



What's New in Interstitial Lung Disease?

Nasreen Khalil, MD, FRCPC, FCCP

Presented at UBC's 4th Annual Advances in Respiratory and Critical Care Medicine, 2003

There are well over 200 causes or conditions associated with pulmonary fibrosis.¹⁻⁴ The most common chronic interstitial lung diseases (ILDs) are (Table 1):

- Idiopathic pulmonary fibrosis (IPF);
- Hypersensitivity pneumonitis (HP);
- Sarcoidosis; and
- Pulmonary fibrosis (associated with collagen vascular diseases, drug-associated interstitial lung disease and non-specific interstitial pneumonia [NSIP]).^{1,2}

What's new in ILD?

A new classification describes idiopathic interstitial pneumonias, clearly distinguishing between the diagnostic terminology of the disease entity and the histological pattern on a surgical lung biopsy.² For example, the diagnosis of the IPF is based on the integration of clinical, radiologic, and histologic findings of usual interstitial pneumonia (UIP) (Table 1).^{1,2} It should be recognized that, as a histologic pattern, UIP may be found in lung biopsies of diseases other than IPF, such as pulmonary fibrosis associated with collagen vascular diseases, asbestosis and chronic drug toxicity, familial IPF, and rare conditions, such as the Hermansky-Pudlak syndrome.^{1,2} Also included in the new classification is NSIP; this is characterized by interstitial inflammation and/or fibrosis that is temporally homogeneous. NSIP is confused with clinical IPF and, on histology, may overlap with UIP.¹ It is recognized by the authors of the new classification that some histologic changes cannot be classified and are referred to as "non-classifiable" idiopathic interstitial pneumonias.¹

Henry's condition

Henry, 68, worked in a coal mine as a teen. He had progressive shortness of breath on exertion. A chest radiograph demonstrated basal reticular pattern, and a high-resolution axial tomography demonstrated subpleural fibrosis and honeycomb cysts. Lung function studies demonstrated:



- Forced vital capacity (FVC): 3.5 L (82% of predicted);
- Forced expiratory volume 1 (FEV1): 3.1 L (91% of predicted);
- FEV1/FVC: 87.3% (109% of predicted); and
- Diffusion of carbon monoxide: 11.9 mL/min/mmHg (42% of predicted).

On diagnostic lung biopsy, there was normal lung, interstitial fibrosis, honeycomb cysts, and numerous fibroblast foci. The histology was compatible with usual interstitial pneumonia of idiopathic pulmonary fibrosis.

Henry took 50 mg of prednisone/day for 6 weeks. After 6 weeks, his FVC was 3.0 L (70% of predicted). Azathioprine was added (150 mg/day), and the steroids were decreased to 20 mg/day.

He died of respiratory failure 4 years after presentation.

A correct diagnosis is important to determine the prognosis and treatment of ILD. The histologic pattern of UIP has a very poor prognosis, and is not responsive to corticosteroids or any other immunosuppressive drugs.⁵⁻¹⁰ However, the other idiopathic

Table 1

Description of histology of the interstitial lung diseases

<u>Nomenclature</u>	<u>Histologic characteristics</u>
Usual interstitial pneumonia	Temporally heterogeneous lesions with normal lung, interstitial fibrosis, honeycomb cysts, and fibroblast foci.
Nonspecific interstitial pneumonia	Temporally homogeneous interstitial inflammation and/or fibrosis.
Organizing pneumonia	Fibrous material in air spaces, patchy involvement with normal lung, fibrosis, and inflammatory changes.
Diffuse alveolar damage	Histology depends on the time interval from the time symptoms to the lung biopsy. Acutely, there is interstitial edema, hyaline membranes, and evidence of injury to the alveolar epithelial and endothelial cells. This stage is followed by interstitial fibrosis and alveolar epithelial cell hyperplasia.
Respiratory bronchiolitis	Patchy inflammation with a peribronchial distribution, with large areas of intervening normal lung parenchyma.
Desquamative interstitial pneumonia	Temporally uniform and diffuse distribution of mononuclear cells in the distal air spaces.
Lymphocytic interstitial pneumonia	Diffuse mixed inflammatory infiltrates of lymphocytes, plasma cells, histiocytes with occasional germinal centres and granulomas.

Taken from: American Thoracic Society and European Respiratory Society: ATS/ERS international consensus classification of idiopathic interstitial pneumonias. *Am J Resp Crit Care Med* 2002; 165(2):277-304.

hospital and ICU mortality rates were 61% and 45% respectively.⁹ Of the patients discharged, over 90% died within a few months after discharge.¹¹ The study demonstrates the poor prognosis of IPF patients who are admitted to the ICU with respiratory failure.⁹ The results from this study should prompt discussions with the patient and family about admission and life support in the event of worsening symptoms.

What's new in collagen vascular diseases?

The association between collagen vascular diseases

interstitial pneumonias have a better prognosis and are responsive to corticosteroids.⁵⁻¹⁰

What's new in IPF?

IPF is a progressive ILD with no known etiology or effective treatment.^{1,2} The life expectancy after presentation and diagnosis is 3 to 5 years.¹⁻¹⁰ In a recent study, the outcome of patients with IPF admitted to the intensive care unit was evaluated.¹¹ In this study, 38 patients with the diagnosis of IPF were admitted to the ICU for worsening respiratory failure.¹¹ The

and ILD is well established.¹² A number of histologic patterns in the lung are seen in patients with collagen vascular diseases.¹²⁻¹³ Using the new classification, a recent review of ILD in collagen vascular diseases demonstrates that NSIP is a very prominent form of ILD in these disorders.¹³ NSIP is a common histologic pattern in progressive systemic sclerosis or scleroderma.¹³ The best supported treatment for NSIP of scleroderma is prednisone and pulse doses of intravenous cyclophosphamide.^{12,13} This combined treatment results in improving the clinical, physiologic, and radiologic

Frequently Asked Questions

1. How is ILD diagnosed?

If the clinical history, physical examination, and findings on high-resolution computed axial tomography are classic for IPF, no further investigations are necessary. Sarcoidosis and, sometimes, hypersensitive pneumonitis can be diagnosed on a transbronchial lung biopsy. The gold standard for the definitive diagnosis of an ILD requires a diagnostic lung biopsy.

2. How is ILD treated, cured, and managed?

There is no known effective treatment or cure for IPF. Some patients achieve stability in lung function with prednisone, 20 mg/day, and azathioprine, 150-200 mg/day. Other ILDs may respond to prednisone alone, or in combination with other immunosuppressive agents.

3. Who is most at risk?

The risk factors are not clearly defined. However, exposure to avian antigens and spores from thermophilic actinomycetes and several other organic antigens may result in hypersensitivity pneumonitis. Well-recognized drugs that result in interstitial lung disease are listed in Table 2. Exposure to asbestos can result in asbestosis. Patients with collagen vascular diseases may develop an ILD.

4. What is the GP's role?

The GP should recognize the presence of an ILD by using the history, chest radiology, and lung function studies. Thereafter, the GP works in partnership with a consulting pulmonary physician, especially one with an expertise in ILD.



Dr. Khalil is an associate professor of medicine in the respiratory division, department of medicine, University of British Columbia. She is a consulting pulmonary physician at the Vancouver General Hospital and St. Paul's Hospital, Vancouver, B.C.

Take-home message



- A new classification of the idiopathic interstitial pneumonias has been described.
- IPF remains the most common idiopathic interstitial pneumonia.
- The prognosis of patients with IPF remains poor.
- NSIP is a common ILD in patients with progressive systemic sclerosis and other collagen vascular diseases. NSIP in scleroderma responds well to corticosteroids combined with cyclophosphamide.
- Many patients with sarcoidosis who are unresponsive to corticosteroids respond to methotrexate.

parameters, and reversing some of the underlying alveolitis in patients with NSIP.^{14,15}

What's new in drug-induced ILDs?

Drug-induced lung disease has been recognized for many years. A recent study reported by Cleverly JR et al. indicates the drugs currently seen to induce ILD are essentially the same as before.¹⁶ Twenty cases were reviewed in this study, and the most common drugs that resulted in ILD were chemotherapeutic agents, nitrofurantoin, and amiodarone.¹⁶

What's new in sarcoidosis?

Sarcoidosis is a multisystemic disease of unknown etiology with non-caseating granulomas involving many organs.^{17,18} The indications for therapy depend on the site of organ involvement, extent of clinical symptoms, and disease activity.^{17,18} Many patients do not require any treatment, while others respond to corticosteroids. In patients with sarcoidosis who do not respond to steroids, methotrexate, a folic acid antagonist, has been found to improve lung func-

Table 2

Common drugs associated with interstitial lung disease

Diagnosis

Bone marrow transplantation

Hodgkins/non-Hodgkins lymphoma

Urinary tract infection

Ischemic heart disease

Other malignancies

Other diagnoses

Drugs

Busulfan, melphalan, cyclophosphamide, carboplatin, methotrexate

BCNU, bleomycin

Nitrofurantoin

Amiodarone

Bleomycin, chlorambucil

Methotrexate, flupenthixol, benzotropine, 5-ASA, cyclophosphamide

BCNU: Bischloroethyl nitrosourea
ASA: Acetylsalicylic acid

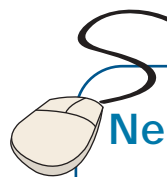
Taken from: Cleaverly JR, Sreaton NJ, Hiorns MP, et al: Drug-induced lung disease: High-resolution CT and histological findings. *Clin Radiol* 2002; 57(4):292-9.

11. Saydain G, Islam A, Afessa B, et al: Outcome of patients with IPF admitted to ICU. *Am J Resp Crit Care Med* 2002; 166(6): 839-42.
12. Kim EA, Lee KS, Johkoh T, et al: J. Interstitial lung diseases associated with collagen vascular diseases: Radiological and histopathologic findings *Radiographics* 2002; 22:S151-65. Erratum in: *Radiographics* 2003; 23(5):1340.
13. Kim DS, Yoo B, Lee JS, et al: The major histological pattern of pulmonary fibrosis in scleroderma is nonspecific interstitial pneumonia, *Sarcoid Vasc Diffuse Lung Dis* 2002; 19(2):121-7.
14. White B, Moore WC, Wigley FM, et al: Cyclophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis. *Ann Intern Med* 2000; 132(12):947-54.
15. Pakas I, Ioannidis JP, Malagari K, et al: Cyclophosphamide with low or high dose prednisolone for systemic sclerosis lung disease. *J Rheumatol* 2002; 29(2):298-304.
16. Cleaverly JR, Sreaton NJ, Hiorns MP, et al: Drug-induced lung disease: High-resolution CT and histological findings. *Clin Radiol* 2002; 57(4):292-9.
17. Vucinic VM: What is the future of methotrexate in sarcoidosis? A study and review. *Curr Opin Pulm Med* 2002; 8(5):470-6.
18. Baughman RP, Lower EE: A clinical approach to the use of methotrexate for sarcoidosis. *Thorax* 1999; 54(8):742-6.

tion.^{17,18} Methotrexate is also suggested for patients failing treatment with corticosteroids, or those with adverse effects from steroids.^{17,18} CME

References

1. American Thoracic Society and European Respiratory Society: ATS/ERS international consensus classification of idiopathic interstitial pneumonias. *Am J Resp Crit Care Med* 2002; 165(2):277-304.
2. American Thoracic Society: Idiopathic pulmonary fibrosis: Diagnosis and treatment, international consensus statement. *Am J Resp Crit Care Med* 2000; 161(2):646-64.
3. Agostini C, Albera C, Bariffi F, et al: First report of the Italian registry for diffuse infiltrative lung disorders (RIPID). *Monaldi Arch Chest Dis* 2001; 56(4):364-8.
4. Coultas D, Zumwalt W, Black W, et al: The epidemiology of interstitial lung disease. *Am J Resp Crit Care Med* 1994; 150(4):967-72.
5. Latsi PI, du Bois RM, Nicholson AG, et al: Fibrotic idiopathic interstitial pneumonia: The prognostic value of longitudinal functional trends. *Am J Respir Crit Care Med* 2003; 168(5):531-7.
6. Flaherty KR, Mumford JA, Murray S, et al: Prognostic implications of physiologic and radiologic changes in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; 168(5):543-8.
7. Flaherty KR, Kazerooni EA, Gross BH, et al: Radiological versus histological diagnosis in UIP and NSIP: Survival implications. *Thorax* 2003; 58(2):143-8.
8. Katzenstein AL, Meyers JL: Idiopathic pulmonary fibrosis: Clinical relevance of pathological classification. *Am J Resp Crit Care Med* 1998; 157(4Pt1):1301-15.
9. Flaherty KR, Toews GB, Travis WD, et al: Clinical significance of histological classification of idiopathic interstitial pneumonia. *Eur Resp J* 2002; 19(2):275-83.
10. Travis WD, Matsui K, Moss JE, et al: Idiopathic nonspecific interstitial pneumonia: Prognostic significance of cellular and fibrosing patterns. Survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. *Am J Surg Pathol* 2000; 24(1):19-33.



Net Reading

American Lung Association

www.lungusa.org/diseases/pulmfibrosis.html