common in patients with ILD.[17] The vital capacity is typically reduced to a greater extent than the total lung capacity and functional residual capacity.[17]

However, these abnormalities are not unique to ILD or idiopathic pulmonary fibrosis and may not occur in all patients with pulmonary fibrosis. In two studies,[18,19] smokers and ex-smokers with interstitial pulmonary fibrosis had preserved lung volumes. Doherty et al[19] compared two groups of patients with cryptogenic fibrosing alveolitis—those with relatively preserved lung volumes and those with

**TABLE 3**

**Physiologic features that may suggest specific diagnoses**

| PHYSIOLOGIC FEATURE | POSSIBLE DIAGNOSES |
|---|---|
| **Airflow obstruction** | Sarcoidosis<br>Lymphangioleiomyomatosis<br>Tuberous sclerosis<br>Interstitial lung disease with superimposed chronic obstructive pulmonary disease |
| **Isolated decrease in diffusing capacity of lung for carbon monoxide** | Interstitial lung disease with superimposed emphysema<br>Pulmonary vascular disease<br>Eosinophilic granuloma<br>Lymphangioleiomyomatosis |

the typical pulmonary restriction—and found that both groups had the same degree of pulmonary fibrosis, but that 86% of patients with preserved volumes had concomitant emphysema vs 19% of those with pulmonary restriction.

In ILD, the diffusing capacity of carbon monoxide is typically reduced to a greater extent than the lung volume at which it is measured,[17] and it appears to be more decreased in idiopathic pulmonary fibrosis than it is in ILD due, for example, to sarcoidosis.[20,21]

Arterial blood gas abnormalities characteristic of idiopathic pulmonary fibrosis include resting hypoxemia and an increase in the alveolar-arterial oxygen pressure difference.[17] Gas exchange abnormalities are more evident during exercise, with hypoxemia being highly prevalent.[22–25] TABLE 3 lists physiologic features and the diagnoses they suggest.

**Surgical lung biopsy is still the gold standard in ILD diagnosis**

### Pulmonary function testing

Pulmonary function testing is a helpful early diagnostic tool in patients with appropriate symptoms, perhaps more so than chest radiography and high-resolution computed tomography (CT).

In one study,[26] 44 dyspneic patients with biopsy-proven ILD had normal chest radiographs but several pulmonary function test abnormalities: the diffusing capacity of lung for carbon monoxide was decreased in 73% of patients, the vital capacity was low in 57%, and the total lung capacity was low in 16%.[26] In another study,[27] three of 25 dyspneic patients with biopsy-confirmed ILD had normal high-resolution CT scans, despite abnormal pulmonary function tests.[27] These data suggest that abnormal pulmonary function tests in patients with symptoms such as breathlessness and cough should prompt further evaluation for ILD.

Unfortunately, pulmonary function tests may be normal despite histologic and radiographic evidence of ILD, even in patients with idiopathic pulmonary fibrosis.[28,29] For example, in one study[30] two patients with biopsy-proven idiopathic pulmonary fibrosis had a diffusing capacity of lung for carbon monoxide greater than 70% of predicted, whereas the alveolar-arterial oxygen pressure difference was increased during both rest and exercise.[30] Therefore, normal pulmonary function test results cannot be assumed to exclude ILD when a patient has clinical or radiographic abnormalities that suggest it, although this is unusual.

### Chest radiography and high-resolution computed tomography

Radiographic studies are usually abnormal in patients with ILD, although chest radiographs and high-resolution CT scans are normal in 10%.[26,27] In general, chest radiographs and high-resolution CT scans show a mixture of interstitial and alveolar infiltrates. The techniques are most helpful, however, when they show characteristics that are "diagnostic" of a specific form of ILD (TABLES 4 AND 5).

The chief drawback with chest radiography in patients with ILD is a specificity of only 50%.[3]

High-resolution CT, on the other hand, has dramatically improved the diagnostic evaluation of patients with ILD. The technique allows a detailed evaluation of the lung parenchyma by using 1-mm to 2-mm slices reconstructed with an algorithm that maximizes spatial resolution.[31,32] Several studies[33] have confirmed that abnormalities not visible with chest radiography can be seen with high-resolution CT.[33] Furthermore, observer variability is less of a factor with high-resolution CT than with chest radiography, and a confident diagnosis is more likely with high-resolution CT.

High-resolution CT is particularly likely to be diagnostic in patients with idiopathic pulmonary fibrosis, lymphangitic carcinoma, sarcoidosis, silicosis, subacute hypersensitivity pneumonitis, and pulmonary alveolar proteinosis.[3] FIGURE 1 shows high-resolution CT scans of a patient with idiopathic pulmonary fibrosis and the characteristic findings of bibasilar interstitial and intralobular reticular opacities, irregular interlobular septal thickening, and subpleural honeycombing in the lower lobes in the absence of ground-glass densities and pleural abnormalities.[34]

The diagnostic sensitivity of high-resolution CT in patients with idiopathic pulmonary fibrosis is estimated at 84%, compared with a sensitivity of 73% for chest radiography.[33] When experienced radiologists interpreting high-resolution CT are confident of the diagnosis of idiopathic pulmonary fibrosis using these features, they are usually correct.[33] The diagnostic sensitivity and specificity for many other forms of ILD are less well defined and depend on the experience of the thoracic radiologist interpreting the study.[33]

## Bronchoscopic procedures

In the diagnosis of ILD, the role of bronchoscopy, including bronchoalveolar lavage and transbronchial biopsy, is unclear.

**Bronchoalveolar lavage** is easy to perform, is associated with little risk, and can be diagnostic in certain occupational exposures to inorganic dusts, malignancy, hematological disease, drug-induced lung disease, and pulmonary alveolar proteinosis.[3] A recent discriminant diagnostic model generated from bronchoalveolar lavage counts in a population of patients with sarcoidosis, hypersensitivity pneumonitis, and idiopathic pulmonary fibrosis was applied to a second group of patients with a similar distribution of ILD: importantly, 94.5% of the patients were correctly diag-

**TABLE 4**

### Parenchymal abnormalities on chest radiography: Associated diagnoses

| ABNORMALITY | POSSIBLE ASSOCIATED DIAGNOSES |
|---|---|
| **Micronodules (< 1.5 mm)** | Alveolar microlithiasis<br>Talc granulomatosis<br>Early pneumoconiosis<br>Thesaurosis (hair spray inhalation)<br>Early pneumocystis<br>Pulmonary alveolar proteinosis |
| **Nodules (up to 1 cm)** | Infection<br>Granulomatous inflammation<br>Pneumoconiosis<br>Cancer<br>Pulmonary hemosiderosis |
| **Linear opacities** | **Acute**<br>Congestive heart failure<br>Atypical pneumonia<br>Collagen vascular disease<br>**Chronic**<br>Idiopathic pulmonary fibrosis<br>Lymphocytic interstitial pneumonitis<br>Collagen vascular disease<br>Asbestosis<br>Radiation pneumonia<br>Drug-induced disease<br>Radiation pneumonitis<br>Lymphangitic tumor<br>Lymphagioleiomyomatosis<br>Sarcoidosis |
| **Honeycombing** | Idiopathic pulmonary fibrosis<br>Eosinophilic granuloma<br>Collagen vascular disease<br>Pneumoconiosis<br>End-stage hypersensitivity pneumonitis |
| **Airspace opacity** | Pulmonary hemorrhage<br>Acute or chronic eosinophilic pneumonia<br>Bronchiolitis obliterans with organizing pneumonia<br>Pulmonary alveolar proteinosis |

ADAPTED FROM ZIESCHE R, HOFBAUER E, WITTMANN K, PETKOV V, BLOCK L. A PRELIMINARY STUDY OF LONG-TERM TREATMENT WITH INTERFERON GAMMA-1B AND LOW-DOSE PREDNISONE IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS. N ENGL J MED 1999; 341:1264–1269, AND
KING JR TE. APPROACH TO THE PATIENT WITH INTERSTITIAL LUNG DISEASE. IN: B. ROSE, EDITOR. UP TO DATE, WELLESLEY, MA. 2000

nosed.[35] Still, the diagnostic role of lavage remains controversial, and definitive diagnosis usually requires biopsy.

**Transbronchial biopsy** can be performed at the same time as bronchoalveolar lavage but carries an additional risk of bleeding and pneumothorax. It can be very useful in the diagnosis of some patients with ILD, as enumerated in TABLE 6.[36] For example, the combination of bronchoalveolar lavage, transbronchial biopsy, and transbronchial mediastinal lymph node aspiration has proven highly sensitive in the diagnosis of sarcoidosis. These procedures were performed by Leonard and colleagues in 13 patients with suspected sarcoidosis and, in combination, provided a sensitivity of 100%.[37]

Unfortunately, transbronchial biopsy is of limited value in the diagnosis of idiopathic pulmonary fibrosis due to the small amount of tissue obtained.

### Surgical lung biopsy

Surgical lung biopsy remains the gold standard for the diagnosis of ILD.[38] In some cases, such as an elderly patient with advanced lung disease and high-resolution CT findings typical of idiopathic pulmonary fibrosis, the risks of surgery may outweigh the benefits in terms of the information it may provide regarding prognosis and treatment.

## ALGORITHMIC APPROACH TO DIAGNOSIS

While the diagnosis of ILD remains a challenging problem, a systematic approach as outlined in this article is helpful. FIGURE 2 presents our approach to evaluating patients with suspected ILD. This algorithm reflects published recommendations.[3,34,39]

In brief, a careful history and physical examination are followed by selected laboratory testing, chest radiography, and pulmonary function testing. A look at the criteria in TABLE 6 will help determine if a bronchoscopic procedure such as bronchoalveolar lavage or transbronchial biopsy will help the diagnosis. If not, or if the results of bronchoscopy are not diagnostic, then high-resolution CT assumes a pivotal role in further diagnostic efforts.

Typical historical features, physical findings, and typical features seen on high-resolution CT (FIGURE 1) offer a high degree of certainty that the patient has idiopathic pulmonary fibrosis.

**TABLE 5**

**Other abnormalities on chest radiography: Associated diagnoses***

| ABNORMALITY | POSSIBLE ASSOCIATED DIAGNOSES |
|---|---|
| **Normal or large lung volumes** | Eosinophilic granuloma<br>Sarcoidosis<br>Lymphangioleiomyomatosis<br>Cystic fibrosis |
| **Upper zone distribution** | Granulomatous inflammation<br>Pneumoconiosis (except asbestosis)<br>Ankylosing spondylitis<br>Cystic fibrosis<br>Infections (tuberculosis, fungal)<br>Drug-induced disease |
| **Lower zone distribution** | Idiopathic pulmonary fibrosis<br>Desquamative interstitial pneumonitis<br>Nonspecific interstitial pneumonitis<br>Drug-induced disease<br>Asbestosis<br>Scleroderma<br>Rheumatoid arthritis |
| **Pleural disease** | Asbestosis<br>Collagen vascular disease<br>Lymphangitic tumor<br>Lymphangioleiomyomatosis<br>Drug-induced disease<br>Sarcoidosis |
| **Pneumothorax** | Eosinophilic granuloma<br>Lymphagioleiomyomatosis<br>Tuberous sclerosis |
| **Mediastinal adenopathy** | Sarcoidosis<br>Lymphoma<br>Infection (tuberculosis, fungal)<br>Berylliosis<br>Amyloidosis<br>Malignancy |

*The chest radiograph may be normal in 10% of patients with interstitial lung disease with no known cause (ie, idiopathic pulmonary fibrosis) or due to collagen vascular disease, desquamative interstitial pneumonitis, hypersensitivity pneumonitis, or sarcoidosis.

### Evidence supporting this algorithmic approach

A prospective study[34] in a referral center with expertise in the evaluation of ILD recently val-

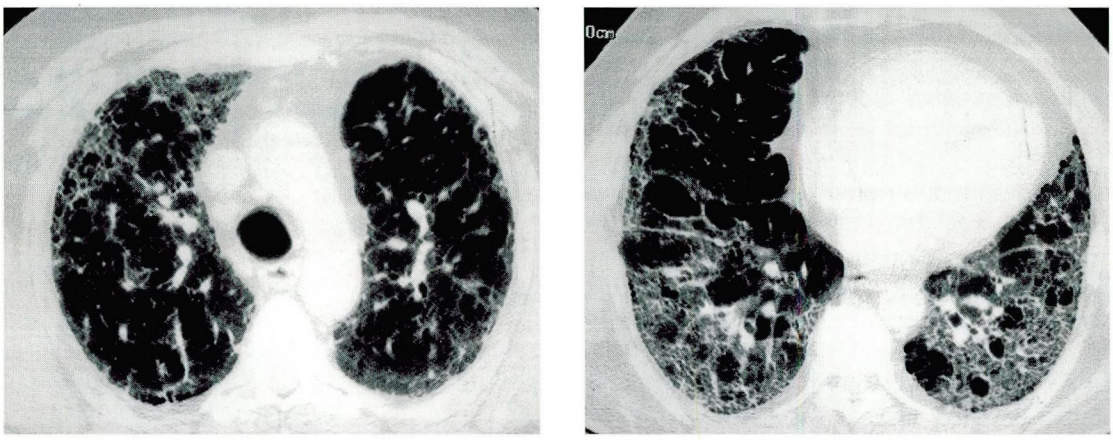

**FIGURE 1.** High-resolution computed tomography scans of the upper lung zones (left) and lower lung zones (right) in a 58-year-old man with progressive breathlessness over the previous 3 years. Both images demonstrate subpleural honeycombing, which is worse in the lower lung zones. Open lung biopsy confirmed the diagnosis of idiopathic pulmonary fibrosis (usual interstitial pneumonitis).

idated a similar diagnostic algorithm. Fifty-nine patients with new-onset ILD (29 with idiopathic pulmonary fibrosis, 13 with granulomatous inflammation, 17 with miscellaneous diseases) were evaluated according to specific clinical and radiographic criteria. A clinical diagnosis was made by an expert clinician after initial evaluation including high-resolution CT and bronchoscopic biopsy. Using surgical lung biopsy as the gold standard, the sensitivity of the algorithm for diagnosing ILD other than idiopathic pulmonary fibrosis as 88.8%, the specificity was 40%, the positive predictive value was 94%, and the negative predictive value was 25%. For idiopathic pulmonary fibrosis, the sensitivity was 62%, specificity 97%, positive predictive value 95%, and negative predictive value 73%.

**In 10% of cases, the x-ray and CT are normal**

Importantly, one third of patients with a final diagnosis of idiopathic pulmonary fibrosis would not have been diagnosed without surgical lung biopsy, despite evaluation by a highly experienced group of physicians. Clearly, a strong suspicion of idiopathic pulmonary fibrosis on clinical and radiographic grounds is quite valuable, although the reverse may not be true.

## PROGNOSIS AND SURVIVAL IN PATIENTS WITH INTERSTITIAL LUNG DISEASE

The overall prognosis for patients with ILD varies widely according to the specific diagnosis. In general, patients with idiopathic pulmonary fibrosis have the worst prognosis, with median survival times ranging from 2 to 5 years after the onset of symptoms.[31] The most common causes of death in these patients are respiratory failure, heart failure, bronchogenic carcinoma, ischemic heart disease, infection, and pulmonary embolism.[40]

Patients with nonspecific interstitial pneumonia[41] have a better prognosis, with an estimated median survival greater than 10 years.[42–44] Patients with bronchiolitis obliterans organizing pneumonia (BOOP), desquamative interstitial pneumonia, and respiratory bronchiolitis-associated ILD have an excellent prognosis.[44]

The prognosis for patients with granulomatous lung diseases such as sarcoidosis or hypersensitivity pneumonitis is generally good. A study of 479 patients with sarcoidosis identified only 13 (3%) deaths due to respiratory failure.[45] Similarly, a study from Finland[46] identified only 13 deaths attributable to hypersensitivity pneumonitis (farmer's lung) over a 10-year period. In both of these studies mortality was associated with the fibrotic changes on chest radiography.

### Lung cancer risk

Progressive pulmonary fibrosis, however, is not the only cause of death in patients with ILD. Patients with silicosis, asbestosis, and idio-

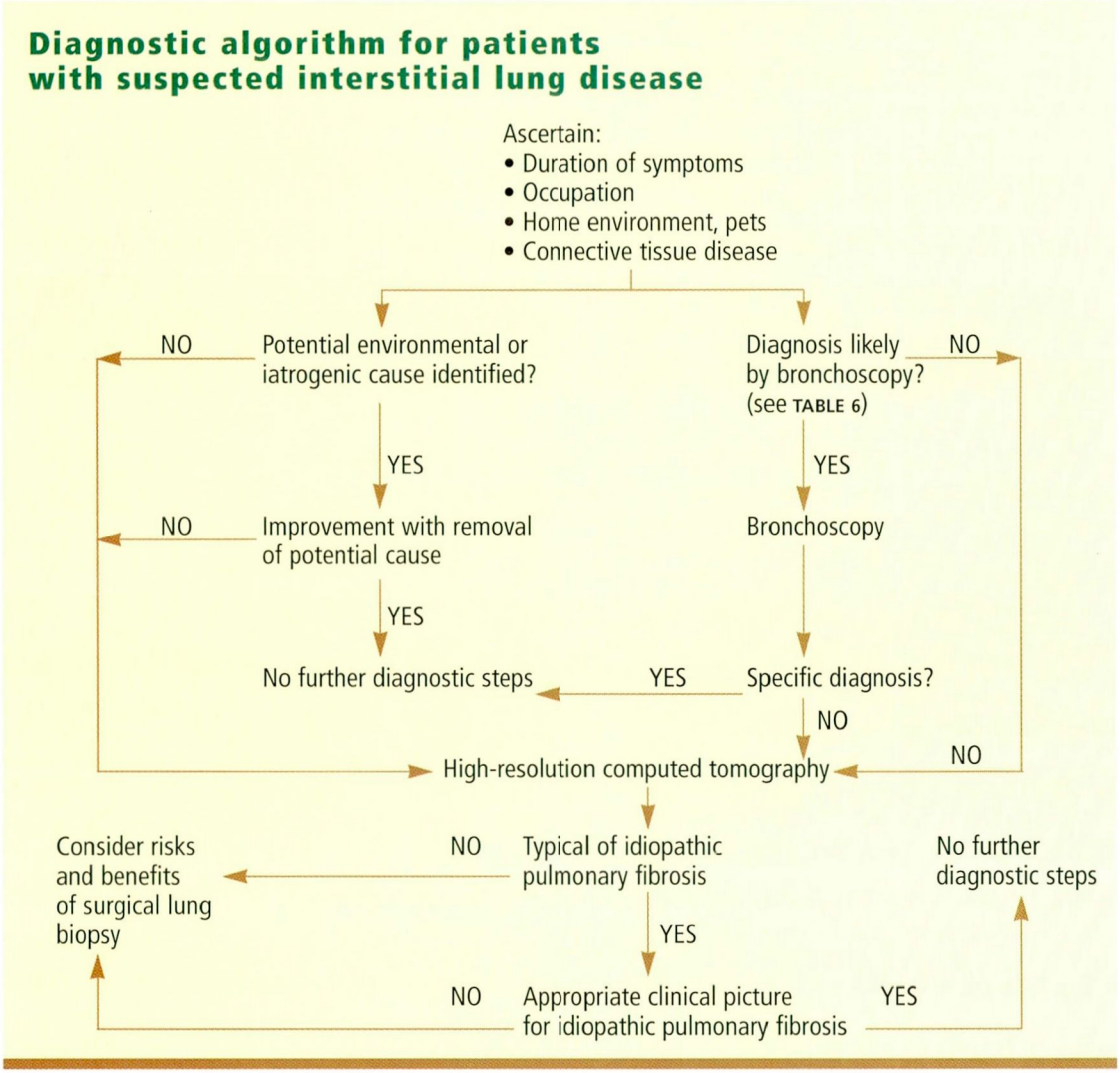


**FIGURE 2**

ADAPTED FROM REFERENCES 3, 34, AND 39.

pathic pulmonary fibrosis have an increased risk of lung cancer compared to the general population. A study from Finland[47] using a cancer registry found the standardized incidence ratio for all cancers to be 1.5 (95% CI, 1.0–2.1) for silicosis patients and 3.7 (95% CI, 2.8-5.0) for asbestosis patients.

Similarly, a recent population-based cohort study of 890 subjects with idiopathic pulmonary fibrosis in the United Kingdom[48] confirmed a markedly increased incidence of lung cancer (RR 7.31, 95% CI, 4.47–11.93) which persisted despite adjustment for smoking history. These patients could potentially benefit from cancer screening, although data addressing this issue are sparse.

## TREATMENT OPTIONS IN INTERSTITIAL LUNG DISEASE

The treatment of ILD is evolving and controversial. For disorders such as sarcoidosis and hypersensitivity pneumonitis, steroid therapy is useful.[3,49,50] Unfortunately, in some cases patients cannot tolerate steroid therapy and second-line immunosuppressive agents may be considered.

For pulmonary sarcoidosis, the recommended corticosteroid dosage is 20 to 40 mg of an intermediate-acting corticosteroid such as prednisone or an equivalent daily for 1 to 3 months.[49] The optimal duration of therapy is controversial, but the current recommenda-

**Silicosis, asbestosis, and idiopathic pulmonary fibrosis increase lung cancer risk**

**TABLE 6**

**When is transbronchial lung biopsy useful in the workup of interstitial lung disease?**

**Very useful when the cause of interstitial lung disease is:**
Sarcoidosis
Lymphangitic carcinomatosis
Alveolar proteinosis
Bronchoalveolar carcinoma
Eosinophilic pneumonia
Berylliosis

**Occasionally useful when the cause of interstitial lung disease is:**
Eosinophilic granuloma
Amyloidosis
Wegener granulomatosis
Pulmonary lymphoma
Hypersensitivity pneumonitis
Pulmonary capillaritis/vasculitis
Lymphocytic interstitial pneumonia
Bronchiolitis obliterans organizing pneumonia

**Not useful when the cause of interstitial lung disease is:**
Unknown (ie, idiopathic pulmonary fibrosis)
Any disease with underlying usual interstitial pneumonitis

ADAPTED FROM SCHWARZ MI. APPROACH TO THE UNDERSTANDING, DIAGNOSIS, AND MANAGEMENT OF INTERSTITIAL LUNG DISEASE. IN: M. SCHWARZ AND T. KING JR, EDITORS. INTERSTITIAL LUNG DISEASE. B. C. DECKER, INC., HAMILTON, ON. 1998: 3–30.

tion is for responders to be tapered to 10 mg every other day, with treatment continued for at least 1 year.

In the minority of patients not responding to or unable to tolerate steroids, alternative agents such as methotrexate, azathioprine, cyclophosphamide, and chlorambucil can be considered.

In hypersensitivity pneumonitis, the first therapy is antigen avoidance. Corticosteroids may be useful, especially for severely ill patients, although their impact on the long-term course of disease is uncertain.[51] The recommended dose of corticosteroids is prednisone 0.5 mg to 1.0 mg per kg of ideal body weight (maximum 60 mg/day) for 1 to 2 weeks, tapering over the next 2 to 4 weeks.[51]

In contrast, idiopathic pulmonary fibrosis responds to high-dose steroid treatment, but only in a minority of cases and with a high incidence of adverse reactions.[52] Currently, the recommended therapy for idiopathic pulmonary fibrosis is combination therapy with low-dose prednisone plus azathioprine or cyclophosphamide.[31]

Unfortunately, there is little evidence that any of the therapies currently available improves survival or quality of life.[31,53,54] However, several encouraging advances are on the horizon.[55,56] Ziesche and colleagues[55] randomized 18 patients with IPF (definite or probably in 15) who had experienced progressive disease despite prednisone therapy to subcutaneous interferon gamma 200 mg three times per week plus low-dose oral prednisolone compared to placebo plus the same dose of oral steroid. Of importance, they demonstrated that pulmonary function improved in the interferon gamma group although it decreased in the placebo group. A large, multicenter study has recently been initiated to confirm these exciting, preliminary findings.

## Authors' recommendation for treatment

Because ILD often responds poorly to therapy, and because of the potential for progressive deterioration over time, we believe all patients with ILD should have at least an initial evaluation by a pulmonologist before starting any form of therapy. The goal of this approach is to facilitate the enrollment of patients into multicenter treatment trials to determine which agents are most beneficial for the various forms of ILD. Such an approach can also facilitate early evaluation and consideration of other therapeutic interventions, such as lung transplantation.

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