Interstitial Lung Disease (ILD) — Types and Symptoms

Interstitial lung disease (ILD) is the inflammation and fibrosis of lung parenchyma. It may be idiopathic (e.g., idiopathic pulmonary fibrosis) or secondary to connective tissue diseases, medications, malignancies, occupational exposure, or allergens. ILDs commonly present with progressive exertional dyspnea and dry cough. Pulmonary function testing shows restrictive lung disease. Lung high-resolution CT and biopsy usually establish the diagnosis. Treatment includes steroids and immunosuppressives.

Definition, Classification, and Prevalence

Definition

Interstitial lung disease (ILD) comprises a heterogeneous group of disorders that cause varying degrees of inflammation and fibrosis of the lung parenchyma, the space between the capillary endothelium and the alveolar epithelium.

Classification

It is useful to categorize ILDs into those with and without a known cause (table 1).
### Table 1: Types of interstitial lung disease

<table>
<thead>
<tr>
<th>Cause unknown</th>
<th>Cause known</th>
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<tbody>
<tr>
<td><strong>Idiopathic interstitial pneumonias (IIP)</strong></td>
<td><strong>Systemic diseases</strong></td>
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<tr>
<td>• Idiopathic pulmonary fibrosis (IPF)</td>
<td>• Connective tissue diseases (CTD)</td>
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<tr>
<td>• Nonspecific interstitial pneumonia (NSIP)</td>
<td>• Rheumatoid arthritis (RA)</td>
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<tr>
<td>• Cryptogenic organizing pneumonia (COP)</td>
<td>• Systemic lupus erythematosus</td>
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<tr>
<td>• Acute interstitial pneumonia (AIP)</td>
<td>• Systemic sclerosis</td>
</tr>
<tr>
<td>• Smoking-related ILD: (respiratory bronchiolitis-associated interstitial pneumonia (RB-AIP), desquamative interstitial pneumonia (DIP), pulmonary Langerhans cell histiocytosis (PLCH))</td>
<td>• Sjogren’s disease</td>
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<td>• Cryptogenic organizing pneumonia (COP)</td>
<td>• Dermatomyositis/polymyositis</td>
</tr>
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<td>• Acute interstitial pneumonia (AIP)</td>
<td><strong>Granuloma disease with vasculitis</strong></td>
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<td>• Churg-Strauss disease</td>
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<thead>
<tr>
<th>Smoking-related/other</th>
<th>Smoking-related ILD</th>
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<tr>
<td>• Respiratory bronchiolitis-associated interstitial pneumonia (RB-AIP)</td>
<td>• Pulmonary Langerhans cell histiocytosis (PLCH)</td>
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<td>• Desquamative interstitial pneumonia (DIP)</td>
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<td>• Desquamative interstitial pneumonia (DIP)</td>
<td><strong>Other:</strong></td>
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<tr>
<td>• Pulmonary Langerhans cell histiocytosis (PLCH)</td>
<td>• Lymphangioleiomyomatosis (LAM)</td>
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<tr>
<th>Smoking-related/other</th>
<th>Exposure-related</th>
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<tr>
<td>• Respiratory bronchiolitis-associated interstitial pneumonia (RB-AIP)</td>
<td><strong>Occupational</strong></td>
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<tr>
<td>• Desquamative interstitial pneumonia (DIP)</td>
<td>• Asbestosis</td>
</tr>
<tr>
<td>• Pulmonary Langerhans cell histiocytosis (PLCH)</td>
<td>• Silicosis</td>
</tr>
<tr>
<td>• Respiratory bronchiolitis-associated interstitial pneumonia (RB-AIP)</td>
<td>• Gases/Fumes</td>
</tr>
<tr>
<td>• Desquamative interstitial pneumonia (DIP)</td>
<td><strong>Treatment-related</strong></td>
</tr>
<tr>
<td>• Pulmonary Langerhans cell histiocytosis (PLCH)</td>
<td>• Radiation, methotrexate, azathioprine, rituximab, tumor-necrosis factor blockers, amiodarone, nitrofurantoin, chemotherapeutics</td>
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<tr>
<td>• Lymphangioleiomyomatosis (LAM)</td>
<td><strong>Other:</strong></td>
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<th>Granulomatous diseases</th>
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<tr>
<td>Sarcoidosis</td>
<td>Hypersensitivity pneumonitis (HP)</td>
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### Prevalence

IPF, sarcoidosis, and ILD associated with connective tissue diseases are the most common types of ILD.

### Approach to ILD

#### History

- **Age:**
  - IPF is rare under 50 years
  - Sarcoidosis, CTD-associated ILD, and LAM are common between 20–40 years
- **Sex:**
  - LAM and CTD-associated ILD, except RA-associated ILD, is frequently found in women
  - IPF and occupational ILDs are more common in men
- **Clinical presentation:**
  - Acute onset (days–weeks): eosinophilic pneumonia, acute interstitial pneumonia, HP, and granulomatosis with polyangiitis, acute exacerbation of IPF
  - Subacute onset (weeks–months) and especially chronic onset (months–years): most other ILDs, especially IPF
- **Symptoms:**
  - Progressive exertional dyspnea (most common)
- Dry cough (very common)
- Fatigue (common)
- Chest pain (uncommon; suggests sarcoidosis)
- Hemoptysis (rare; suggests vasculitis, LAM)

- Past medical history:
  - CTD or symptoms of CTD such as Raynaud’s phenomena
  - Malignancy, which may indicate dermatomyositis-associated ILD
  - Asthma may suggest eosinophilic granulomatosis with polyangiitis (also known as Churg-Strauss)

- Drug history: important medications associated with ILD are listed above
- Family history: having a close relative with IIP is a strong risk factor for ILD, especially IPF
- Social history:
  - Smoking history is present in almost all cases of DIP and the majority of IPF patients
  - Exposure history such as to asbestos or birds (HP)

**Physical examination**
- End-inspiratory fine crackles in lung bases (common finding, especially in IPF)
- Wheezing is uncommon (may be found in HP, Churg-Strauss disease, sarcoidosis)
- Severe disease findings: cyanosis, digital clubbing, cor pulmonale

**Laboratory Studies**
- Autoantibody detection may help with the diagnosis of some CTDs

**Pulmonary Function Testing**
- DLCO shows reduction
- Most show a restrictive pattern (image 1)

![Flow-volume loop showing a restrictive pattern with reduced lung volumes compared to normal. An obstructive pattern is shown for comparison.](image1.png)

Image 1: Flow-volume loop (orange line) showing a restrictive pattern with reduced lung volumes compared to normal (red line). An obstructive pattern (green line) is shown for comparison. By Lecturio
Imaging:
- Chest X-ray may be suggestive of a type of ILD
  - Peripheral reticular pattern in lower lung zones + small cystic spaces suggests IPF
  - Central nodular pattern in mid to upper lung zones + hilar lymph node enlargement suggests sarcoidosis
- Chest CT:
  - Standard initial test
  - May confirm the diagnosis of IPF in the right setting and obviate the need for lung biopsy
  - Better defines disease extent and features (e.g., honeycombing)
  - Helps exclude comorbidities (e.g., pneumothorax) or differential diagnosis (e.g., malignancy)
  - Helps determine the best location for biopsy

Lung biopsy
- Establishes diagnosis; performed via fiberoptic bronchoscopy or surgery

Differential diagnosis
- Cardiovascular disease (e.g., heart failure)
- Diffuse infections (e.g., pneumocystis pneumonia)
- Malignancy (e.g., bronchoalveolar cell carcinoma):
  - Note that ILDs such as cryptogenic organizing pneumonia may occur secondary to dermatomyositis and malignancy; however, lung malignancies such as bronchoalveolar cell carcinoma can mimic the symptoms and signs of ILD.

Individual Forms of ILD

Idiopathic pulmonary fibrosis (IPF)
- Most common ILD of unknown cause
- Commonly diagnosed in 5th or 6th decade
- Male > female
- Frequently associated with smoking
- 3-5-year survival rate is 50%
- May be associated with acute exacerbations
- Lung HRCT shows a pattern of usual interstitial pneumonia (UIP): subpleural reticular pattern with posterior-basal predominance with more advanced fibrotic features such as honeycombing and traction bronchiectasis (image 2)
- Histopathology shows a pattern of UIP: subpleural reticulation, honeycombing, fibroblasts, skipped lesions with preserved architecture (temporal and spatial heterogeneity)
- Treatment: physical therapy and supplemental oxygen; antifibrotic therapy (pirfenidone); lung transplantation if the patient meets criteria
Non-specific interstitial pneumonia (NSIP)

- Commonly diagnosed in non-smoking females in their 5th decade
- May be idiopathic or commonly associated with CTDs
- 5-year survival rate is 80%
- Lung HRCT shows diffuse and symmetric subpleural ground glass and reticular opacities; traction bronchiectasis may be seen; honeycombing and peribronchial thickening is uncommon
- Histopathology shows uniform interstitial inflammation and fibrosis without honeycombing
- Treatment: physical therapy and supplemental oxygen; steroids and immunosuppressive therapy; lung transplantation if the patient meets criteria

Cryptogenic organizing pneumonia

- Commonly diagnosed in 6th or 7th decade
- Presents with pneumonia-like symptoms (dyspnea, cough, fever, fatigue, hypoxemia) and restrictive pattern on pulmonary function testing
- May be idiopathic or secondary to polymyositis, medications, or malignancy
- Lung HRCT shows migratory, patchy, subpleural consolidations + ground glass opacities ± a rim of subpleural sparing known as the halo sign (characteristic) (image 3)
- Treatment: steroids and immunosuppressives

Smoking-related ILD

- Occurs in heavy smokers in the 5th or 6th decade
- Honeycombing is typically absent
- Biopsy confirms diagnosis
- Treatment includes smoking cessation and immunosuppressive therapy

CTD-associated ILD and granulomatous ILD

Table 2 shows the typical features of systemic sclerosis (a common cause of CTD-associated ILD), sarcoidosis (most common granulomatous ILD), and IPF (most common idiopathic ILD).

<table>
<thead>
<tr>
<th></th>
<th>IPF</th>
<th>Systemic Sclerosis Associated ILD</th>
<th>Sarcoïdosis</th>
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<tbody>
<tr>
<td>Symptoms</td>
<td>Older adult with gradual shortness of breath and dry cough</td>
<td>Gradual shortness of breath and dry cough, fatigue, skin tightening, Raynaud phenomenon, reflux, dysphagia</td>
<td>Asymptomatic or with gradual shortness of breath and cough, fatigue, palpitations, joint pain, eye, and skin involvement</td>
</tr>
<tr>
<td>Signs</td>
<td>Crackles at lung bases and digital clubbing</td>
<td>Crackles, skin thickening and joint swelling, telangiectasias</td>
<td>None or crackles, skin findings, joint swelling, lymphadenopathy</td>
</tr>
<tr>
<td>Exposures</td>
<td>Tobacco smoke</td>
<td>Mostly unknown</td>
<td>Mostly unknown</td>
</tr>
</tbody>
</table>
Bilateral peripheral reticular pattern in lower posterior lung zones; honeycombing; tractional bronchiectasis; UIP pattern is diagnostic

UIP or NSIP pattern, dilated esophagus, pulmonary vascular dilation

Mediastinal/hilar lymphadenopathy, reticulonodular peribronchiovascular involvement

UIP pattern (fibroblastic foci, honeycombing, spatial heterogeneity)

NSIP pattern with occasional UIP features

Non-caseating granuloma

3-5 year survival: 50%

10-year survival: 70–80%

Overall good survival

Table 2: Typical features of more common ILDs

**Complications of ILD**

- Acute exacerbations of IIPs:
Accelerated phase of lung injury in a patient with an underlying ILD
- Acute onset (< 30 days) respiratory distress and hypoxemia more severe than what was previously experienced by the underlying ILD and not explained by other causes (e.g., pneumonia, heart failure)
- Most commonly described in IPF
- Lung HRCT shows a change in the pattern previously observed due to the underlying ILD with patchy bilateral ground-glass opacities and consolidation in dependent regions.
- Histopathology shows diffuse alveolar damage.
- Treatment is supportive as no proven therapy exists; lung transplantation may provide cure
- Mortality rate > 85%

- Pulmonary hypertension
- Pneumonia
- Ischemic heart disease
- Thromboembolic disease
- Lung cancer

References


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