# Interstitial Lung Disease

Interstitial lung disease (ILD) encompasses a heterogeneous group of disorders characterized by inflammation and fibrosis of the lung interstitium, leading to impaired gas exchange and progressive respiratory failure. This guide provides physician assistant (PA) students with a comprehensive framework to understand the types, causes, pathophysiology, diagnostic tests, imaging findings, and treatment strategies for ILD, including management of a decompensated ILD flare, with case scenarios to apply the knowledge.

## Introduction and Pathophysiology

ILD involves the lung interstitium, the space between the alveolar epithelium and capillary endothelium, where gas exchange occurs. The pathophysiology typically follows a pattern of injury, inflammation, and fibrosis:

**Initial Injury:** Environmental exposures (e.g., asbestos), autoimmune processes (e.g., rheumatoid arthritis), or unknown triggers (e.g., idiopathic pulmonary fibrosis [IPF]) cause alveolar epithelial damage.

**Inflammation:** Release of cytokines (e.g., TGF-β, IL-1) leads to inflammatory cell infiltration (e.g., lymphocytes, macrophages).

**Fibrosis:** Dysregulated repair processes result in fibroblast proliferation, collagen deposition, and interstitial scarring, reducing lung compliance and impairing gas exchange.

**Hypoxemia:** Fibrotic tissue and vascular remodeling (e.g., pulmonary hypertension) lead to ventilation-perfusion (V/Q) mismatch and diffusion limitation.

ILD can progress to end-stage lung disease, with acute exacerbations (flares) causing rapid deterioration, often requiring hospital management.

## Clinical Presentation

### History:

**Symptoms:** Progressive dyspnea on exertion, non-productive cough, fatigue, weight loss.

**Risk Factors:** Occupational exposures (e.g., silica, asbestos), smoking, autoimmune diseases (e.g., rheumatoid arthritis [RA], scleroderma), drug exposure (e.g., amiodarone, nitrofurantoin), family history of ILD.

**Systemic Symptoms:** Joint pain, rash (connective tissue disease [CTD]), Raynaud's phenomenon, fever (hypersensitivity pneumonitis [HP]).

### Physical Exam:

**General:** Cyanosis, digital clubbing (common in IPF).

**Pulmonary:** Fine, end-inspiratory crackles ("Velcro" rales, especially in IPF), wheezing (if HP or sarcoidosis).

**Cardiac:** Signs of pulmonary hypertension (PH) in advanced disease (e.g., RV heave, loud P2, TR murmur).

**Other:** Joint swelling (RA), skin changes (scleroderma), lymphadenopathy (sarcoidosis).

## Diagnostic Tests and Studies

### Initial Labs:

**CBC:** Anemia (chronic disease), eosinophilia (eosinophilic pneumonia).

**ESR/CRP:** Elevated in inflammatory ILDs (e.g., CTD-ILD, sarcoidosis).

**ANA, RF, Anti-CCP, Anti-Jo-1:** Screen for CTD (e.g., scleroderma, RA, polymyositis).

**Serum ACE, Calcium:** Elevated in sarcoidosis.

**Hipersensitivity Panel:** For HP (e.g., antibodies to mold, bird proteins).

### Pulmonary Function Tests (PFTs):

**Restrictive Pattern:** Reduced total lung capacity (TLC), forced vital capacity (FVC), and diffusing capacity for carbon monoxide (DLCO).

**DLCO:** Severely reduced in ILD due to impaired gas exchange; often earliest abnormality.

### Bronchoalveolar Lavage (BAL):

**Lymphocytosis:** Suggests HP, sarcoidosis, or cellular NSIP.

**Neutrophilia:** Seen in IPF, acute exacerbations.

**Eosinophilia:** Indicates eosinophilic pneumonia.

### Lung Biopsy:

**Surgical Lung Biopsy:** Gold standard for definitive diagnosis (e.g., UIP pattern in IPF, granulomas in sarcoidosis); reserved for unclear cases.

**Transbronchial Biopsy:** Useful for sarcoidosis (granulomas); less diagnostic yield for fibrotic ILDs.

### Imaging:

**Chest X-Ray:** Reticular opacities, honeycombing (late-stage IPF), bilateral hilar lymphadenopathy (sarcoidosis).

**High-Resolution CT (HRCT):**

**IPF (UIP Pattern):** Subpleural, basal-predominant reticular opacities, honeycombing, traction bronchiectasis; minimal ground-glass opacities (GGO).

**NSIP:** Diffuse GGO, reticular opacities, often peribronchovascular; less honeycombing.

**Sarcoidosis:** Bilateral hilar lymphadenopathy, upper lobe-predominant nodules, perilymphatic distribution.

**HP:** Centrilobular nodules, GGO, mosaic attenuation (air trapping), "tree-in-bud" in chronic HP.

**COP:** Patchy consolidation, GGO, "tree-in-bud" (endobronchial spread).

**Eosinophilic Pneumonia:** Peripheral GGO, consolidation ("photographic negative of pulmonary edema").

## Different Types and Causes

### Idiopathic Interstitial Pneumonias (IIPs):

**Idiopathic Pulmonary Fibrosis (IPF):** Most common; UIP pattern on HRCT/biopsy; associated with smoking, older age (>50 years).

**Non-Specific Interstitial Pneumonia (NSIP):** Cellular or fibrotic; often associated with CTD (e.g., scleroderma).

**Cryptogenic Organizing Pneumonia (COP):** Often post-infectious or drug-related; responsive to steroids.

**Acute Interstitial Pneumonia (AIP):** Rapid onset, diffuse alveolar damage (DAD); ARDS-like presentation.

### Connective Tissue Disease-Associated ILD (CTD-ILD):

**Causes:** RA, scleroderma, polymyositis/dermatomyositis, SLE, Sjögren's syndrome.

**Patterns:** NSIP most common; UIP, LIP (lymphoid interstitial pneumonia) in Sjögren's.

## Hypersensitivity Pneumonitis (HP):

**Causes:** Inhaled antigens (e.g., farmer's lung [moldy hay], bird fancier's lung [avian proteins]).

**Forms:** Acute (reversible), subacute, chronic (fibrotic).

## Sarcoidosis:

**Cause:** Unknown; immune-mediated granulomatous inflammation.

**Features:** Non-caseating granulomas, multi-system involvement (lungs, lymph nodes, eyes, skin).

## Drug-Induced ILD:

**Causes:** Amiodarone, nitrofurantoin, methotrexate, bleomycin.

**Patterns:** NSIP, OP, or DAD depending on the drug.

## Occupational/Environmental ILD:

**Causes:** Asbestosis, silicosis, coal worker's pneumoconiosis.

**Features:** Upper lobe-predominant in silicosis; pleural plaques in asbestosis.

## Other:

**Eosinophilic Pneumonia:** Acute or chronic; often idiopathic or drug-related.

**Lymphangioleiomyomatosis (LAM):** Rare, affects young women; cystic lung disease, associated with tuberous sclerosis.

## Table: Common Types of ILD and Their Causes

| Type | Subtype/Cause | Common Features | HRCT Findings |
|---|---|---|---|
| Idiopathic | IPF | Older males, smoking history, UIP pattern | Subpleural, basal reticular opacities, honeycombing |
| Idiopathic | NSIP | Often CTD-associated, better prognosis | Diffuse GGO, reticular opacities, peribronchovascular |
| CTD-ILD | RA, Scleroderma | Systemic symptoms (joint pain, rash) | NSIP pattern most common, some UIP |
| HP | Mold, bird proteins | Exposure history, acute/subacute/chronic | Centrilobular nodules, GGO, mosaic attenuation |
| Sarcoidosis | Unknown | Non-caseating granulomas, multi-system | Hilar lymphadenopathy, upper lobe nodules |

| Type | Subtype/Cause | Common Features | HRCT Findings |
|---|---|---|---|
| Drug-Induced | Amiodarone, Nitrofurantoin | Drug exposure history | NSIP, OP, or DAD patterns |
| Occupational | Asbestosis, Silicosis | Occupational exposure | Upper lobe nodules (silicosis), pleural plaques (asbestosis) |

## Treatment

### General Principles:

**Treat underlying cause:** (e.g., remove offending drug, manage CTD).

**Supportive care:** Supplemental oxygen (SpO2 >90%), pulmonary rehabilitation, vaccination (influenza, pneumococcal).

**Consider lung transplantation:** for end-stage disease.

### Specific Treatments by Type:

- IPF:
  - **Antifibrotics:** Pirfenidone 801 mg PO TID (slows FVC decline); nintedanib 150 mg PO BID (inhibits tyrosine kinases).
  - **Supportive:** Avoid corticosteroids (no benefit, increased mortality); oxygen for hypoxemia.
- NSIP/CTD-ILD:
  - **Immunosuppression:** Prednisone 0.5-1 mg/kg/day PO (taper over weeks), often with azathioprine 2 mg/kg/day PO or mycophenolate mofetil (MMF) 1-1.5 g PO BID.
  - **CTD-Specific:** Treat underlying disease (e.g., methotrexate for RA, cyclophosphamide for scleroderma).
- Sarcoidosis:
  - **Corticosteroids:** Prednisone 20-40 mg PO daily for symptomatic disease (e.g., lung nodules, lymphadenopathy); taper over 6-12 months.
  - **Steroid-Sparing:** Methotrexate 10-15 mg PO weekly or anti-TNF agents (e.g., infliximab) for refractory cases.
- HP:
  - **Antigen Avoidance:** Remove exposure (e.g., bird removal, change work environment).
  - **Corticosteroids:** Prednisone 0.5-1 mg/kg/day PO for acute/subacute HP; taper over weeks.
- COP:
  - **Corticosteroids:** Prednisone 0.5-1 mg/kg/day PO x 6-12 weeks; high response rate.
- Drug-Induced ILD:
  - **Discontinue Offending Drug:** Immediate cessation (e.g., stop amiodarone).
  - **Corticosteroids:** Prednisone 0.5-1 mg/kg/day PO if severe or persistent symptoms.

## Management of Decompensated ILD Flare:

- An acute exacerbation of ILD (e.g., in IPF) is characterized by rapid worsening of dyspnea, new GGO on HRCT, and hypoxemia, often triggered by infection, aspiration, or unknown causes.
- Supportive Care:
  - **Oxygen Therapy:** High-flow nasal cannula or non-invasive ventilation (NIV) to maintain SpO2 >90%; avoid over-oxygenation (risk of CO2 retention in COPD overlap).
  - **Fluid Management:** Diuretics (e.g., furosemide 40 mg IV) if volume overload, but cautious use to avoid preload reduction in PH.
- Treat Infection:
  - **Broad-spectrum antibiotics:** (e.g., cefepime 2 g IV q8h + vancomycin 15 mg/kg IV q12h) if infection suspected; adjust based on cultures.
  - **Antiviral/antifungal therapy:** if indicated (e.g., oseltamivir for influenza, voriconazole for aspergillosis).
- Corticosteroids:
  - **High-dose pulse therapy:** Methylprednisolone 500-1000 mg IV daily x 3-5 days, then taper (e.g., prednisone 1 mg/kg/day PO).
  - Use in IPF flares is controversial (no proven benefit, risk of infection); reserved for non-IPF ILDs (e.g., COP, NSIP) or suspected inflammatory trigger.
- Immunosuppression:
  - **Cyclophosphamide:** 500-750 mg/$m^2$ IV monthly for severe CTD-ILD or NSIP flares.
  - **Consider IVIG or rituximab:** in refractory cases (e.g., polymyositis-ILD).
- Advanced Support:
  - **Mechanical ventilation:** if NIV fails; use low tidal volumes (6 mL/kg) to minimize barotrauma.
  - **ECMO:** as a bridge to recovery or transplant in refractory hypoxemia.
- Monitoring:
  - **Daily ABG:** to assess oxygenation/CO2 levels.
  - **HRCT:** to confirm GGO, rule out PE or infection.
  - **Monitor for secondary PH:** (ECHO, RHC if feasible); avoid vasodilators unless confirmed WHO Group 1 PH.

# Treatment

## General Principles:

**Treat underlying cause:** (e.g., remove offending drug, manage CTD).

**Supportive care:** Supplemental oxygen (SpO2 >90%), pulmonary rehabilitation, vaccination (influenza, pneumococcal).

**Consider lung transplantation:** for end-stage disease.

## Specific Treatments by Type:

- IPF:
  - **Antifibrotics:** Pirfenidone 801 mg PO TID (slows FVC decline); nintedanib 150 mg PO BID (inhibits tyrosine kinases).
  - **Supportive:** Avoid corticosteroids (no benefit, increased mortality); oxygen for hypoxemia.
- NSIP/CTD-ILD:
  - **Immunosuppression:** Prednisone 0.5-1 mg/kg/day PO (taper over weeks), often with azathioprine 2 mg/kg/day PO or mycophenolate mofetil (MMF) 1-1.5 g PO BID.
  - **CTD-Specific:** Treat underlying disease (e.g., methotrexate for RA, cyclophosphamide for scleroderma).
- Sarcoidosis:
  - **Corticosteroids:** Prednisone 20-40 mg PO daily for symptomatic disease (e.g., lung nodules, lymphadenopathy); taper over 6-12 months.
  - **Steroid-Sparing:** Methotrexate 10-15 mg PO weekly or anti-TNF agents (e.g., infliximab) for refractory cases.
- HP:
  - **Antigen Avoidance:** Remove exposure (e.g., bird removal, change work environment).
  - **Corticosteroids:** Prednisone 0.5-1 mg/kg/day PO for acute/subacute HP; taper over weeks.
- COP:
  - **Corticosteroids:** Prednisone 0.5-1 mg/kg/day PO x 6-12 weeks; high response rate.
- Drug-Induced ILD:
  - **Discontinue Offending Drug:** Immediate cessation (e.g., stop amiodarone).
  - **Corticosteroids:** Prednisone 0.5-1 mg/kg/day PO if severe or persistent symptoms.

## Management of Decompensated ILD Flare:

- An acute exacerbation of ILD (e.g., in IPF) is characterized by rapid worsening of dyspnea, new GGO on HRCT, and hypoxemia, often triggered by infection, aspiration, or unknown causes.
  - Supportive Care:
    - **Oxygen Therapy:** High-flow nasal cannula or non-invasive ventilation (NIV) to maintain SpO2 >90%; avoid over-oxygenation (risk of CO2 retention in COPD overlap).
    - **Fluid Management:** Diuretics (e.g., furosemide 40 mg IV) if volume overload, but cautious use to avoid preload reduction in PH.
  - Treat Infection:
    - **Broad-spectrum antibiotics:** (e.g., cefepime 2 g IV q8h + vancomycin 15 mg/kg IV q12h) if infection suspected; adjust based on cultures.
    - **Antiviral/antifungal therapy:** if indicated (e.g., oseltamivir for influenza, voriconazole for aspergillosis).
  - Corticosteroids:
    - **High-dose pulse therapy:** Methylprednisolone 500-1000 mg IV daily x 3-5 days, then taper (e.g., prednisone 1 mg/kg/day PO).
      - Use in IPF flares is controversial (no proven benefit, risk of infection); reserved for non-IPF ILDs (e.g., COP, NSIP) or suspected inflammatory trigger.
  - Immunosuppression:
    - **Cyclophosphamide:** 500-750 mg/$m^2$ IV monthly for severe CTD-ILD or NSIP flares.
    - **Consider IVIG or rituximab:** in refractory cases (e.g., polymyositis-ILD).
  - Advanced Support:
    - **Mechanical ventilation:** if NIV fails; use low tidal volumes (6 mL/kg) to minimize barotrauma.
    - **ECMO:** as a bridge to recovery or transplant in refractory hypoxemia.
  - Monitoring:
    - **Daily ABG:** to assess oxygenation/CO2 levels.
    - **HRCT:** to confirm GGO, rule out PE or infection.
    - **Monitor for secondary PH:** (ECHO, RHC if feasible); avoid vasodilators unless confirmed WHO Group 1 PH.

## Table: Treatment Approaches for ILD Types

| ILD Type | Primary Treatment | Medications/ Interventions | Notes |
|---|---|---|---|
| IPF | Antifibrotics, supportive | Pirfenidone, Nintedanib, oxygen | Avoid corticosteroids; transplant referral |
| NSIP/CTD-ILD | Immunosuppression | Prednisone, Azathioprine, MMF | Treat underlying CTD; monitor for infection |
| Sarcoidosis | Corticosteroids, steroid-sparing | Prednisone, Methotrexate, Infliximab | Taper steroids over months; multi-system evaluation |
| HP | Antigen avoidance, corticosteroids | Prednisone, antigen removal | Chronic HP may progress to fibrosis |
| COP | Corticosteroids | Prednisone | High response rate; 6-12 week course |
| Drug-Induced | Discontinue drug, corticosteroids | Prednisone | Immediate cessation of offending agent |

## Key Pearls

**Pathophysiology:** ILD involves alveolar injury, inflammation, and fibrosis, leading to impaired gas exchange.

**Types:** IPF (UIP), NSIP (CTD), sarcoidosis (granulomas), HP (antigen-driven), drug-induced, occupational.

**Diagnosis:** HRCT for patterns (e.g., UIP in IPF, GGO in NSIP); PFTs (restrictive, low DLCO); biopsy if unclear.

**Imaging:** IPF (honeycombing), sarcoidosis (hilar nodes), HP (centrilobular nodules), COP (consolidation).

**Treatment:** Antifibrotics for IPF, immunosuppression for CTD-ILD/NSIP, antigen avoidance for HP, steroids for sarcoidosis/COP.

**Decompensated Flare:** Oxygen, high-dose steroids, treat infection; NIV preferred, ECMO for refractory cases.

**Prognosis:** IPF worst prognosis (median survival 3-5 years); NSIP, HP better with treatment.

## References

**UpToDate:** “Interstitial Lung Disease: Diagnosis and Management” (2025). UpToDate ILD

**ATS/ERS:** “Guidelines for the Diagnosis of Idiopathic Pulmonary Fibrosis” (2024). ATS Guidelines

**CHEST:** “Management of Acute Exacerbations of ILD” (2023). CHEST ILD

**NEJM:** “Antifibrotic Therapy in IPF: Advances and Challenges” (2024). NEJM IPF

## Case Scenarios

### Case 1: A 68-Year-Old Male with Progressive Dyspnea

- Presentation: A 68-year-old male with a history of smoking presents with a 1-year history of dyspnea and dry cough. Exam shows fine crackles at lung bases, digital clubbing, SpO2 92% on room air.
- Labs/HRCT/PFTs: ANA negative, FVC 65% predicted, DLCO 50% predicted. HRCT shows subpleural, basal reticular opacities, honeycombing, minimal GGO.
- Diagnosis: idiopathic Pulmonary Fibrosis (IPF) → Dyspnea, crackles, UIP pattern on HRCT, restrictive PFTs.
- Management: Start pirfenidone 801 mg PO TID (slows disease progression). Supplemental oxygen for SpO2 <90%. Avoid corticosteroids (no benefit). Refer for lung transplant evaluation (progressive disease). Pulmonary rehab and vaccinations (influenza, pneumococcal). Follow-up with pulmonology.

### Case 2: A 52-Year-Old Female with Acute Worsening

- Presentation: A 52-year-old female with known RA-ILD (NSIP pattern) presents with acute worsening dyspnea, fever, and hypoxemia over 3 days. Exam shows T 38°C, SpO2 86% on room air, diffuse crackles.
- Labs/HRCT: CRP 50 mg/L, HRCT shows new diffuse GGO, no PE. BAL negative for infection.
- Diagnosis: Acute Exacerbation of RA-ILD (NSIP) → Rapid worsening, new GGO, likely inflammatory flare.
- Management: Admit to ICU. High-flow oxygen to maintain SpO2 >90%. Start methylprednisolone 1000 mg IV daily x 3 days, then prednisone 1 mg/kg/day PO. Empirical antibiotics (cefepime 2 g IV q8h + vancomycin 15 mg/kg IV q12h) until infection ruled out. Use BiPAP if needed (avoid intubation). Monitor ABG, HRCT for response. Add cyclophosphamide 750 mg/m$^2$ IV if refractory. Follow-up with rheumatology.

## Case 3: A 40-Year-Old Male with Cough and Fatigue

- Presentation: A 40-year-old male farmer presents with chronic cough, fatigue, and dyspnea for 6 months. Exam shows mid-inspiratory squeaks, no clubbing, SpO2 94% on room air.
- Labs/HRCT/PFTs: Hypersensitivity panel positive for avian antigens, FVC 70% predicted, DLCO 60% predicted. HRCT shows centrilobular nodules, mosaic attenuation.
- Diagnosis: Hypersensitivity Pneumonitis (Chronic) → Exposure history, HRCT findings, restrictive PFTs.
- Management: Advise antigen avoidance (remove birds, improve ventilation). Start prednisone 0.5 mg/kg/day PO x 4 weeks, then taper. Supplemental oxygen if SpO2 <90%. Monitor PFTs, HRCT for response. Refer to pulmonology for long-term management.