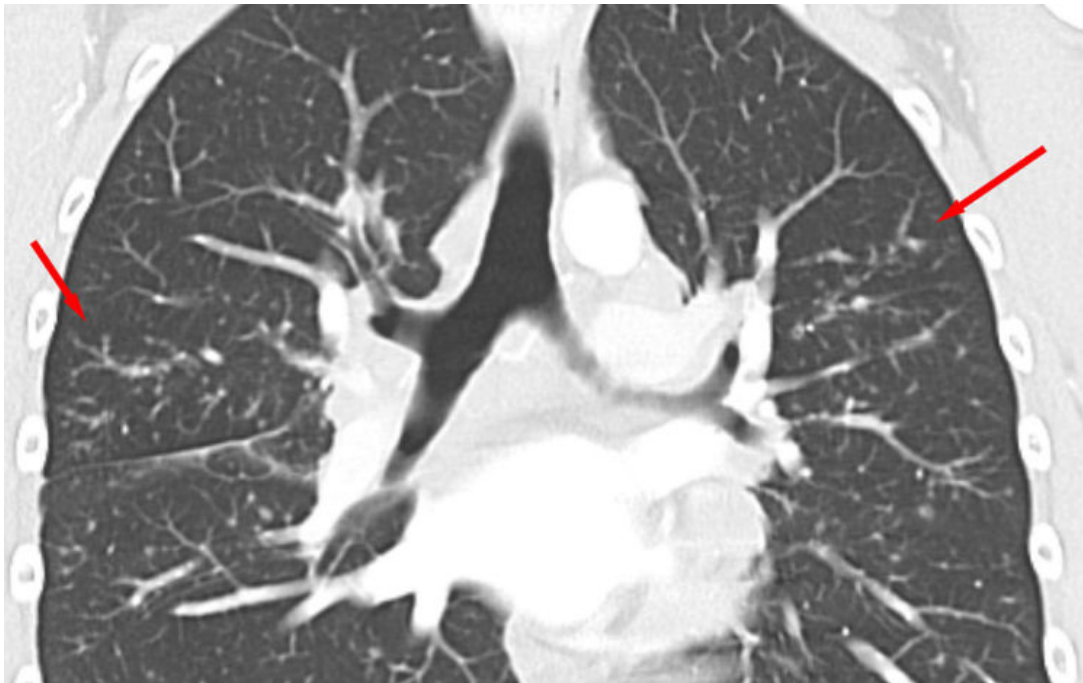


## Interstitial Lung Disease (ILD) — Types and Symptoms

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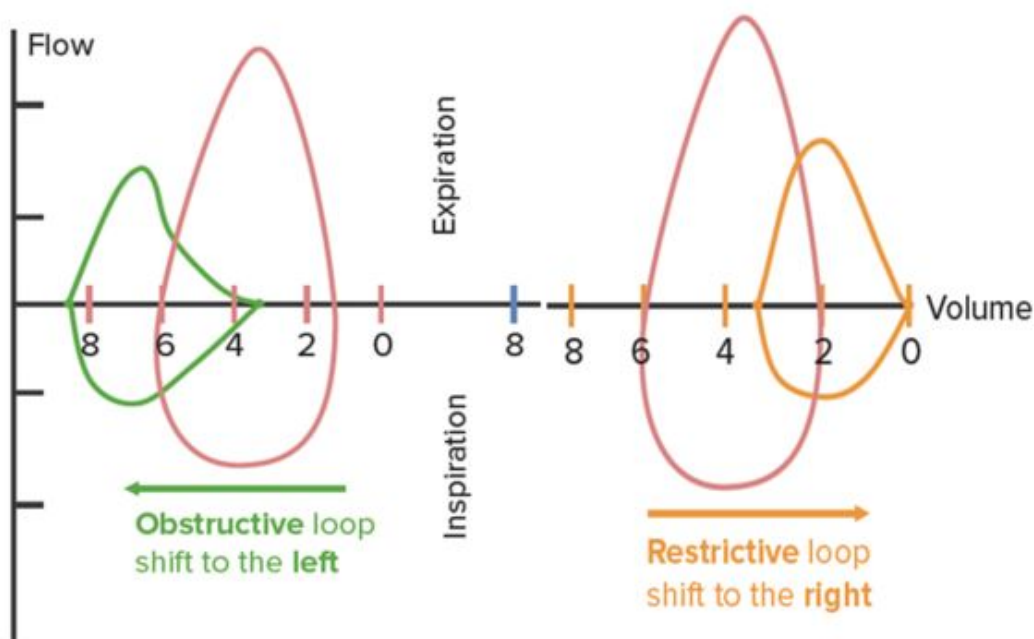
**Patients with interstitial lung disease usually present with progressive exertional dyspnea, cough, and hypoxemia. Computed tomography imaging of the lungs can reveal fibrosis or granulomatous disease. Symptomatic treatment with oxygen supplementation might be needed but specific treatment should also be tried because some conditions are known to respond to medical therapy. Lung transplantation should be available as an option for patients who do not respond to medical therapy.**



### Definitions Related to Interstitial Lung Disease

Interstitial lung diseases are part of the Restrictive Lung Disease category. Restrictive Lung Diseases can be extra-pulmonary, pleural or parenchymal. They all restrict lung expansion, with the result of a smaller lung volume available for breathing and air exchange. This causes increased work of breathing and impairs ventilation.

A key indicator of Restrictive Lung Disease is a decreased forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), with FVC being more affected than FEV1, giving a ratio **higher** than 80 %. Conversely, in obstructive Lung disease, such as COPD, the ratio is lower than 0.7, indicating an increased residual volume, a decreased FEV1 compared to FVC.



In the lung parenchyma, Restrictive Lung Disease is characterized by **interstitial lung fibrosis** and in some conditions **granulomatous formation**. While the etiology of some of these diseases can be identified, the majority of the cases happen without an apparent cause. There are **more than 200 different types** of interstitial lung diseases.

**Here are the most common:**

- Pneumoconiosis caused by long-term exposure to dusts, especially in coal mining, such as Asbestosis
- Radiation fibrosis, usually from cancer treatment
- Amiodarone, bleomycin, and methotrexate
- [Rheumatoid arthritis](#)
- Hypersensitivity pneumonitis due to an allergic reaction to inhaled particles
- Acute respiratory distress syndrome (ARDS), a severe lung condition occurring in response to a critical illness or injury
- Infant respiratory distress syndrome due to a deficiency of surfactant in the lungs of a baby born prematurely
- Granulomatous diseases of the lung, such as tuberculosis

**A significant number of patients develop pulmonary fibrosis of unknown etiology:**

- Idiopathic pulmonary fibrosis
- Idiopathic interstitial pneumonia
- Sarcoidosis
- Eosinophilic pneumonia
- Lymphangioleiomyomatosis
- Pulmonary Langerhans' cell histiocytosis
- Pulmonary alveolar proteinosis

## Fibrosing lung diseases

**Idiopathic pulmonary fibrosis**, historically known as idiopathic or **cryptogenic** fibrosing alveolitis, is a chronic and ultimately fatal disease characterized by a progressive decline in lung function. PF belongs to a large group of more than 200 lung diseases known as interstitial lung diseases (ILDs), characterized by the involvement of lung interstitium.

In this group of conditions that includes fibrosing **alveolitis** and **systemic sclerosis** cause pulmonary fibrosis by **continuous injury and repair of the lung tissue**. The alveolar walls are usually thickened due to extracellular deposition of collagen and interstitial fibrosis. The prevalent theory is that the initial or repetitive injury in IPF occurs to the alveolar epithelial cells, or pneumocytes, which line the majority of the alveolar surface.

When type I AECs are damaged or lost, it is thought that type II AECs undergo proliferation to cover the exposed basement membranes. They eventually die and the remaining cells spread and undergo a differentiation process to become type I AECs. Under pathologic conditions and in the presence of transforming growth factor-beta (TGF $\beta$ ), **fibroblasts** accumulate in these areas of damage and differentiate into myofibroblasts that secrete collagen. **Secondary and primary pulmonary hypertension** can also induce lung fibrosis.

**Lymphangiomyomatosis** is a disease that only affects women and has been associated with smooth muscle cell hypertrophy, interstitial lung fibrosis, and lung cystic formation.

### Different causes of pulmonary fibrosis and their characteristics

Cause of PF	Disease pattern	Notes
Idiopathic	Bibasal symmetric Progressive	Median age 70 years, 66 % men, 33 % women
Connective tissue associated	Bibasal symmetric Progressive	Median age 50 to 60 years, men = women, e.g., rheumatoid arthritis, systemic sclerosis, dermatomyositis
Pneumoconiosis	Variable	E.g., asbestosis = bibasal PF, similar to IPF
Drugs	Acute or chronic onset	E.g., chemotherapy agents (bleomycin, cyclophosphamide), nitrofurantoin, amiodarone
Radiotherapy	Within the radiotherapy field Acute or chronic onset	Characteristics straight edge on X-ray
Post-ARDS	Acute onset, bilateral	Dates to ITU admission with ARDS
End stages of other ILDs	Upper lobe disease	Sarcoidosis and hypersensitivity pneumonitis

## Granulomatous lung diseases

Granulomatous lung diseases are characterized by the formation of granulomas in the lung that consists of inflammatory cells infiltrates. **Sarcoidosis**, and **chronic beryllium exposure** cause granulomatous lung disease. **Tuberculosis** is an infective lung disease that is associated with lung granuloma formation.

# Epidemiology of Interstitial Lung Disease

The exact prevalence of the different types of interstitial lung diseases is believed to be extremely low but the prevalence of the collective of the diseases is estimated to be **50 per 100,000**.

Occupational exposure to **coal dust** has been associated with **pneumoconiosis**, while exposure to **beryllium** might induce granulomatous lung disease. **Asbestos** exposure has also been linked to fibrosing lung disease.

Other possible risk factors of interstitial lung disease include the use of **amiodarone**, **radiation exposure**, **tobacco smoking**, and **gender** in lymphangioleiomyomatosis.

Lymphangioleiomyomatosis is a condition that can be found only in females especially those with **tuberous sclerosis**. Age is a very important non-modifiable risk factor for interstitial lung disease because these conditions are commonly found in the elderly.

Patients affected by interstitial lung disease often suffer **significant morbidity** because the condition is progressive. Despite our current understanding of the pathogenesis of the condition, **mortality** remains high in interstitial lung diseases.

## Pathophysiology of Interstitial Lung Disease

While all interstitial lung diseases share the common end-point of continuous lung injury and repair that leads to **fibrosis** and/or **granuloma formation**, the exact first steps in the pathogenesis of the condition are different per the type of interstitial lung disease.

### Cryptogenic fibrosing alveolitis (or **idiopathic pulmonary fibrosis**)

Patients with this condition have **chronic deposition of inflammatory cells** that include macrophages and neutrophils in the lung's interstitial tissue. Eventually, a **vicious cycle** starts where immune cells recruit more immune cells and tissue injury ensues.

The **inflammatory response** in cryptogenic fibrosing alveolitis is believed to be the first step in the pathogenesis of the condition. The **release of different cytokines, mostly Transforming Growth Factor Beta, (or TGF-beta)** triggers cellular proliferation, fibroblast activation and the deposition of collagen and fibrosis.

**Exposure to dust** and **tobacco smoking** are believed to be the first insult to the lung tissue which results in the accumulation of immune cells. Additionally, **certain polymorphisms in the major histocompatibility complex genes** have been linked to an increased risk of the disease, further emphasizing the role of the immune response in the pathogenesis of the condition.

### Systemic sclerosis

Systemic sclerosis is an **autoimmune disease** that is clearly linked to the **major histocompatibility complex genes**. Patients usually have **serum antinuclear antibodies**.

Patients develop **fibrosing alveolitis** due to the activation of the immune system, the

activation of the inflammatory response and continuous lung tissue injury and repair. Therefore, the pathogenesis seems similar to cryptogenic fibrosing alveolitis.

## Lymphangiomyomatosis

Patients affected by this condition develop **multiple lung cysts**. Patients develop **lymphatic vessels hyperplasia, smooth muscle cell proliferation, and lung fibrosis**. The condition is linked to **tuberous sclerosis**, another genetic disorder that is characterized by the formation of tubercula, which are believed to be related to an uncontrolled inflammatory response among other pathologic mechanisms.

## Sarcoidosis

**Activation and deposition of T-cells and mononuclear immune cells** is the hallmark of sarcoidosis associated lung disease. Activated immune cells usually accumulate in a granuloma configuration. Sarcoidosis might have an infectious etiology as it has been linked to **mycobacterium infection**, but this finding remains debatable.

### Manifestations of extrapulmonary sarcoid

<b>Eyes:</b> 25 %	Uveitis, scleritis
<b>Neurological:</b> 5—20 %	<ul style="list-style-type: none"> <li>• Cranial nerve palsies</li> <li>• Peripheral neuropathy</li> <li>• CNS deposits</li> </ul>
<b>Parotid and salivary glands:</b> 5 %	<ul style="list-style-type: none"> <li>• Conduction defects</li> <li>• Fatal arrhythmias</li> <li>• Restrictive cardiomyopathy</li> </ul>
<b>Skin:</b> 25 %	<ul style="list-style-type: none"> <li>• Lupus pernio (non-tender blue nodules, especially in scars)</li> <li>• Erythema nodosum</li> </ul>
<b>Nose:</b> rare	Nasal destruction
<b>Endocrine:</b> 5 %	<ul style="list-style-type: none"> <li>• Hypercalcemia</li> <li>• Hypopituitary and diabetes insipidus (pituitary granulomas)</li> </ul>
<b>Liver:</b> 60 %	Hepatosplenomegaly, abnormal liver function tests
<b>Spleen:</b> 40 %	Splenomegaly
<b>Joints:</b> 15—20 %	Arthralgia
<b>Extrathoracic lymph nodes</b>	

## Clinical Presentation of Interstitial Lung Disease

Patients with interstitial lung diseases present with **non-specific symptoms** that include dyspnea, unexplained weight loss, fatigue and in some cases fever. **Cough** is another common symptom among these patients.

Patients with systemic causes of interstitial lung disease such as systemic sclerosis or sarcoidosis can have symptoms related to the systemic illness. For example, patients with systemic sclerosis can develop **cutaneous sclerosis**, or **difficulty swallowing** while patients with sarcoidosis can present with **joint pain**.

**Occupational history** is important in interstitial lung diseases as exposure to certain chemicals and dusts is known to increase the risk. Additionally, **the family history** of the disease can be evident in some patients due to the previously discussed link between genetic and disease predisposition. **Smoking history** should be explored in patients with respiratory symptoms.

**Tuberous sclerosis** is a systemic illness and patients can have **epilepsy**, **cognitive impairment**, and increased risk of **malignancies** in addition to their lung disease. Physical examination usually confirms the presence of **troubled breathing** and **pulmonary function tests** might show some impairment but **imaging studies combined with histopathological examination** remain the mainstay diagnostic tools for interstitial lung diseases.

## Diagnostic Work-up for Interstitial Lung Disease

**High resolution computed tomography** is perhaps one of the most important investigations in the diagnostic work-up of patients presenting with interstitial lung disease. Patients have a picture that is consistent with **idiopathic lung fibrosis**, i.e. **reticular pattern background with grown-glass appearance**.



**Image:** "CT scan of nodular sarcoidosis. Nodular lung lesions are reported in up to 4% of cases of sarcoidosis." by Yale Rosen from USA - Nodular sarcoidosis - CT scan Uploaded by CFCF. License: [CC BY-SA 2.0](https://creativecommons.org/licenses/by-sa/2.0/)

If combined with **histopathological examination of a lung biopsy**, the diagnostic yield is usually good enough. Patients might have a picture of either **fibrosing alveolitis** or **granulomatous lung disease**.

**Immune cell infiltrates**, **smooth muscle cell hyperplasia**, and **fibrosis** are common in fibrosing alveolitis diseases. On the other hand, patients with granulomatous disease usually have lung granulomas that consist of multiple layers of activated T-cells and mononuclear cells.

**Serologic testing** might be useful in case of systemic sclerosis. **Autoantibodies** are commonly identified and are believed to be related to the pathogenesis of the condition. Patients with **anti-topoisomerase autoantibody** are at risk of pulmonary fibrosis. Topoisomerases are enzymes that cut one of the two strands of double-stranded DNA, relax the strand, and reanneal the strand. Those with **anti-centromere autoantibodies**

usually have limited cutaneous disease.

**Serum calcium and angiotensin-converting enzyme levels** might be elevated in patients with sarcoidosis.

## Treatment of Interstitial Lung Disease

Patients with a confirmed diagnosis of cryptogenic fibrosing alveolitis (Idiopathic pulmonary fibrosis) should be started on **prednisolone** 0.5 mg/kg and **azathioprine** 3 mg/kg for one month. After that, prednisolone dosage should be brought down to 10 mg per day slowly and continued for one year.

Patients who fail to respond to medication or who have progressive lung disease are possible candidates for **single lung transplantation**.

Patients with systemic sclerosis-related interstitial lung disease might benefit from **cyclophosphamide**. **Pulmonary hypertension** is a common complication in systemic sclerosis-related interstitial lung disease and should be treated promptly if encountered. **Sildenafil, which acts by inhibiting cGMP-specific phosphodiesterase type 5 (phosphodiesterase 5, PDE5), an enzyme that promotes degradation of cGMP, and increases blood flow** can be used for pulmonary hypertension in these patients.

Patients with lymphangiomyomatosis benefit from **sirolimus**, which was found to decrease the rate of complications associated with the disease. Unfortunately, the response is usually short-lived.

Patients with **pleural effusions** should undergo **surgical obliteration of the pleural space** because the recurrence rate is high after aspiration of the effusions. Those who develop **hypoxemia** should be started on **supplemental oxygen therapy** and if they are smokers should be encouraged to **stop smoking**.

**Lung transplantation** is an option but patients should understand that disease recurrence in the transplanted lung has been reported in the range of 1–33 %, with sarcoidosis being the most frequently recurrent disease.

Patients with sarcoidosis related lung disease usually respond to **corticosteroids**. Patients should be started on **prednisone** 40 mg/day which should be tapered down over six months and then maintained on 10 mg every other day for the rest of their lives. Patients who wish not to take prednisone or who are intolerable to steroids should take **methotrexate**. **Cyclophosphamide** is usually unsuccessful in the management of pulmonary disease in patients with sarcoidosis.

## References

Bourke, Stephen C. and Howell Clague. 2000. Review of Cryptogenic Fibrosing Alveolitis, Including Current Treatment Guidelines. Postgraduate Medical Journal 76(July 1999):618-24.

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[Management of interstitial lung disease associated with connective tissue disease](#) via nih.gov

[Lymphangioleiomyomatosis Treatment & Management](#) via medscape.com

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