PAKISTAN CHEST SOCIETY

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STRIVING FOR PULMONARY CARE

Clinical Practice Guidelines

Interstitial Lung Diseases

PAKISTAN CHEST SOCIETY-2026

Guidelines on Interstitial Lung Diseases

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Preface

Interstitial lung diseases (ILDs) are increasingly recognized worldwide. In Pakistan, with the growing availability of high-resolution CT (HRCT) of the chest, these conditions are being diagnosed more frequently, highlighting the need for locally relevant clinical guidelines. In this context, it is a humble effort to present the Guidelines on Interstitial Lung Diseases (ILDs) developed by the Pakistan Chest Society. These guidelines cover major ILD subtypes, including Idiopathic Pulmonary Fibrosis (IPF), Non-Specific Interstitial Pneumonia (NSIP), Hypersensitivity Pneumonitis, Connective Tissue Disease–related ILDs, as well as selected rare ILDs.

Developed by a dedicated working group, these recommendations integrate current international evidence with regional clinical experience. They emphasize comprehensive clinical evaluation, HRCT pattern recognition, appropriate laboratory workup, and the importance of a multidisciplinary approach to ensure early and accurate diagnosis, along with evidence-based management strategies tailored to resource-variable settings.

The aim of these guidelines is to standardize care, improve diagnostic accuracy, and enhance patient outcomes across diverse healthcare environments. I sincerely acknowledge the valuable contributions of all working group members and reaffirm our commitment to advancing respiratory care through evidence-based practice.

Prof. Muhammad Ashraf Jamal
HOD Pulmonology Department RLKU
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Message by the President

Pakistan Chest Society

Interstitial lung diseases (ILDs) constitute a diverse and complex group of disorders requiring multidisciplinary evaluation. These guidelines underscore the importance of accurate classification, appropriate use of imaging and histopathology, and individualized management strategies. The Pakistan Chest Society hopes this document will facilitate earlier diagnosis and more coordinated care for patients with ILDs.

Prof. Shereen Khan
President
Pakistan Chest Society

Message by the Chairman

Guideline Committee, Pakistan Chest Society

It is my pleasure to present the Pakistan Chest Society's Guidelines for the Diagnosis and Management of Interstitial Lung Diseases (ILD). ILDs are increasingly recognized in Pakistan, with idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, and connective-tissue–related ILDs forming the majority of cases nationwide. This growing burden highlights the need for early identification and uniform standards of care.

The Working Group for Guidelines of Management of Interstitial Lung Diseases under my Chairmanship has reviewed the best available international evidence, including recommendations from the European Respiratory Society, the British Thoracic Society, and regional experiences, while adapting them to the realities of our healthcare system. These guidelines review the etiology, diagnosis and management of Interstitial Lung Diseases in Pakistan.

These guidelines emphasize accurate diagnosis through detailed clinical history, HRCT, pulmonary function testing, and multidisciplinary discussion. They also outline practical management pathways, including the use of antifibrotic therapy for progressive fibrosing ILDs, appropriate immunosuppression where indicated, and essential supportive care such as pulmonary rehabilitation, vaccination, and oxygen therapy.

Pakistan has made important progress with national ILD registries and increasing awareness, yet challenges remain—particularly late presentation, variable access to antifibrotics, and no facility for transplant options. These recommendations aim to support clinicians with clear, locally relevant strategies to improve outcomes for ILD patients across the country.

I thank all committee members and contributors for their dedication, and I commend these guidelines to the respiratory community.

Prof. Muhammad Ashraf Jamal
Chairman Guideline Committee
Pakistan Chest Society

Pakistan Chest Society

Guideline Committee

Prof. Muhammad Ashraf Jamal

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Interstitial lung diseases

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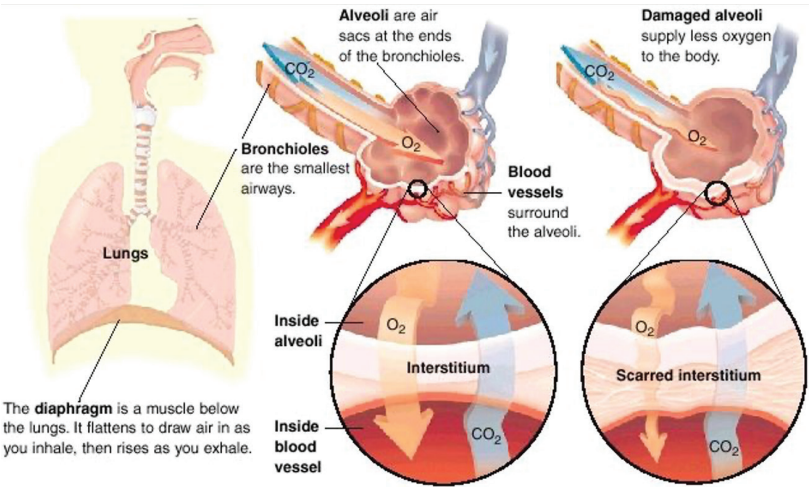
Chapter 01:
Introduction to ILDs

Interstitial lung disease (ILD) encompasses a heterogeneous group of more than 200 pulmonary disorders characterized by varying degrees of inflammation and fibrosis of the lung interstitium. These conditions can lead to progressive lung dysfunction, significantly impacting patients' quality of life and overall health [1].

It is a key fact that this disease entity presents significant diagnostic and therapeutic challenges, demanding a nuanced understanding of its complex pathophysiology and diverse etiologies [2]. Thus, understanding ILD is crucial for healthcare providers to offer timely and effective management, improving patient outcomes.

The interstitium becomes the primary site of pathological change in ILD as shown in Figure 1. [1,3] The inflammation, fibrosis and architectural distortion impede effective gas exchange, leading to clinical manifestations such as progressive dyspnea, nonproductive cough, and reduced exercise tolerance.

Figure 01



The etiology of ILD can be multifactorial, including environmental and occupational exposure, autoimmune and connective tissue diseases, drug-induced lung injury, and idiopathic forms, the latter including idiopathic pulmonary fibrosis (IPF) being most common [3].

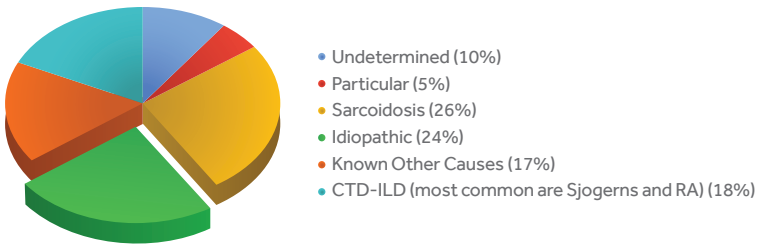
A comprehensive diagnostic approach is necessary in managing ILD, often necessitating a multidisciplinary team comprising pulmonologists, radiologists, and pathologists. High-Resolution Computed Tomography (HRCT) remains the cornerstone imaging modality, providing critical insights into the pattern and extent of interstitial involvement [4].

Pulmonary function tests, including spirometry and diffusing capacity for carbon monoxide, are one of the few essential investigations necessary for assessing the functional impact and monitoring disease progression. In selected cases, surgical lung biopsy may be warranted to secure a definitive histopathological diagnosis.
The management includes a comprehensive approach including addressing comorbidities, optimizing supportive care with supplemental oxygen, and considering lung transplantation for advanced disease. Therapeutic strategies for ILD are tailored to the specific subtype and underlying cause[5]. Corticosteroids and immunosuppressive agents are commonly employed in inflammatory ILDs, while antifibrotic agents such as pirfenidone and Nintedanib have shown efficacy in slowing the progression of IPF [6].

Continued research and clinical trials are crucial to unraveling the pathogenesis of ILD and developing innovative treatments. As pulmonology consultants, staying abreast of these advancements is vital to enhancing patient outcomes and quality of life in this challenging and evolving field of respiratory medicine.

Epidemiology:
ILDs are classified as those associated with Known Causes and those that are Idiopathic. The most common identifiable causes are exposure to environmental and occupational agents, especially to organic or inorganic dust.

Figure 2



Classification
Classification Anchors and Cross cutting Principles

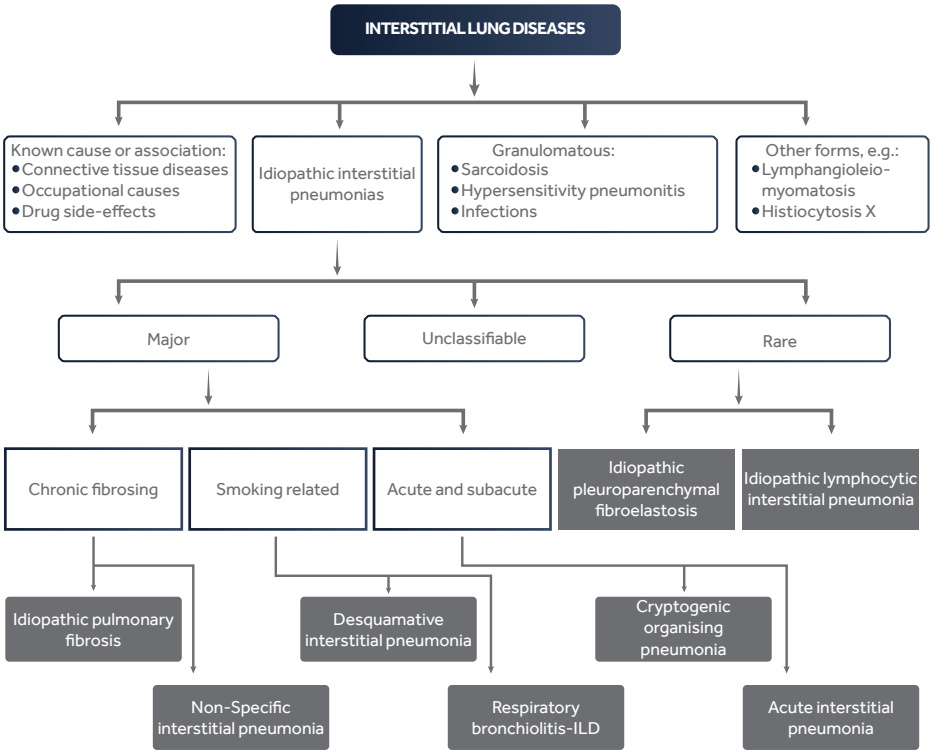
2. 1. Updated classification (ERS/ATS 2025)

- Pattern first approach across idiopathic and secondary IPs; major biopsy/radiology patterns: UIP, NSIP, and Bronchiolocentric Interstitial Pneumonia (BIP); alveolar filling disorders as a parallel concept. New terminology includes Alveolar Macrophage Pneumonia (AMP) for DIP and idiopathic DAD for AIP.
- This favors MDT based synthesis (history–HRCT–BAL–pathology) — crucial when surgical tissue is limited.

2. 2. Progressive pulmonary fibrosis (PPF) across non IPF ILDs (ATS/ERS/JRS/ALAT 2022)

- PPF is defined by ≥2 of:
  (1) Worsening symptoms
  (2) Physiological decline (e.g., absolute FVC or DLCO drop)
  (3) Radiologic progression within 1 year. Consider antifibrotics

Figure 3



Chapter 02:
Idiopathic Pulmonary Fibrosis

Introduction

Idiopathic Pulmonary Fibrosis (IPF), previously also known as cryptogenic fibrosing alveolitis (CFA), is a chronic, progressive, and ultimately fatal interstitial lung disease characterized by fibrosis of the lung parenchyma with no identifiable cause. It is classified as a form of idiopathic interstitial pneumonia (IIP), with a histopathological and radiological pattern consistent with usual interstitial pneumonia (UIP) [7, 8, 9].

IPF is the most common form of spontaneously occurring diffuse parenchymal lung disease within the IIP spectrum. Other IIPs include nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), acute interstitial pneumonia (AIP), lymphocytic interstitial pneumonia (LIP), and cryptogenic organizing pneumonia (COP) (as shown in figure 3).

While UIP is a hallmark feature of IPF, it is not pathognomonic; UIP patterns on high-resolution computed tomography (HRCT) or lung biopsy can also be observed in other interstitial lung diseases, so diagnosis requires careful exclusion of alternative causes.

IPF primarily affects older adults and carries a poor prognosis, with a median survival of approximately 3 to 5 years following diagnosis [7]. Clinically, it presents with gradual onset of exertional dyspnea and a nonproductive cough, eventually progressing to irreversible scarring and decline in lung function.

The pathogenesis of IPF involves aberrant wound-healing responses to microscopic alveolar injury, leading to excessive extracellular matrix deposition and destruction of the normal alveolar architecture [10]. The etiology remains unknown, hence the term "idiopathic."

Diagnosis is often challenging and is based on clinical evaluation, imaging, and sometimes histopathology, with HRCT playing a pivotal role. In some cases, a lung biopsy is required to establish a definitive diagnosis.

Current treatment strategies aim to slow disease progression using antifibrotic agents such as pirfenidone and nintedanib. However, lung transplantation remains the only curative option for eligible patients [7]

Pathogenesis

Idiopathic Pulmonary Fibrosis (IPF) is a chronic interstitial lung disease characterized by progressive fibrosis of the lung parenchyma. Although its exact cause remains unknown, IPF is now understood to result from an aberrant wound-healing response following repetitive epithelial injury. Instead of resolving, these injuries lead to the activation of fibroblasts and

persistent extracellular matrix (ECM) deposition, causing irreversible architectural distortion. Multiple factors—including genetic predisposition, environmental exposures, aging, and epigenetic changes—are thought to contribute to disease initiation and progression.

1. Etiologic Risk Factors

While the term "idiopathic" suggests an unknown cause, several risk factors have been associated with the development of IPF. Environmental triggers such as cigarette smoke, air pollutants, occupational exposures, chronic micro aspiration, and viral infections may initiate alveolar injury. Host-related factors like advanced age, male gender, and a history of gastroesophageal reflux disease (GERD) are also prevalent in IPF patients. In some cases, certain medications and autoimmune conditions may act as cofactors. These exposures and comorbidities likely trigger abnormal repair processes in genetically susceptible individuals, promoting fibrosis rather than resolution [11,12].

2. Genetic Susceptibility

Genetic predisposition plays a central role in both familial and sporadic cases of IPF. Although most cases are sporadic, familial pulmonary fibrosis (FPF) and syndromic forms such as Hermansky-Pudlak syndrome (HPS) are often present earlier and are linked to specific gene mutations [11,12,13]. While several genetic polymorphisms have been reported among patients with sporadic cases of IPF, none are well-established.

Genome-wide association studies (GWAS) have identified key genetic loci, most notably a promoter variant in the MUC5B gene, which is present in more than one-third of IPF patients and increases disease risk by altering mucin production and epithelial repair [14-17]. Mutations in surfactant-related genes (SFTPC, SP-A2, ABCA3) impair surfactant metabolism and disrupt alveolar homeostasis [18]. Variants in telomerase complex genes (TERT, TERC, RTEL1) lead to telomere shortening, which impairs cellular replication and regenerative capacity in the lung epithelium [19]

Multiple other gene variants (e.g., AKAP13, KIF15, FAM13A, TOLLIP) contribute to IPF risk by affecting epithelial repair and signaling pathways; polygenic risk scores (PRS) can predict susceptibility, with top-risk individuals having up to 7x higher odds of IPF development. [20,21]

An important distinction exists between genetic variants that increase susceptibility to IPF and those that influence disease progression or survival. For example, while the MUC5B variant significantly increases disease risk, it has been paradoxically associated with improved survival in some cohorts [15-17]. Similarly, TOLLIP variants influence both susceptibility and prognosis, though findings vary across studies. This separation suggests that disease initiation and progression may be governed by distinct molecular pathways. Understanding these differences is vital for identifying prognostic biomarkers and tailoring therapeutic interventions [22]

3. Epithelial–Fibroblast Dysfunction Model

The dominant model of IPF pathogenesis centers on dysfunctional interactions between alveolar epithelial cells and mesenchymal cells. Following injury, instead of initiating normal repair, alveolar type II cells fail to differentiate into type I cells, likely due to disrupted basement membranes and altered cellular signaling. This impaired epithelial regeneration leads to the release of profibrotic mediators like transforming growth factor-beta (TGF-β 1), which recruit fibroblasts and induce their differentiation into myofibroblasts. These myofibroblasts accumulate in fibroblastic foci, producing excess collagen and ECM, which drives progressive fibrosis. Histologically, IPF is notable for the presence of fibrotic zones adjacent to areas of relatively preserved lungs, without significant inflammation, distinguishing it from classic inflammatory fibrotic diseases [23,24]

4. Disease Perpetuation and Progression

IPF is uniquely characterized by ongoing fibrosis in the absence of overt inflammation. Although inflammation may initiate the fibrotic process, its resolution appears impaired in IPF, resulting in continuous fibroblast activation and ECM deposition. Histopathology shows fibrotic foci and honeycomb change rather than active immune cell infiltration. This indicates a self-sustaining fibrotic process independent of inflammation, which explains the ineffectiveness of immunosuppressive therapies in IPF [25]

5. Genetic and Molecular Drivers of Disease Progression

Beyond susceptibility, specific genes have been linked to disease progression, lung function decline, and survival outcomes. For instance, variants in PCSK6 have been associated with transplant-free survival and influence TGF-β activation and ECM remodeling. PKN2-AS1 correlates with lung function decline but not mortality, while a TLR3 variant has been linked to more rapid disease progression in multiple cohorts [26]. Additionally, transcriptomic analyses have identified PTPN9 and SNRPB2 as potential modulators of prognosis, though their exact roles remain unclear [27,28]. These findings highlight the importance of genetic profiling in predicting disease courses and personalizing care.

6. Biomarkers of Disease Progression

Blood-based biomarkers are gaining attention for their potential to predict disease activity, prognosis, and response to treatment. Elevated levels of surfactant proteins (SP-A, SP-D), KL-6, and matrix metalloproteinases (e.g., MMP-7) reflect ongoing epithelial injury and fibrosis [29]. Other markers such as LOXL2, which promote collagen cross-linking, are directly involved in ECM remodeling [30]. Proteomic studies have identified over 100 proteins correlated with survival, including latent TGF-β binding protein 2, integrin β6, and collagen α1 (XXIV). Furthermore, patients stratified into high-risk biomarker classes exhibited worse outcomes but appeared to respond better to antifibrotic therapy, offering a potential route for precision medicine in IPF [31].

Clinical Presentation

Overview and Symptomatology

Idiopathic Pulmonary Fibrosis (IPF) usually presents insidiously in adults over the age of 50,

with a higher prevalence among males and a strong association with a history of cigarette smoking. The hallmark symptoms are progressive exertional dyspnea and a chronic, nonproductive cough, which typically evolve over months to years. These symptoms may be mistakenly attributed to aging or deconditioning early in the disease course, leading to diagnostic delays. Patients under the age of 50 or those with a family history of fibrotic lung disease or features suggestive of telomeropathies (e.g., premature graying, bone marrow dysfunction) should be evaluated for familial pulmonary fibrosis (FPF) and referred for genetic counseling and testing where appropriate [32]

Physical Examination Findings

On examination, the most characteristic finding is the presence of fine, bibasilar inspiratory crackles—often described as "Velcro-like" which are usually heard at the lung bases. Digital clubbing is present in 45-75% of patients, though it is more often associated with advanced disease. Early-stage disease may have subtle or asymmetric auscultatory findings, and advanced disease can present with end-inspiratory squeaks from traction bronchiectasis [33]. Signs of hypoxemia, particularly during exertion, are common and may progress to resting hypoxemia as the disease advances. Rarely, patients report systemic symptoms such as fatigue, low-grade fever, myalgias, or arthralgias, but these are not prominent features of IPF.

Clinical Course and Complications

IPF follows a generally progressive course with variable rates of decline. Some patients experience a slow but steady deterioration in lung function, while others may remain stable for months before undergoing sudden worsening due to acute exacerbations. These exacerbations are characterized by deterioration of symptoms within 30 days, new bilateral ground-glass opacities and/or consolidations on a background of reticular or honeycomb pattern, excluding pulmonary infection, left heart failure and pulmonary embolism often requiring hospitalization and carrying a high risk of mortality 34. With disease progression, complications such as pulmonary hypertension, respiratory failure, and weight loss further reduce quality of life.

History Taking in Suspected IPF

A thorough history is essential when evaluating a patient with suspected interstitial lung disease (ILD). Key aspects include tobacco use, onset and progression of dyspnea and cough, occupational and environmental exposures (e.g., dusts, birds, molds, chemicals), and medication history (e.g., amiodarone, nitrofurantoin, chemotherapy). Inquiries should also assess symptoms or signs of connective tissue disease (e.g., joint pain, Raynaud phenomenon, dry eyes or mouth, muscle weakness, rashes) and for family history of ILD or systemic disorders suggestive of telomeropathies or inherited fibrosis syndromes.

Laboratory Testing

There are no specific laboratory tests for diagnosing IPF; rather, serologic studies are used to exclude alternative causes, particularly systemic autoimmune rheumatic diseases. A typical serologic workup may include antinuclear antibodies (ANA), rheumatoid factor (RF), anti-CCP antibodies, and inflammatory markers such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). In selected cases, further testing (e.g.,

anti-synthetase antibodies, anti-SS-A/SS-B, anti-Scl-70, MDA-5) may be warranted based on clinical suspicion. Routine measurement of circulating biomarkers (e.g., MMP-7, KL-6,surfactant proteins) is not currently recommended for diagnosis due to limited specificity and high false positive [35]

Pulmonary Function Testing (PFT)

Pulmonary function testing is important in both the diagnosis and longitudinal monitoring of IPF. Patients typically exhibit a restrictive ventilatory pattern with reduced forced vital capacity (FVC) and a normal or elevated FEV1/FVC ratio. The diffusing capacity for carbon monoxide (DLCO) is usually reduced, often early in the disease. As IPF progresses, further reductions in FVC, DLCO, and six-minute walk distance are common, reflecting worsening disease severity. Oxygen desaturation with exertion may be one of the earliest physiologic abnormalities.

Chest Imaging

Imaging plays a critical role in the diagnosis of IPF. A standard chest radiograph may show reticular opacities, particularly in the lower lung zones, but these findings are nonspecific. High-resolution computed tomography (HRCT), however, is essential and often diagnostic. The radiologic usual interstitial pneumonia (UIP) pattern, which is the hallmark of IPF, is characterized by subpleural, basilar-predominant reticular opacities, traction bronchiectasis, and honeycombing, with an absence of features suggesting an alternative diagnosis. While the UIP pattern is strongly associated with IPF, it can also be seen in connective tissue disease-related ILD, asbestosis, and chronic hypersensitivity pneumonitis, making it critical to interpret HRCT findings in the clinical context. The presence of pleuroparenchymal fibroelastosis (PPFE) in a subset of IPF patients may indicate a worse prognosis and faster functional decline.

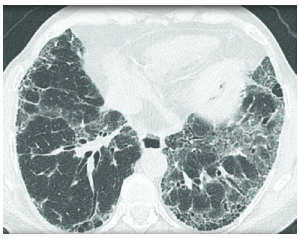
ATS/ERS/JRS/ALAT HRCT Diagnostic Categories

The 2022 ATS/ERS/JRS/ALAT guidelines classify HRCT findings into four diagnostic groups [see Figure 4 (a) & (b)]:

- Definite UIP
- Probable UIP
- Indeterminate UIP
- Alternative diagnosis

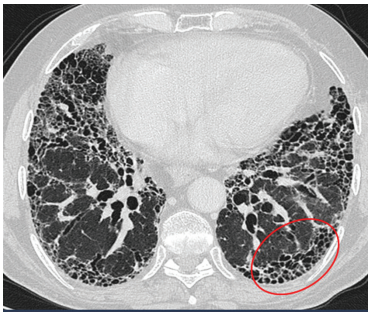
Figure 04 (a):

Definite UIP pattern. Transverse high-resolution computed tomography (HRCT) image shows subpleural basal honeycombing (more evident in the left lung) with traction bronchiectasis, and reticular opacities.



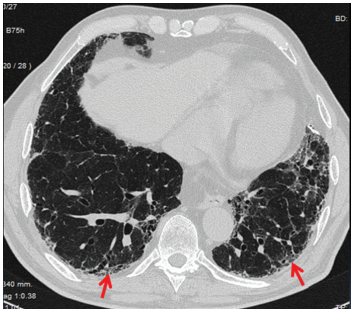
HRCT Patterns of UIP

Typical UIP Pattern



Honeycombing

Probable UIP Pattern



Traction bronchiectasis without honeycombing

Figure 4 (b):
Definite UIP pattern (on left) and Probable UIP pattern (on right)

In cases where HRCT shows a definite or probable UIP pattern, and clinical features are consistent with IPF, further tissue diagnosis may not be necessary [36]. A multidisciplinary discussion (MDD) involving pulmonologists, radiologists, and pathologists is the gold standard for diagnosis. If HRCT findings are indeterminate or suggest an alternative diagnosis, and the clinical picture is unclear, lung biopsy may be considered. Surgical lung biopsy is the gold standard for UIP diagnosis but carries risks, including 1.7% mortality and 6.5% infection rates [35]. Transbronchial Cryobiopsy has fewer severe complications (<1%) in expert centers, though minor bleeding (30%) and pneumothorax (9%) are common [36, 37]

Factors such as older age, male sex, multiple comorbidities, and use of long-term oxygen therapy increase the risk of poor outcomes after elective lung biopsy [38]. Biopsy should be avoided during acute exacerbations, or in patients with significant comorbidities, or physiologic compromise.

Diagnostic Procedures to Rule Out Alternative Diagnoses
Procedures like bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) are not typically used to diagnose IPF but may help exclude other ILDs. BAL may be useful when hypersensitivity pneumonitis, eosinophilic pneumonia, sarcoidosis, or infection is suspected. However, BAL cellular profiles overlap among fibrotic ILDs and are not diagnostic for IPF. TBLB samples are often too small to confirm UIP but may identify alternative pathologies in select cases (e.g., sarcoidosis, lymphangitic carcinomatosis). Thus, their use is generally limited to specific clinical scenarios.

Histopathologic Features of UIP and Probable UIP
When lung biopsy is performed, a diagnosis of UIP is supported by patchy dense fibrosis, architectural distortion with honeycombing, a subpleural and Para-septal distribution, and the presence of fibroblastic foci. If only some of these features are seen but no alternative

features are present, the diagnosis is classified as probable UIP. Fibroblastic foci—clusters of fibroblasts and myofibroblasts within the interstitium—are especially important, as they represent areas of active fibrogenesis and are a histopathologic hallmark of IPF[35].

Correlation of Imaging and Histology

When biopsies are obtained, the results must be interpreted alongside HRCT and clinical findings within a multidisciplinary team. A histopathologic finding of UIP or probable UIP, in the appropriate radiologic and clinical context, supports a confident diagnosis of IPF. Conversely, histology showing features of an alternative diagnosis (e.g., granulomas, airway-centered inflammation) precludes IPF. Discordant histology among different lung lobes is not uncommon, but in most cases, disease progression follows a pattern consistent with IPF if UIP is present in at least one lobe [35, 39]

Special Consideration: Short Telomere Syndrome (STS)

In patients with features suggestive of short telomere syndrome (STS)—such as premature graying, macrocytosis, cytopenias, or family history of ILD—evaluation of telomere length and genetic testing in patients as well as first degree relatives should be considered. Patients who are found to have STS need to be screened for bone marrow and hepatic dysfunction. [40].

Differential Diagnosis of UIP on HRCT

Because the UIP pattern is not exclusive to IPF, the differential diagnosis includes:

- **Systemic autoimmune rheumatic diseases-associated ILD** (e.g., rheumatoid arthritis, systemic sclerosis)
- **Asbestosis**, suggested by pleural plaques on HRCT, Asbestos bodies on histology and relevant occupational exposure
- **Chronic hypersensitivity pneumonitis**, Chronic hypersensitivity pneumonitis may mimic UIP on imaging but often shows centrilobular nodules, lobular air-trapping (decreased areas of perfusion), and upper lobe honeycombing on HRCT; histology may reveal poorly formed granulomas or giant cells. [23]
- **Nonspecific interstitial pneumonia (NSIP)** typically presents on HRCT with diffuse ground-glass opacities, reticulation, and traction bronchiectasis, but usually lacks honeycombing. Diagnosis often requires histopathologic confirmation via lung biopsy.
- **Drug-induced pulmonary fibrosis**, particularly from agents like bleomycin, methotrexate, and nitrofurantoin
- **Radiation-induced lung injury** is damage to the lung tissue caused by radiation therapy, usually occurs in two phases: Acute pneumonitis and later pulmonary fibrosis
- **Pulmonary Langerhans cell histiocytosis**, which shows upper to mid-lobe predominant cysts and nodules, and interstitial thickening in young smokers (While not always needed for the diagnosis) the histology typically shows cysts and aggregates of Langerhans-like dendritic cells (identified by CD207, S-100, and CD1a positivity on immunostaining) surrounding smaller bronchioles. [41].

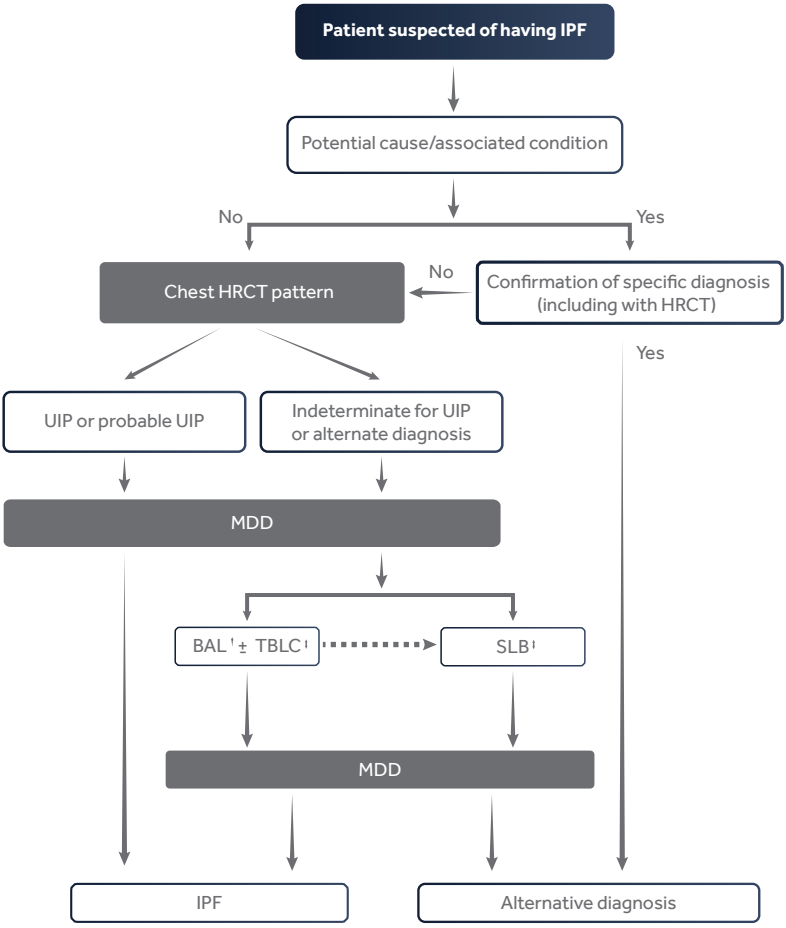
In all cases, clinical correlation is essential to distinguish IPF from these mimics.

Mimics of Honeycombing on HRCT

Certain conditions can mimic honeycombing:

- **Airspace enlargement with fibrosis (AEF)**, commonly seen in smokers, tends to involve upper and mid-lung zones with thinner-walled cysts that do not abut the pleura (42).
- **Combined pulmonary fibrosis and emphysema (CPFE)** shows upper-lobe emphysema and lower-lobe fibrosis. Thick-walled cystic spaces resembling honeycombing may be present but differ in internal architecture (43).
- **Pleuroparenchymal fibroelastosis (PPFE)** shows dense fibrosis of the upper lobes and pleura and can be idiopathic or drug related.

Figure 5: Diagnostic algorithm in suspected IPF



Management of Idiopathic Pulmonary Fibrosis (IPF)

1. Assessment of Disease Severity and Prognosis

Disease severity in IPF is typically classified into mild, moderate, and advanced stages based on symptoms, high-resolution CT (HRCT), and pulmonary function tests (PFTs) [44]

- **Mild IPF:** May be asymptomatic or present with mild dyspnea and dry cough. HRCT shows reticular opacities and honeycombing in <10% of the lung, usually subpleural and basilar. PFTs show normal or mildly reduced FVC, DLCO, and a normal/slightly elevated P(A-a)O2.
- **Moderate IPF:** Characterized by dyspnea on moderate exertion, FVC 50–70% predicted, DLCO 45–65%, P(A-a)O2 21–30 mmHg. HRCT shows reticular abnormalities in 20–30% of the lung and honeycombing <5% .
- **Advanced IPF:** Dyspnea with mild exertion, need for supplemental oxygen, extensive honeycombing on HRCT (>5% in ≥3 zones). PFTs show FVC <50%, DLCO <50%, and significant oxygen desaturation during the 6-minute walk test (6MWT). P(A-a)O2 >30 mmHg and room-air oxygen saturation below 88 percent.

The **Gender-Age-Physiology (GAP) index** predicts 1-, 2-, and 3-year mortality using age, gender, FVC, and DLCO [45]

2. Medical Therapy

Antifibrotic Agents

Two antifibrotic medications are recommended for slowing disease progression and reducing exacerbation frequency [46]

A. Nintedanib

- **Mechanism:** Tyrosine kinase inhibitor targeting growth factor receptors [47]
- **Dose:** 150 mg twice daily (100 mg if poorly tolerated) [48]
- **Adverse Effects:** Diarrhea (most common), nausea, vomiting, elevated LFTs [48]
- **Monitoring:** Baseline and repeat LFTs; caution in hepatic impairment. Avoid in Child-Pugh B/C liver disease [48]. After initiation, LFTs should be repeated monthly for three months, every three months thereafter, and as clinically indicated. Dose modification or interruption may be necessary for liver enzyme elevations. A pregnancy test should be performed prior to initiation of therapy in female patients of child-bearing age, and conception avoided until at least three months after the last dose
- **Efficacy:** Slows FVC decline and delays time to first exacerbation [49]
- **Drug Interactions:** CYP3A4 and P-glycoprotein substrates; increases bleeding risk on anticoagulation [50]
- **Missed dose:** If a dose is missed, the next dose should be taken at the next scheduled time. Do not make up a missed dose.
- AST or ALT >3 times to <5 times ULN (without signs of liver damage): Interrupt treatment or reduce dosage to 100 mg every 12 hours. Once liver enzymes have returned to baseline values after treatment interruption, reintroduce therapy at 100 mg every 12 hours; may subsequently increase to 150 mg every 12 hours.

- AST or ALT >5 times ULN or >3 times ULN with signs or symptoms of liver damage: Discontinue therapy.
- Consider treatment interruption in patients with new or worsening proteinuria.

B. Pirfenidone

- **Mechanism:** Antifibrotic and anti-inflammatory mechanism [47]
- **Dose:** Pirfenidone is initiated at a dose of 200 mg (dose available in Pakistan) three times a day. After one week, the dose is increased to 400 mg (two capsules) three times a day, and after the second week to the full dose of 800 mg (three capsules) three times a day. A slower ramp may be used due to side effects, kidney function impairment, or in the setting of mild liver disease. Pirfenidone should always be taken with food [51]
- **Adverse Effects:** Nausea (most common), rash, diarrhea, photosensitivity, dizziness, fatigue [51]
- **Monitoring:** LFT prior to starting, Monthly LFTs for 6 months, then every 3 months. Avoid in severe liver impairment (Child-Pugh C). End-stage kidney disease requiring dialysis: Use is not recommended
- **Efficacy:** Reduces decline in lung function and possibly mortality [47]
- **Drug Interactions:** The dose of pirfenidone should be reduced in the presence of strong or moderate CYP1A2 inhibitors (e.g. ciprofloxacin) [51]
- **ALT/AST >3 to ≤5 times ULN without hyperbilirubinemia or symptoms:** As clinically appropriate, may continue current dose, may reduce dose, or may temporarily discontinue therapy. Once aminotransferase elevations have resolved, may be re-titrated to the recommended daily dose.
- **ALT/AST >3 to ≤5 times ULN with hyperbilirubinemia or symptoms:** Permanently discontinue therapy.
- **ALT/AST >5 times ULN (regardless of serum bilirubin concentrations):** Permanently discontinue therapy.
- Pirfenidone is primarily metabolized via the CYP1A2 enzyme pathway and is subject to interactions with both inhibitors and inducers of this system. Strong or moderate CYP1A2 inhibitors—such as ciprofloxacin, diazoxide choline, and primaquine—can elevate pirfenidone levels, potentially increasing the risk of toxicity and requiring dose adjustments and close monitoring. Conversely, CYP1A2 inducers like tobacco smoke, cannabis, and even certain foods like broccoli can lower pirfenidone concentrations, reducing its effectiveness. Co-administration with photosensitizing agents (e.g., aminolaevulinic acid, porfimer, temoporfin, verteporfin) may increase the risk of photosensitivity and should be avoided or closely monitored. Although food lowers the peak concentration of pirfenidone, it improves its overall tolerability. Grapefruit products should be avoided due to their potential to interfere with pirfenidone metabolism. When used with other drugs such as nerandomilast or ciprofloxacin, therapy adjustments may be necessary. Additionally, patients should avoid smoking, as it significantly induces CYP1A2 and diminishes pirfenidone's therapeutic effect.

Nerandomilast (PDE4B inhibitor)

- May be an alternative option for patients who are unable to tolerate anti-fibrotic or those with progressive disease despite treatment.

- Nerandomilast is a phosphodiesterase 4B selective inhibitor and has both anti-fibrotic and immunomodulatory effects.
- Reduces FVC decline by 24–38% [63]
- More effective when combined with nintedanib; GI side effects are common.
- Nerandomilast is mainly metabolized by the CYP3A4 enzyme, making it vulnerable to interactions with both inducers and inhibitors of this pathway. Strong and moderate CYP3A4 inducers, such as rifampin, can significantly decrease nerandomilast levels and should be avoided. On the other hand, strong CYP3A4 inhibitors like ketoconazole may increase its concentrations, requiring a dose adjustment to 9 mg twice daily. Moderate inhibitors may not require a dose change but do call for close monitoring. While pirfenidone may reduce nerandomilast levels, no dose adjustment is currently recommended. Drugs such as clofazimine and systemic fusidic acid may elevate levels of CYP3A4 substrates, including nerandomilast, potentially requiring dose modifications or closer monitoring. Additionally, nerandomilast may enhance the blood pressure-lowering effects of riociguat, so patient monitoring is advised.

3. Supportive Care

Supportive strategies include:

- Supplemental oxygen
- Smoking cessation
- Pulmonary rehabilitation
- Vaccination (influenza, pneumococcus)
- Palliative care for refractory dyspnea and cough

4. Lung Transplantation

ILD is the leading cause of lung transplantation in United States with median post-transplant survival of almost 5 years [52]

Referral Criteria [53]

- DLCO <40% predicted
- FVC <80% predicted
- Desaturation <89% on exertion
- Any functional limitation

Listing Criteria:

- ≥10% FVC decline in 6 months (≥5% may suffice)
- ≥15% DLCO decline
- 6MWT <250m or desaturation <88%
- Pulmonary hypertension
- Hospitalization for acute exacerbation

Bilateral Lung Transplant (BLT) may have superior long-term survival compared to Single Lung Transplant (SLT) [52]

Risk Factors:

- T**elomerase mutations (TERT, TR):** Associated with bone marrow failure post-transplant [54]
- **Systemic corticosteroids:** High-dose therapy may impair survival; low-dose appears safe [55]

5. Therapies Not Recommended in IPF

Ineffective or Harmful Treatments:

- Prednisone + Azathioprine + NAC: Increased mortality (PANTHER trial) [56]
- NAC monotherapy: No benefit, potential cardiac risk [56]
- Anticoagulation with warfarin: Increased mortality [57]
- Maintenance antibiotics: No benefit (TMP-SMX) [58]
- Endothelin receptor antagonists: Not beneficial; may be harmful [59]
- Sildenafil (PDE-5 inhibitors): No proven benefit in IPF [60]

GERD Treatment

- No recommendation for empiric therapy. Symptomatic GERD may be treated pharmacologically or surgically [61]

6. Emerging and Investigational Therapies

Combination Therapy

- For patients with progressive disease on single agent, combination of Pirfenidone and Nintedanib.
- Limited experience of combination therapy [62]

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Chapter 03:
Nonspecific Interstitial Pneumonia (NSIP)

Introduction

- Nonspecific Interstitial Pneumonia (NSIP) is distinct clinicopathologic pattern of interstitial lung disease characterized by relatively uniform interstitial inflammation and/or fibrosis with temporal homogeneity.
- NSIP is a chronic interstitial pneumonia (IP) that is called "nonspecific" because it lacks the histopathologic features that characterize usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), or acute interstitial pneumonia (AIP).[1]
  NSIP can be idiopathic, but mostly associated with CTD, Hypersensitivity, HIV or Drug
- toxicity. It was formally recognized in the ATS/ERS multidisciplinary classification and described as a distinct histopathologic/radiologic pattern (cellular and fibrotic variants).

Incidence / prevalence (global)

Reported frequency of NSIP among ILD cohorts varies widely (often 10–30% of non-IPF IIP series), reflecting case-mix, center referral bias, and whether CTD-ILDs are included. Many series report NSIP as the second most common IIP after IPF or as a major pattern in CTD-ILD.

Pakistan's data

Pakistani tertiary-center series report NSIP as a substantial proportion (examples: ~10–25% of ILD cohorts in single-center studies/registries). National registry and hospital series from Pakistan report NSIP frequencies in that range, but true population incidence is unknown (no robust population-based incidence study to date). Local work emphasizes the importance of excluding secondary causes (CTD, HP)[2]

Causes of NSIP

- **Idiopathic**
- **Connective tissue diseases:** NSIP is the most common ILD pattern in patients with Systemic Sclerosis, but also seen in Polymyositis- Dermatomyositis, Rheumatoid Arthritis and Sjogren Syndrome.[3, 4]
- **Interstitial Pneumonia with Autoimmune features**
- **Drugs:** Many drugs, including but not limited to flecainide, amiodarone, methotrexate, carmustine, nitrofurantoin, statins, and chlorambucil, have been associated with an NSIP pattern[5]
- **Several studies have noted that a high proprotions of patients with NSIP have underlying features suggestive of CTD.[6,7,8]**
- **Hypersenstivity Pneumonitis**
- **HIV infection**

Pathophysiology

- Pathogenesis is heterogeneous — immune-mediated/inflammatory pathways predominate in some patients, fibrogenic pathways in others; overlapping with

autoimmune/CTD biology is common.

- Potential contributors to the development and progression of NSIP include epithelial injury, dysregulated repair, abnormal immune response and abnormal fibroblast function leading to excess collagen deposition.
- NSIP is characterized by relatively uniform interstitial inflammation and/or fibrosis. The cellular subtype shows predominantly interstitial lymphoplasmacytic inflammation (potentially steroid-responsive). The fibrotic subtype shows more collagen deposition and architectural distortion but typically lacks the temporal heterogeneity and honeycombing of UIP.
- The histopathology of NSIP is characterized by homogeneous appearance of dense or loose interstitial fibrosis with mild to moderate interstitial inflammation with temporal homogeneity AND absence of fibroblast foci, dense alveolar septal fibrosis, granuloma, organizing pneumonia, conspicuous infiltrates of lymphocytes or eosinophils.[10,11,12]

Types (histologic / radiologic)[13]

- **Cellular NSIP:** mainly inflammatory, better prognosis, often responds well to immunosuppression.
- **Fibrotic NSIP:** predominant fibrosis, slower progression, worse prognosis than cellular NSIP but generally better than UIP.[14]

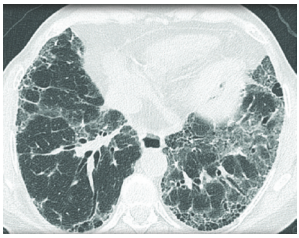
Clinical Features

- Idiopathic NSIP occurs in middle aged nonsmoker females (67 %), NSIP associated with CTD has equal distribution among male & females.
- **Respiratory**
  - Progressive exertional dyspnea, persistent dry cough, reduced exercise tolerance that has developed sub acutely over weeks to months.[9]
- **Systemic / constitutional**
  - About one third patients have fever or flue-like symptoms, fatigue, malaise, weight loss (less prominent than in some other ILDs).
  - Patients with underlying CTD may have symptoms of the CTD.
  - Occasional patients with Idiopathic NSIP may develop signs and symptoms of CTD after the diagnosis of NSIP.
- **Physical examination:**
  - Bibasilar inspiratory crackles (velcro crackles), digital clubbing less common (only 10%).
  - Signs of associated CTD (arthritis, rashes, sicca) that must be actively sought.
- **Imaging:**
  - Chest Radiograph shows bilateral basal predominant hazy areas or reticulation with or without volume loss
  - HRCT features are variable in NSIP. The characteristic manifestations are ground glass opacities, reticulations and traction bronchiectasis involving mainly in lower lung zones (temporal homogeneity). Honeycombing is absent at presentation but may develop as fibrosis progress.[15]
  - The findings helpful to differentiate NSIP from UIP include the extent of ground glass greater than reticulations, Only subpleural sparing is enough, and bilateral sharp demarcation between basal fibrosis and normal lung on coronal sections (straight

edge sign).

- The HRCT features of Idiopathic NSIP compared with CTD NSIP are similar.

Idiopathic NSIP: Clinical Decision Algorithm (ATS / ERS / BTS–aligned)



Evaluation

NSIP is suspected in subacute history of shortness of breath and cough with radiographic evidence of interstitial lung disease.

1. Clinical evaluation: Thorough history (exposures, drugs, CTD symptoms, HIV), physical exam (pulmonary & non pulmonary).

2. Lab tests: No lab test is specific for NSIP, the usual lab tests include CBC, RFTs, LFTs, BNP, Urine C/E. In patients without known CTD, get ANA, RF, Anti CCP and if CTD is suspected then appropriate serologic testing.

3. HRCT: After suspicion on X ray chest, first-line imaging is HRCT chest. Typical NSIP patterns: diffuse or basal predominant ground-glass opacities ± reticulation, subpleural sparing possible; honeycombing uncommon.

4. Pulmonary Function Tests; PFTs differentiate between obstructive and restrictive impairment and to know the gas transfer defect. The tests include Spirometry, Lung volumes, DLCO and six-minute walk test with oximetry. Although PFTs do not help in diagnosis of NSIP but helpful in assessing the baseline impairment, monitoring, response to therapy and prognosis. In NSIP, PFTs demonstrate restrictive pattern, decreased DLCO and de-saturation during ambulatory oximetry.

5. Bronchoalveolar Lavage: BAL is not specific for NSIP, it is used to rule out other causes like infection, hemorrhage, malignancy.

6. Exclude known causes: serologic testing for CTD, environmental exposure history, drug review, infection screening. ATS/ERS emphasize ruling out secondary causes before labeling Idiopathic NSIP.

Diagnosis

1. Definitive diagnosis of NSIP requires histopathologic evidence by surgical lung biopsy accompanied by Multidisciplinary team.

2. Multidisciplinary Team discussion (MDT): Pulmonologist + Radiologist ± Pathologist is the diagnostic gold standard; (pathology used when imaging is non-diagnostic.)

When to go for biopsy:

Definitive diagnosis of NSIP requires histopathologic evidence.

- Surgical lung biopsy via VATS is the standard.
- Transbronchial Cryobiopsy (Cryo-TBB) is gaining acceptance but is not considered to be a replacement for surgical lung biopsy.

- Transbronchial lung biopsy (TBLB) has a low yield so generally avoided when NSIP is suspected
- Consider surgical lung biopsy when non-invasive tests and MDT discussion cannot confidently distinguish NSIP from other patterns (e.g., atypical UIP). Decision depends on patient fitness and whether biopsy will change management.[16]
- The Histopathology of NSIP is characterized by the following features
- Diffuse alveolar wall thickening by uniform fibrosis
- Preservation of the alveolar architecture when examined with elastin stains
- Expansion of alveolar septa by variably dense infiltrate of predominantly mononuclear inflammatory cells.
- Overall pattern suggests temporal homogeneity

Differential Diagnosis

- Other idiopathic interstitial pneumonias
- Hypersensitivity pneumonitis
- Immunoglobulin G4 (IgG4)-related systemic disease
- Hermansky-Pudlak syndrome

Treatment

The treatment of NSIP depends on cause, severity and progression of disease.

Avoidance of contributory exposures – Patients with NSIP due to a drug or inhaled exposure, remove the inciting exposure, this alone may be adequate treatment. Patients with exposure to potential culprit drugs (e.g., amiodarone, methotrexate, nitrofurantoin, statins) or inhalational agents (eg, organic dusts) should avoid further exposure.

Observation for Mild Disease – (MICO): Patients who have mild disease based on minimal symptoms and near normal pulmonary function may be observed for a period of time without treatment. This approach is limited to patients with mild, stable disease with close follow up. Symptoms and pulmonary function should be reassessed every three to six months, and therapy initiated if there is progression. [17]

Initial Therapy for Moderate to severe Disease

- **Corticosteroids:** The usual regimen is the equivalent of oral prednisone 0.5 - 1 mg/kg (e.g., 40 to 60 mg/day) per day for the first month, followed by 30-40 mg for another two months. Initial pulse methylprednisolone may be used for more severe disease. For patients who respond, prednisone is gradually tapered, as tolerated, to 5 to 10 mg daily or on alternate days by the end of 6 to 9 months with attempted cessation after one year. Patients who relapse when Prednisone is tapered or discontinued, low dose prednisone is maintained for long periods.[18]
- **Immunosuppressants**

  • For patients with more severe disease at presentation, worsening lung function despite glucocorticoids, or inability to taper glucocorticoids, add another immunosuppressive agent such as mycophenolate or azathioprine[19,20,21]

  • **Azathioprine** — A common regimen is to start with 25 to 50 mg/day and increase by 50 mg increments every 7 to 14 days up to 1.5 to 2 mg/kg per day but not exceeding a maximum total dose of 200 mg/day. A lower dose is indicated in the setting of acute or chronic kidney disease.

- **Mycophenolate mofetil** — Mycophenolate mofetil (MMF) is an inhibitor of lymphocyte proliferation that is often used in the treatment of CTD associated NSIP and has shown efficacy in the treatment of interstitial lung disease associated with systemic sclerosis (scleroderma). The target dose of MMF is generally between 2 and 3 g daily, usually in two divided doses (eg, 0.75 to 1.5 twice daily). Starting with lower doses, such as 500 mg twice daily, and increasing to the target dose over three to four months may improve a patient's gastrointestinal tolerance of MMF.
- Methotrexate is not recommended for Idiopathic NSIP.

Refractory Disease

- **Cyclophosphamide** — For patients who have rapidly progressive initial disease or have progressed despite glucocorticoids and a second line immunosuppressive agent, treatment with cyclophosphamide (CYC) may have a beneficial effect[22]
- **Rituximab** — Rituximab, the chimeric immunoglobulin G1 (IgG1) monoclonal antibody to CD20-positive B cells, has shown mixed results in case series of connective tissue disease-associated interstitial lung disease (CTD-ILD).[23]

Fibrotic or Progressive NSIP

- **Nintedanib (antifibrotic):** Shown to slow decline in FVC in progressive fibrosing ILDs (INBUILD trial) across multiple non-IPF fibrosing ILD subgroups, including NSIP pattern in some patients — therefore recommended as an option for progressive fibrosing NSIP[24,25]
- Pirfenidone data is less robust for non-IPF ILD but under active investigation

Side-effect profiles

- **Corticosteroids:** weight gain, hyperglycemia, hypertension, osteoporosis, infection risk, myopathy, mood changes — long-term toxicity notable; use lowest effective dose and bone protection.
- **Mycophenolate mofetil (MMF):** gastrointestinal (diarrhea, nausea), leukopenia, infection risk; generally, better tolerated than cyclophosphamide. Monitor blood counts and LFTs.
- **Azathioprine:** bone marrow suppression, hepatotoxicity, increased infection risk; TPMT testing advisable before use.
- **Cyclophosphamide:** haemorrhagic cystitis, bone marrow suppression, infertility risk, infection; reserved for severe disease given toxicity.
- **Rituximab:** infusion reactions, prolonged B-cell depletion hypogammaglobulinaemia and infection risk (including reactivation of hepatitis B); monitor immunoglobulins and infections.
- **Nintedanib:** most common adverse event is diarrhoea; others include nausea, elevated liver enzymes, and bleeding risk (antiplatelet/anticoagulant caution). Dose adjustments frequently required
- **Pirfenidone:** nausea, dyspepsia, photosensitivity rash, elevated transaminases; monitor LFTs.

Relapse / Exacerbation management:

- **Relapse of inflammatory NSIP:** increase corticosteroid dose and consider adding or intensifying steroid-sparing immunosuppression (eg MMF, azathioprine, or cyclophosphamide depending on severity).
- **Progressive fibrosis despite immunosuppression:** consider antifibrotic therapy (nintedanib), enrollment in clinical trials, or, in selected autoimmune cases, biologic agents (rituximab) as rescue therapy.

Supportive Treatment

Pulmonary rehabilitation, supplemental oxygen, vaccination and management of comorbidities are essential supportive measures.

Monitoring

The response to therapy is monitored at one month and then at 3-6 months interval or early if patient response worsening of symptoms.

- Clinical symptoms, development of extra pulmonary symptoms.
- Six-minute walk test
- Monitoring drug side effects
- Serial PFTs and DLCO (every 3–6 months initially or per clinical course).
- Imaging (HRCT) as clinically indicated to assess progression or complications.

Future drugs & ongoing trials (notable trials / directions)

Antifibrotic expansion & combination therapy:

- Trials are testing antifibrotics (nintedanib, pirfenidone) in non-IPF fibrosing ILD subsets and in combination with immunosuppressants (e.g. Nintedanib + MMF or Pirfenidone). INBUILD and several follow-up subgroup analyses support nintedanib for progressive fibrosing ILD; ongoing work is refining which patients (by physiology/biology) benefit most

Biologic & targeted immune therapies

- Trials of Rituximab combined with MMF (e.g., EVER-ILD / RECITAL / related trials) have shown promise for ILD with NSIP pattern in improving short-term FVC; larger/longer studies are ongoing. Some studies showed benefits at 6 months though not always sustained to 12 months — still an active area of research. [26]

Novel pathways / Imaging biomarkers

- Studies exploring novel anti-fibrotic agents, kinase inhibitors, anti-inflammatory biologics, and precision-medicine approaches (biomarkers to select antifibrotic vs immunosuppression) are ongoing; Xenon MRI and advanced imaging are under investigation to detect early progression. ClinicalTrials.gov contains multiple active trials for progressive fibrosing ILD and combinations (nintedanib/pirfenidone + other agents).

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Chapter 04:
Hypersensitivity Pneumonitis

Introduction

Hypersensitivity Pneumonitis (HP), also called Extrinsic Allergic Alveolitis, is an immune-mediated inflammatory lung disease caused by repeated inhalation of a wide range of environmental antigens, most commonly organic dusts, fungi, or animal proteins[1]. These antigens trigger a hypersensitivity reaction in susceptible individuals, leading to inflammation of the alveoli and small airways. The condition can be present in acute, subacute, or chronic forms, with symptoms ranging from shortness of breath, cough, and fever to progressive respiratory failure and fibrosis in chronic cases.

HP is often associated with occupational or environmental exposures, for example, in farmers (from moldy hay, leading to "farmer's lung"), bird breeders ("bird fancier's lung"), or workers exposed to metalworking fluids. Early recognition and removal of the offending antigen are crucial to prevent irreversible lung damage. Diagnosis typically involves a combination of clinical history, imaging (especially high-resolution CT), pulmonary function tests, bronchoalveolar lavage, and sometimes lung biopsy.

Etiological Agents and At-Risk Populations in HP

Hypersensitivity pneumonitis (HP) results from inhalation of a wide variety of airborne organic antigens. Over 300 causative agents have been identified, often linked to specific occupations or hobbies. The following are common etiological agents and the populations at increased risk:[2,3,4]

1. Farming, Vegetable, and Dairy Cattle Workers

- Exposure to moldy hay and organic dust containing thermophilic actinomycetes, such as Saccharopolyspora rectivigula and Micropolyspora faeni.
- Classic example: Farmer's lung.

2. Exposure to Ventilation Systems and Water Reservoirs

- Aerosolized water from hot tubs, cooling towers, and humidifiers can harbor non-tuberculous mycobacteria, especially the Mycobacterium avium complex.
- This leads to Hot Tub Lung; a form of HP linked to contaminated water sources.[5]

3. Bird and Poultry Handlers

- Antigens from bird droppings, feathers, and serum proteins.
- Causes Bird Fancier's Lung or Pigeon Breeder's Disease, common among pet bird owners, poultry workers, and bird breeders.

4. Animal Handlers and Laboratory Workers

- Exposure to proteins from animal urine, serum, or dander, including lab rodents and other pets.
- Known as Laboratory Workers' Lung or Animal Handler's Lung.

5. Grain, Flour, and Malt Processing Workers

- Inhalation of fungal spores such as Aspergillus fumigatus and Aspergillus clavatus from moldy grains and malted barley.
- Commonly caused by Malt Workers' Lung or Grain Workers' Lung.

6. Lumber Milling, Construction, and Woodworking

- Exposure to mold spores, including Alternaria species, found in damp or decaying wood dust.
- Referred to as Wood Dust Pneumonitis

7. Chemical, Plastic, Paint, Spray, and Electronic Industries

- Exposure to chemical agents such as toluene diisocyanates (used in plastics and paint), and microbial contaminants like Bacillus subtilis found in detergent powders.
- Examples include Chemical Workers' Lung and Detergent Workers' Lung.

8. Textile Industry Workers

- Inhalation of cotton dust leading to Byssinosis (also called "Brown Lung Disease").
- Exposure to flock fibers in upholstery or textile processing can cause Flock Workers' Lung.

Additional Notable At-Risk Groups and Agents

- Mushroom Workers: Exposure to Thermoactinomyces species in compost and mushroom spores.
- Coffee Bean Workers: Moldy coffee bean dust exposure leading to Coffee Workers' Lung.
- Fish Processing Workers: Exposure to fish proteins and molds.
- Air Conditioner and Humidifier Maintenance Workers: Exposure to various microbial contaminants.

Pathogenesis

Immunopathogenesis and Genetic Susceptibility of Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease triggered by inhalation of a wide variety of environmental antigens, including microbial proteins, animal particles, and chemicals. Pathogenesis is complex and involves a dynamic interplay between **innate** and a**daptive immune responses**, as well as individual genetic susceptibility.

Immunopathogenesis

The immunological mechanisms underlying HP differ between acute and chronic presentations

- In **acute HP**, repeated inhalation of an offending antigen leads to the production of **antigen-specific IgG antibodies.** Subsequent re-exposures trigger **immune complex (Type III hypersensitivity)** formation in the alveoli, leading to complement activation and recruitment of neutrophils, which mediate lung inflammation. Symptoms often resemble flu-like illness and appear within hours of antigen exposure.

- In **subacute and chronic HP,** the disease is driven primarily by a **Type IV hypersensitivity reaction,** dominated by **CD4+ Th1 lymphocytes,** which release pro-inflammatory cytokines such as **interferon-gamma (IFN-γ)** and **tumor necrosis factor-alpha (TNF-α)**. These promote granulomatous inflammation and eventual fibrosis. Th17 cells have also been implicated in sustaining chronic inflammation, while regulatory T cells (Tregs) play a counterbalancing, anti-inflammatory role. An imbalance favoring Th1/Th17 over Tregs may contribute to persistent inflammation and lung damage.[6]
- **Toll-like receptors (TLRs),** particularly **TLR-2** and **TLR-9,** are involved in recognizing microbial antigens and activating innate immune responses, further amplifying inflammation. **Dendritic cells** and **alveolar macrophages** also play key roles in antigen presentation and cytokine production.

As the disease progresses, **chronic HP** can result in architectural distortion of the lung, honeycombing, and features resembling **Usual interstitial pneumonia (UIP),** making it difficult to differentiate from **Idiopathic pulmonary fibrosis (IPF).**

Fibrosis Development and Immune Dysregulation

Not all patients develop fibrosis. Those who do often show:

- An increased **CD4+/CD8+ T cell ratio** in bronchoalveolar lavage (BAL),
- Elevated **Th17 levels,**
- Persistent alveolar inflammation despite antigen removal.

This suggests that **immune dysregulation,** rather than mere antigen exposure, plays a key role in disease progression.

Genetic Susceptibility

Only a subset of exposed individuals develops HP, highlighting the importance of **host genetic factors.** Several genetic associations have been identified:

- **MHC class II alleles (e.g., HLA-DR and DQ):** Specific polymorphisms have been linked to increased risk, particularly in avian-related HP and farmer's lung.
- **MUC5B** promoter variant (rs35705950): Commonly associated with idiopathic pulmonary fibrosis, this variant has also been linked to chronic fibrotic HP, suggesting shared fibrotic pathways.
- **Telomere-related gene mutations (e.g., TERT, TERC, RTEL1):** Found in a subset of patients with fibrotic HP, these mutations result in shortened telomeres and are associated with **early-onset disease, poorer prognosis,** and **increased risk of respiratory failure.**
- **Familial clustering:** Observed particularly in Japanese summer-type HP, where genetic predisposition may be compounded by shared environmental exposures (e.g., moldy wooden homes in humid climates).

Environmental and Epigenetic Factors

In addition to genetics, other individual risk factors may include:

- **Smoking status** (interestingly, some studies suggest smokers are at lower risk, possibly due to immunosuppressive effects on alveolar macrophages),
- **Age and gender** (older age is associated with fibrotic forms),
- Occupational exposures (e.g., farming, bird breeding, hot tub use, metalworking),
- **Epigenetic modifications,** such as DNA methylation changes, may influence immune cell behavior and inflammatory responses.

To summarize, the pathogenesis of hypersensitivity pneumonitis is multifaceted, involving antigen exposure, dysregulated immune responses, and genetic susceptibility. While acute forms are typically reversible, chronic HP can lead to irreversible fibrosis and progressive lung dysfunction. Understanding the immunologic and genetic basis of HP is essential for improving diagnosis, guiding therapy, and identifying high-risk individuals. Ongoing research into molecular biomarkers and personalized approaches holds promise for the future management of this complex disease.

Updated Classification of Hypersensitivity Pneumonitis (HP)

In response to the limitations of earlier classification systems, the **American Thoracic Society (ATS), Japanese Respiratory Society (JRS),** and **Asociación Latinoamericana de Tórax (ALAT)** released updated clinical guidelines in 2020.

These guidelines proposed a new, more clinically relevant framework that divides HP into two primary categories: **Nonfibrotic** and **Fibrotic phenotypes.** This distinction is based on the presence or absence of **fibrosis,** determined through high-resolution imaging or histopathological analysis. Symptoms do not vary distinctly between these subtypes due to overlapping patterns observed in traditional acute, subacute, and chronic HP presentations. The **nonfibrotic** form is characterized by purely **inflammatory changes** without evidence of lung scarring, while the fibrotic form includes either a **combination of inflammation** and **fibrosis** or **predominantly fibrotic tissue.** This binary classification is considered more objective and prognostically valuable than the traditional scheme, as it better reflects disease behavior, response to treatment, and long-term outcomes.

The older model—which categorized **HP as acute, subacute, or chronic**—has become less favored, as it implies a linear progression that does not apply to all patients. Many individuals may present directly with fibrotic HP without a documented history of preceding acute or subacute phases. Moreover, these clinical phases often overlap, making precise classification difficult in practice.

By shifting toward a fibrosis-based classification, clinicians can better stratify patients, predict prognosis, and tailor management strategies accordingly. This newer model also aligns HP with other forms of interstitial lung disease, such as idiopathic pulmonary fibrosis (IPF), where fibrosis is a key driver of disease progression and outcome.

Clinical Features

Symptoms of Hypersensitivity Pneumonitis (HP)

The clinical presentation of hypersensitivity pneumonitis (HP) varies significantly depending on the **duration, intensity** of **antigen exposure,** and whether the disease is in its **nonfibrotic (inflammatory) or fibrotic (scarring) form**. Symptoms can be acute, subacute, or chronic, but these categories often overlap in real-world cases.

1. Acute Symptoms (Hours to Days After Exposure)

These typically occur in individuals with **intense** or **sudden exposure** to a known antigen (e.g., mold, bird droppings, or certain chemicals). Symptoms usually appear 4–8 hours after exposure and resemble a **flu-like illness,** which may resolve spontaneously if exposure is avoided.

- Fever and chills
- Cough, usually dry
- Shortness of breath (dyspnea)
- Chest tightness or discomfort
- Fatigue and malaise
- Muscle aches (myalgia)
- Headache
- Tachypnea (rapid breathing)

These episodes are often **recurrent,** occurring after repeated exposure, and may be mistaken for viral infections.

2. Subacute Symptoms (Days to Weeks After Repeated Exposure)

Subacute HP develops with **intermittent or low-level exposure** and has a more **gradual onset** than the acute form.

- Persistent dry cough
- Progressive shortness of breath, especially on exertion
- Mild fever or chills
- Fatigue
- Unintentional weight loss
- Chest discomfort

Patients may not associate symptoms with environmental exposure, leading to delayed diagnosis.

3. Chronic Symptoms (Months to Years of Ongoing Exposure)

Chronic HP results from **prolonged antigen exposure** and is often associated with fibrotic changes in the lung. Symptoms are insidious and can mimic other chronic interstitial lung diseases like idiopathic pulmonary fibrosis (IPF).

- Chronic cough (usually dry but may be productive in some cases)
- Progressive dyspnea, even at rest in advanced stages
- Clubbing of fingers (in some patients)
- Midinspiratory crackles (Velcro-like sounds) on lung auscultation
- Fatigue and exercise intolerance
- Weight loss and general decline in health

In fibrotic HP, symptoms may be irreversible even after antigen exposure is eliminated, highlighting the importance of early diagnosis and intervention.

Additional Clinical Clues

- **Temporal relationships to exposure:** Symptoms often worsen after contact with specific environments (e.g., barns, bird cages, hot tubs).
- **Relief during time away:** Many patients notice improvement when removed from the exposure setting (e.g., on vacation).
- **Recurrent episodes:** Especially in early or acute HP, repeated exposures trigger similar symptom clusters.

Initial Evaluation of Hypersensitivity Pneumonitis (HP)

When to Suspect HP

HP should be considered in individuals with unexplained respiratory symptoms, especially if:

- There's a history of **environmental or occupational exposure** (e.g., farming, bird handling, metalworking).
- Symptoms improve with **antigen avoidance.**
- Imaging or lung function tests suggest **interstitial lung involvement.**

Diagnostic Goals

- **Identify a potential inciting antigen**
- **Determine disease severity**
- **Classify disease subtype** (nonfibrotic vs fibrotic)
- **Establish a confident diagnosis** (possibly without biopsy)

Stepwise Diagnostic Approach

1. Exposure History

- Critical first step; includes occupational, avocational, environmental (home), and pet exposures.
- Note: No exposure is found in up to **60% of cases.**

2. Laboratory Tests

- General labs (ESR, CRP, LDH) are nonspecific.
- **Serologic IgG testing (precipitins):**
  - May support exposure, not diagnostic of disease.
  - High false-positive rate (e.g., in farmers, bird handlers).
  - Negative results do not rule out HP.
- **Skin testing and IgE-based allergy tests are not useful.**

3. Pulmonary Function Tests (PFTs)

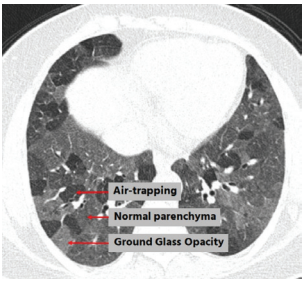
- **Typical pattern:** Restrictive + Reduced DLCO + exertional desaturation.
- Obstructive or mixed patterns are also possible.
- Not diagnostic of HP or useful in distinguishing fibrosis.

4. High-Resolution CT (HRCT)

- **HRCT** with volumetric acquisition and thin section < 1.5mm contiguous or overlapping images plays an important role, preferred to chest radiographs. Two series of images should be obtained with patient supine: one at deep inspiration and another at one second after prolonged expiration.

HRCT Findings of **HP** are as follows:

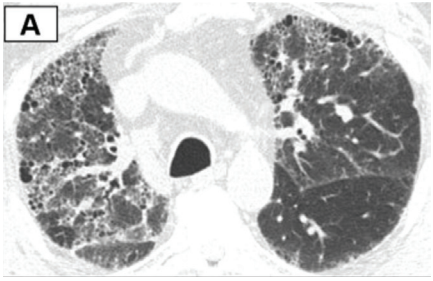
Non-Fibrotic/ Cellular:

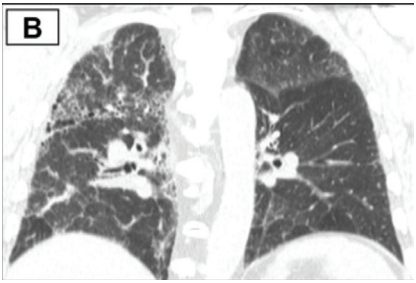


Most common finding is diffuse **GGOs[8].**
For HRCT typical of HP, it must also demonstrate one or more of the following:
a. Small poorly defined **centrilobular nodules < 5mm**
b. Multilobar areas of decreased attenuation and vascularity or expiratory air trapping. The combination of GGOs, decreased attenuation or vascularity is called **mosaic pattern.**
c. Normal Lung, GGOs and decreased vascularity or attenuation also called as **three density sign** or **Head Cheese Sign.**

Fibrotic HP:ThreeTypes

1. Typical HP:
It is the combination of irregular linear or coarse reticulations with lung distortion. The fibrosis has random distribution, mid lung zone predominant location, relatively sparing bases. The combination of reticulations, and three density sign is highly specific for HP[9]
2. Compatible with HP:
It includes a UIP pattern, extensive GGOs and typical opacities in variant distribution such as peribronchovascular or subpleural
3. Indeterminate for HP:
It includes patterns like Idiopathic interstitial pneumonias such as UIP, Probable UIP, indeterminate UIP, Fibrotic NSIP or OP.





5. Bronchoalveolar Lavage (BAL)

- Useful to detect lymphocytic alveolitis:
  - Lymphocytes >20% (often >30–50%)
  - Smoking reduces BAL lymphocytes
- BAL helps differentiate HP from IPF when HRCT is unclear.

6. Lung Biopsy

Used when diagnosis remains uncertain after history, imaging, and BAL:

- **Transbronchial Biopsy (TBLB):**
  - Low yield, especially in fibrotic disease (~30–40%).
- **Cryobiopsy:**
  - Larger sample than TBLB; approaching surgical biopsy accuracy.
  - Risks: bleeding, pneumothorax.
- **Surgical Lung Biopsy (VATS):**
  - Gold standard when needed.
  - Reserved for cases with unclear diagnosis or atypical features.

7. Histopathology

Nonfibrotic HP:

- Triad:
  - Cellular bronchiolitis (lymphocytes)
  - Poorly formed non-necrotizing granulomas
  - Chronic cellular interstitial pneumonitis

Fibrotic HP:

- Features of UIP or fibrotic NSIP
- Multinucleated giant cells, granulomas, Schaumann bodies
- May be subtle or absent; need expert pathology review

8. Inhalation Challenge

- Rarely used, lacks standardization.
- Environmental re-exposure may support diagnosis.
- Specific inhalation challenge (SIC) only in specialized centers or research settings.

Clinical Prediction Models

- Consider: age, exposure (birds/down), imaging features (mosaic attenuation, GGO), presence of precipitins, BAL lymphocytosis, and symptoms (e.g., symptom recurrence after exposure).
- HP score >63: high specificity (91%) but low sensitivity (~50%).

Antigen Avoidance Trial

- **Useful when diagnosis is unclear.**
- Resolution of symptoms/imaging changes supports diagnosis.
- Especially helpful in nonfibrotic HP.
- Limited utility in fibrotic HP, as changes may be irreversible.

Treatment:
Treatment of Hypersensitivity Pneumonitis (HP) by Clinical Subtype

1. Acute HP
Rapid onset (within 4–8 hours of exposure) with flu-like symptoms, cough, dyspnea, fever, and malaise.
Usually reversible if diagnosed early and exposure is removed.

Treatment Approach

- **Immediate antigen avoidance**
  - Key intervention—symptoms often resolve within days
- **Supportive care**
  - Oxygen therapy if hypoxic
  - Antipyretics for fever
- **Corticosteroids (optional)**
  - May be used in severe or prolonged cases
  - Prednisone 0.5–1 mg/kg/day for 1–2 weeks, followed by a taper

Prognosis

- Excellent with prompt antigen removal
- Recurrence is common with re-exposure

2. Subacute HP

- **Insidious onset** over weeks to months
- Features include cough, dyspnea, fatigue, and weight loss
- Symptoms may fluctuate with intermittent exposure

Treatment Approach

- Strict antigen avoidance
  - Critical to prevent progression to fibrosis
- Corticosteroids
  - Prednisone 0.5–1 mg/kg/day for 2–4 weeks, then gradual taper over 1–3 months
  - Monitor response (symptoms, PFTs, imaging)

- Pulmonary function monitoring
  - Baseline and follow-up spirometry and DLCO

Prognosis

- Often reversible with early treatment
- May progress to chronic/fibrotic HP if exposure persists or diagnosis is delayed

3. Chronic HP (Fibrotic HP)

Gradual onset with persistent cough, progressive dyspnea, and irreversible lung fibrosis
May mimic idiopathic pulmonary fibrosis (IPF)

Treatment Approach

Antigen Avoidance

- Antigen avoidance can improve survival but does not reverse the disease.
- Still essential, though effect is limited once fibrosis is established

Pharmacologic Therapy

Medication	Role
Corticosteroids	Prednisolone 30mg/day (0.5mg/kg in a patient weighing <60kg) for 4-8 weeks, followed by tapering to 10-20 mg/day by 3 months after initiation. Steroids are mostly helpful with inflammatory features i.e., GGOs on HRCT, BAL Lymphocytosis>20%, or histopathological cellular interstitial pneumonia or granuloma.
Immunosuppressives	Mycophenolate Mofetil, azathioprine – may help in inflammatory component
Antifibrotics	Patients with chronic HP and progressive fibrosis, treatment with Anti fibrotic agents may slow disease progression. Nintedanib (preferred), Pirfenidone (not studied) shows to slow progression in fibrotic HP. Antifibrotic therapy is added to immunosuppressive therapy.

Nintedanib is FDA-approved for progressive fibrosing interstitial lung diseases, including chronic HP

Supportive Care

- Oxygen therapy: if hypoxemic at rest or with exertion
- Pulmonary rehabilitation
- Vaccinations: influenza, pneumococcal, COVID-19
- Smoking cessation

Lung Transplantation

- Consider advanced cases with progressive respiratory failure
- Referrals should be early, especially in younger patients or those with rapid decline

Prognosis

- Variable; worse in those with:
  - Honeycombing or UIP pattern on HRCT
  - Persistent antigen exposure
  - Late diagnosis

Summary Table

Subtype	Key Features	Main Treatment	Prognosis
Acute HP	Sudden onset, flu-like symptoms	Antigen avoidance, steroids (if severe)	Excellent if early
Subacute HP	Gradual symptoms over weeks	Antigen avoidance + corticosteroids	Good if treated early
Chronic HP (Fibrotic)	Persistent symptoms, irreversible fibrosis	Antigen avoidance, immunosuppressants , antifibrotics, lung transplant in severe cases	Variable; often progressive

Prognosis of Hypersensitivity Pneumonitis (HP)

- Outcome varies depending on the **type of antigen, exposure duration,** and **individual immune response.**
- **Acute HP:** Patients who completely avoid the antigen usually recover lung function fully, though recovery can take years.
- **Bird fancier's lung** tends to have a worse prognosis than farmer's lung.
- **Pulmonary fibrosis** presence on biopsy predicts a poorer outcome.
- About 60% of patients with chronic fibrotic HP show disease progression over two years, similar to idiopathic pulmonary fibrosis (IPF).
- **The ILD-GAP model** (considering age, sex, lung function, and disease subtype) helps predict mortality risk in chronic HP.
- **HRCT imaging** findings such as traction bronchiectasis and honeycombing correlate with higher mortality and worse survival.
- Certain **histopathologic patterns** (fibrotic NSIP, UIP) and features like fibroblast foci predict poorer outcomes.
- Development of **pulmonary hypertension** in chronic HP signals more severe disease and worse survival.
- **Farmer's lung:** Generally better prognosis; most recover with minor lung function impairment, though up to 50% develop mild chronic lung changes.
- **Bird fancier's lung:** Often more severe, with higher mortality linked to longer exposure and persistent domestic antigen presence.
- Failure to identify causative antigen is associated with worse survival.

Prevention

- Reducing exposure to causative antigens is the most effective preventive measure.
- Environmental controls such as improving ventilation, enclosing sources of microbial antigens, and maintaining humidity below 60% help limit exposure.
- Prompt repair of water damage and regular cleaning reduce microbial growth indoors.
- Use of personal protective equipment (masks or respirators) may be helpful when antigen avoidance is not possible, though evidence of their effectiveness is limited.
- Proper maintenance of heating, ventilation, and air conditioning systems is critical to prevent antigen buildup.

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Chapter 05:
Connective Tissue Disease Related ILDs (CTD-ILDs)

Introduction

Connective tissue diseases (CTDs) are systemic immune-mediated disorders characterized by immune dysregulation and multi-organ involvement, including frequent pleuro-pulmonary manifestations. The respiratory tract can be affected at multiple levels—respiratory muscles, pleura, conducting airways, small airways, pulmonary interstitium and pulmonary vasculature—either in isolation or combination.

The term CTD-ILD is increasingly being replaced by broader terminology such as **Systemic autoimmune rheumatic disease–associated ILD (SARD-ILD),** which includes a wider range of immune-mediated rheumatological conditions. SARD associated with ILD include rheumatoid arthritis, systemic sclerosis, Sjogren disease, idiopathic inflammatory myopathies, mixed connective tissue disease, systemic lupus erythematosus, ANCA-associated vasculitis and axial spondyloarthropathy. [1]

Epidemiology

ILD is a common extra-articular manifestation of systemic autoimmune rheumatological disorders with overall prevalence of 40%: out of which, the highest prevalence has been reported in MCTD (66%) and SSc (34-65%) and the lowest in SLE (about 6%). [2]

Pathophysiology

Initially, lymphocyte activation drives inflammation and interstitial injury; at this stage, immunomodulatory therapy may reduce inflammation and can partially or completely reverse early fibrotic remodeling. Fibrosis results from an exaggerated wound-healing response to immune-mediated lung injury. If immune activation persists, profibrotic cytokines activate fibroblasts, which then differentiate into myofibroblasts, migrate into the alveolar interstitium, and drive fibrogenesis. In later disease, myofibroblasts deposit excess extracellular matrix, causing irreversible architectural distortion and, in advanced cases, subpleural honeycombing—representing a final common pathway across fibrotic ILDs regardless of the underlying CTD.

Clinical Presentation

- CTD-ILD commonly presents with exertional dyspnea and chronic cough.
- Constitutional symptoms such as fatigue, low-grade fever, weight loss, myalgias, and arthralgias are not uncommon.
- Clinical history should be evaluated for features of an underlying systemic autoimmune rheumatic disease e.g., Raynaud phenomenon, puffy fingers or skin thickening, morning stiffness, sicca symptoms (dry eyes/mouth), photosensitive rash or oral ulcers, proximal muscle weakness (± myalgia), digital ulcers, dysphagia or reflux, and symptoms suggestive of vasculitis (e.g., sinus symptoms, epistaxis, neuropathy, or hemoptysis). Drug exposure and infection risk should also be assessed, as both may mimic or worsen ILD.

- On examination, fine end-inspiratory "Velcro" crackles are common; digital clubbing may occur, particularly in fibrotic phenotypes.
- Extra-pulmonary signs suggestive of CTD-ILD include synovitis, various cutaneous signs **(malar rash for SLE and heliotrope rash, Gottron's papules and shawl sign for dermatomyositis), digital ulceration, telangiectasia, calcinosis, sclerodactyly, and proximal muscle weakness**

Phenotypic Patterns of Interstitial Lung Disease in CTD ILDs

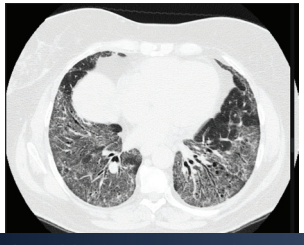
The HRCT pattern of interstitial lung disease varies across systemic autoimmune rheumatic diseases and provides important information regarding prognosis, monitoring strategy, and treatment selection. The distribution of radiological phenotypes differs by underlying disease. NSIP is the predominant HRCT pattern across most CTD-ILDs, particularly in systemic sclerosis–ILD, idiopathic inflammatory myositis–ILD, mixed connective tissue disease, and many cases of primary Sjögren syndrome, accounting for approximately 27–76% of cases in pooled analyses [4]. UIP occurs more frequently in rheumatoid arthritis–associated ILD, where it may predominate (≈46%) and is generally associated with a more fibrotic trajectory +. Organizing pneumonia (OP) and lymphoid interstitial pneumonia (LIP) are less common overall but may be encountered in inflammatory phenotypes, with OP reported most often in idiopathic inflammatory myopathies (≈16%) and LIP most strongly associated with Sjögren syndrome (≈7%) [4]. Systemic lupus erythematosus–ILD typically demonstrates non-UIP inflammatory patterns, whereas undifferentiated connective tissue disease shows heterogeneous imaging features reflecting variable disease evolution.

Imaging in CTD-ILD

High-resolution CT (HRCT) is essential to confirm ILD, define the radiologic pattern, and support subtyping and management decisions.

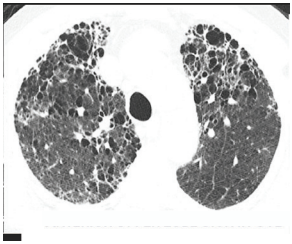
Key HRCT patterns

- **NSIP: Basal-predominant** ground-glass opacities with reticulation and traction bronchiectasis, often with peribronchovascular extension and relative subpleural sparing

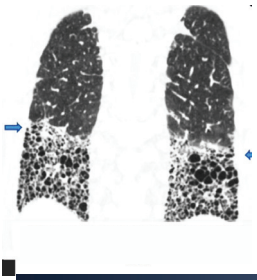


NSIP ASSOCIATED WITH CTD-ILD

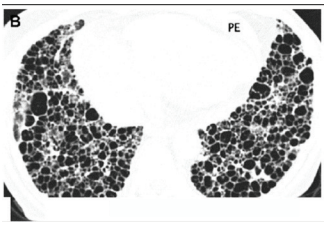
- **UIP: Subpleural, basal-predominant fibrosis with reticulation and traction bronchiectasis;** honeycombing is required for definite UIP, while its absence is labelled probable UIP. UIP in CTD-ILD may look identical to IPF, but clues to an autoimmune cause can include the straight-edge sign, exuberant honeycombing (honeycombing involving >70% of fibrotic areas), and the anterior upper-lobe sign.[3]



ANTERIOR UPPER LOBE SIGN IN CTD

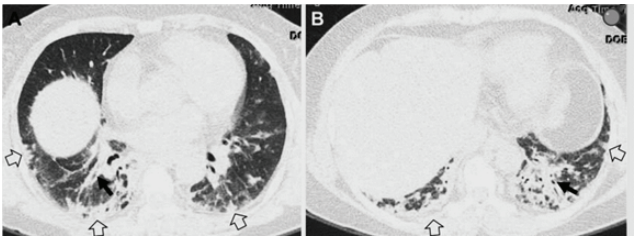


STRAIGHT EDGE SIGN IN CTD-UIP



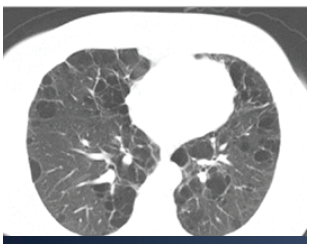
EXUBERANT HONEYCOMBING

- **OP:** Typically, bilateral consolidation, often with subpleural and lower-zone predominance; most commonly linked with inflammatory myopathies.



ORGANIZING PNEUMONIA IN A PATIEN WITH DERMATOMYOSITIS

- **LIP: Peribronchovascular cysts**, with or without ground-glass change and/or reticulation; most closely associated with Sjogren disease.



LIP IN SJOGREN DISEASE

Features suggesting an underlying CTD on HRCT include multicompartment involvement (e.g., esophageal dilatation, pleural and/or pericardial involvement) and subpleural sparing.

Screening for ILDs in Different CTDs

Screening for interstitial lung disease is an essential component of the evaluation of patients with systemic autoimmune rheumatic diseases, as early lung involvement may be clinically silent yet prognostically significant. Screening recommendations were developed from predefined PICO and narrative clinical questions relevant to CTD-ILDs.

PICO-based recommendations:

- **PICO 1:** Should pulmonary function tests (FVC and DLCO) replace HRCT for ILD screening in CTD patients?

Recommendation: HRCT should not be replaced by pulmonary function tests for screening of ILD in patients with CTDs. Spirometry and DLCO are appropriate as baseline and follow-up assessments but are not sufficient as a standalone screening substitute for HRCT.

- **PICO 2:** Should lung ultrasound replace HRCT for ILD screening in CTD/SARD patients?

Recommendation: HRCT should not be replaced by lung ultrasound for screening of ILD in patients with CTDs. Lung ultrasound may be used as an adjunct in selected settings, but it does not substitute for HRCT in ILD screening

- **Narrative 1:** Which CTD/SARD patients should be screened for ILD?

Recommendation: All patients with systemic sclerosis and mixed connective tissue disease should undergo ILD screening. In rheumatoid arthritis, Sjögren syndrome, and idiopathic inflammatory myopathies, screening is recommended in the presence of clinical or serological risk factors, while screening may be considered in other patients on a case-by-case basis.

- **Narrative 2:** How often should CTD/SARD patients be screened for ILD?

Recommendation: Screening frequency should be risk-stratified and determined by the underlying CTD, baseline findings, and clinical course. Patients at higher risk or with early abnormalities require closer interval reassessment, whereas stable low-risk patients may be followed at longer intervals, in line with the screening and monitoring pathway outlined in this guideline.

The following recommendations summarize the committee's evidence-based approach to screening for interstitial lung disease in patients with systemic autoimmune rheumatic diseases.

CTD subtype	Who should be screened with HRCT at/near CTD diagnosis
Systemic sclerosis (SSc)	All patients.
Mixed connective tissue disease (MCTD)	All patients.
Idiopathic inflammatory myopathies (IIM)	Patients with ILD risk factors (anti-synthetase syndrome, clinically amyopathic dermatomyositis, mechanic's hands, arthritis; myositis-associated autoantibodies (anti-synthetase, anti-MDA-5, anti-Ro52) should be screened. In addition, most IIM patients without risk factors can be screened, except inclusion body myositis.

Rheumatoid arthritis (RA)	Patients with ILD risk factors (older age, smoking history, male sex, elevated rheumatoid factor (RF), anti-CCP antibodies, increased inflammatory markers, high articular disease activity) can be screened.
Sjogren disease (SjD)	Patients with ILD risk factors (older age, male sex, active extrapulmonary organ involvement, increased inflammatory markers) can be screened.
Systemic lupus erythematosus (SLE)	No specific screening statement; use clinical judgement and local practice.

Risk Factors for Interstitial Lung Disease in CTDs

Clinical, serological, and disease-related factors may increase the likelihood of interstitial lung disease across systemic autoimmune rheumatic diseases. Recognition of these risk factors helps identify patients who may benefit from early screening and closer monitoring.

Category	Systemic Sclerosis (SSc)	Rheumatoid Arthritis (RA)	Idipathic Inflammatory Myopathies (IIM)	Primary Sjögren Syndrome (SjD)
Demographics	Longer disease duration	Older age; male sex; smoking history	Older age	Older age; male sex
Circulating markers / Serology	Increased KL-6; anti-topoisomerase I (ATA)	Elevated ESR; anti-CCP antibodies; high rheumatoid factor	Elevated CRP/ESR; anti-synthetase antibodies; anti-MDA5; anti-Ro52	Elevated CRP; anti-Ro52
Extrapulmonary disease features	Diffuse cutaneous SSc; higher mRSS	Higher articular disease activity	Anti-synthetase syndrome; clinical amyopathic dermatomyositis; skin involvement; arthritis/arthralgia; fever	Presence of extrapulmonay involvement

Diagnostic Approach in CTD-ILDs

Diagnosis of CTD

Each systemic autoimmune rheumatic disease is diagnosed when patients meet the diagnostic criteria proposed by the American College of Rheumatology and the European Alliance of Associations for Rheumatology (ACR/EULAR). However, some patients do not fulfil these criteria but exhibit typical signs and symptoms of CTD/SARD-ILD and are classified under the term IPAF [5]

Interstitial pneumonia with autoimmune features (IPAF)

Diagnosis of IPAF requires at least one positive finding from any two of the following three domains

- Clinical Domain
- Serological Domain
- Morphological Domain [5]

When to Suspect CTD-ILD?

- In all patients presenting with ILD, an underlying systemic autoimmune rheumatic disease should be assessed by clinical findings, autoantibody testing, imaging results and histopathological features if suggestive.
- CTD-ILD more often affects younger individuals, is more frequent in women, and is commonly seen in never-smokers. [6]
- ILD may be the initial manifestation of CTD leading to an initial classification as idiopathic interstitial pneumonia. Approximately 15% of patients initially diagnosed with idiopathic interstitial pneumonia are subsequently found to have an underlying systemic autoimmune rheumatic disease [7]. Furthermore, the absence of a confirmed systemic diagnosis at presentation does not exclude CTD-ILD, as pulmonary involvement may precede systemic features in around 25% of cases [8]

Pulmonary function Tests

- Baseline evaluation should include spirometry, lung volumes (where available), and DLCO.
- CTD-ILD typically demonstrates restriction with reduced lung volumes and reduced DLCO.
- A normal or preserved FVC does not exclude ILD, especially in early disease.
- The six-minute walk test (6MWT) with continuous oximetry is recommended at baseline in patients without musculoskeletal limitations (not helpful if there is significant musculoskeletal involvement due to CTD e.g., in IIM), to assess functional capacity and exertional desaturation and to provide a baseline functional status

Serological Testing for autoantibodies in CTD-ILDs

Core autoantibodies

The following tests should be ordered in all patients with ILD undergoing evaluation for CTD-ILD: [5]

- Antinuclear antibody (ANA), including titre and immunofluorescence pattern
- Rheumatoid factor (RF)
- Anti–cyclic citrullinated peptide antibody (anti-CCP)
- Myositis antibody panel (myositis-specific and myositis-associated antibodies)

Supportive tests

Inflammatory markers such as ESR and CRP may be checked as supportive baseline tests, but they are nonspecific and are not included in serology-based classification criteria. Similarly, Creatine Phosphokinase (CPK) can support suspicion of inflammatory myopathy when clinically indicated, but they do not substitute for autoantibody testing. [5]

Extended Serological Evaluation

Extended serology (ENA Profile) should be requested in any of the following circumstances:

- A positive result on baseline autoimmune screening
- Clinical features suggestive of a systemic autoimmune rheumatic disease
- Radiological features that support an autoimmune-associated ILD phenotype
- Unexplained, progressive, or severe ILD.

An extractable nuclear antigen (ENA) profile should include anti-Ro (SSA), anti-La (SSB), anti-RNP, anti-Smith, anti–topoisomerase I (anti–Scl-70), anti–PM/Scl, and anti-synthetase antibodies (where not already covered within the myositis panel). Anti–double stranded DNA (anti-dsDNA) should be ordered when an SLE phenotype is suspected and anti MDA5 when a rapidly progressive ILD is suspected. [5]

Interpretation and Clinical Application

ANA results should be documented with both titre and pattern, as patterns help in clinical interpretation. A homogeneous pattern can support an SLE spectrum diagnosis, while centromere, speckled, and nucleolar patterns is usually seen in systemic sclerosis and overlap syndromes. [9]

Antibodies with important clinical implications

- Anti-Scl-70 positivity supports systemic sclerosis spectrum disease and is associated with higher risk of progressive ILD. [10]
- Anti-CCP positivity supports rheumatoid arthritis phenotype and is associated with increased risk of RA-ILD. [10]
- Anti-synthetase antibodies support anti-synthetase syndrome and help risk stratify myositis-associated ILD. Anti-Jo-1 is the most common (approximately 74%), followed by anti-PL-7 (approximately 14%) and anti-PL-12 (approximately 10%); anti-PL-7 and anti-PL-12 are associated with higher prevalence and greater severity of ILD. [11]
- Anti-MDA5 is associated with rapidly progressive ILD and should be treated as a high-risk feature requiring urgent specialist input and close monitoring. [11]

Bronchoscopy, BAL, and lung biopsy

Bronchoscopies with BAL and Lung Biopsy are not required for the diagnosis of CTD-ILDs. These can be considered to rule out infections or if some alternate diagnosis is under consideration. [12]

Multidisciplinary Approach

A multidisciplinary team comprising of Pulmonologists, Radiologists, Rheumatologists and histopathologist is usually needed for the compact diagnosis and management of CTD-ILD.

Baseline assessment package

Component	What to include
Clinical evaluation	Respiratory symptoms, duration, smoking and exposures; occupational history; medication history; comorbidities; CTD activity and organ involvement; oxygen saturation at rest and with exertion.
Imaging	Baseline HRCT (thin-section protocol)
Functional Status	Spirometry, lung volumes (if available), DLCO; 6MWT with oximetry (if feasible).
Cardiovascular assessment	Echocardiography for pulmonary hypertension and right heart function when clinically indicated (particularly systemic sclerosis, disproportionate DLCO reduction, or exertional desaturation).
Laboratory and safety tests	FBC, renal function, liver enzymes; screening for chronic infections prior to immunosuppression
Patient-reported outcomes	Standardized dyspnea and cough assessment and health-related quality of life measures when feasible.

Assessing Severity and Risk of Progression

At ILD diagnosis, patients should be stratified by current severity and risk of future progression. Practical risk assessment is based on a combination of clinical features, HRCT extent and pattern, and pulmonary function. Factors that typically indicate higher risk include older age, male sex, smoking, greater extent of fibrosis on HRCT, UIP pattern, lower baseline FVC and DLCO, and biomarkers or CTD phenotypes associated with aggressive lung disease. In myositis-associated ILD, anti-MDA5 antibodies and rapidly worsening symptoms over weeks to months signal high risk and warrant early aggressive therapy.
Severity can be assessed pragmatically as mild, moderate, or severe using the combination of symptom burden, need for oxygen, HRCT extent, and physiologic impairment. Risk stratification should be repeated at each follow-up visit because CTD activity and ILD behavior can change over time.

Monitoring and follow-up

Monitoring aims to:

- Detect progression early
- Identify treatment response or toxicity, and
- Recognize complications such as pulmonary hypertension or infection

Each follow-up visit should include interval history for dyspnea, cough, exercise tolerance, and acute infective symptoms, as well as examination and pulse oximetry. PFTs are the cornerstone of longitudinal monitoring, and HRCT is used when there is suspected progression or at routine intervals in higher-risk patients.

Suggested monitoring schedule

Follow-up intervals should be individualized based on duration of ILD, Risk for progression and type of ILD.

Clinical Scenario	PFT Schedule	HRCT Schedule	Other
High-risk or early disease course	Lung function testing every 3–6 months for the first 12–24 months, then every 6–12 months thereafter.	Repeat HRCT at ~12 months to establish trajectory, then annually if clinically indicated (new/worsening symptoms, physiologic decline, or treatment escalation).	6MWT (if feasible) and symptom-based PROMs every 6–12 months.
Lower-risk, stable disease	Lung function testing every 6–12 months.	Repeat HRCT only if clinically indicated (symptoms or PFT deterioration), or every 24 months where risk is uncertain and HRCT access allows.	6MWT and symptom assessment every 12 months.
Myositis-ILD with rapid progression risk	Lung function testing every 3–6 months in the first year; more frequent assessment may be required during induction therapy or rapid progression.	In high-risk disease, repeat HRCT at 3–6 months if clinical course is rapidly evolving; otherwise reassess at 12 months and thereafter as clinically indicated.	Close clinical review during the first 3–6 months is essential; evaluate for infection and treatment toxicity at each visit.

Interpreting change and defining progression

Any apparent change in symptoms or physiology should be interpreted in context. A fall in DLCO may reflect pulmonary hypertension; a fall in FVC may be confounded by chest wall restriction or myopathy. Progression should therefore be determined using a composite assessment that includes symptoms, PFTs, and HRCT. When progression is suspected, ensure adequate treatment adherence and exclude alternative explanations such as infection, heart failure, pulmonary embolism, and drug toxicity.

Treatment goals

The primary goals are stabilization or improvement of symptoms and lung function, prevention of irreversible fibrosis, minimization of treatment-related toxicity, and preservation of quality of life. For some patients with advanced fibrotic disease, goals may shift toward symptom control, oxygen optimization, and timely referral for lung transplantation assessment where feasible.

Treatment:

General Principles

Management of CTD-ILD is multifactorial and depends on the underlying CTD, the ILD pattern and phenotype (predominantly fibrotic or predominantly inflammatory), and the baseline functional status and overall severity of disease. The mainstay of treatment is immunosuppression, most commonly using glucocorticoids and steroid-sparing immunosuppressants. In patients with a fibrotic phenotype, antifibrotic therapy is recommended.

For practical decision-making, treatment is individualized using the following categories, and each CTD-ILD is discussed according to this framework:

1. First-line treatment
2. Progressive disease despite first-line treatment, defined by any of the following:
- Relative decline in FVC percentage predicted of at least 10% over 24 months
- Relative decline in FVC percentage predicted of 5–10% together with worsening symptoms and/or progression on HRCT over 24 months [13]

3. Rapidly progressive ILD, defined as progression leading to a high oxygen requirement or the need for intubation within days to weeks, without an alternative cause. [14]

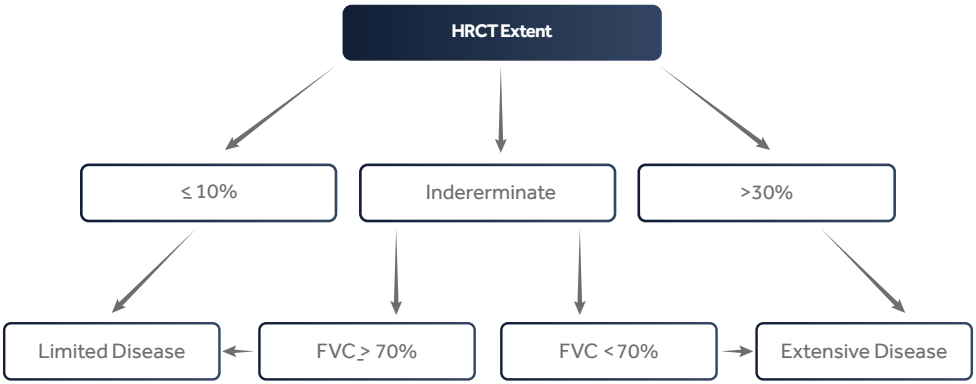
Disease-specific Management

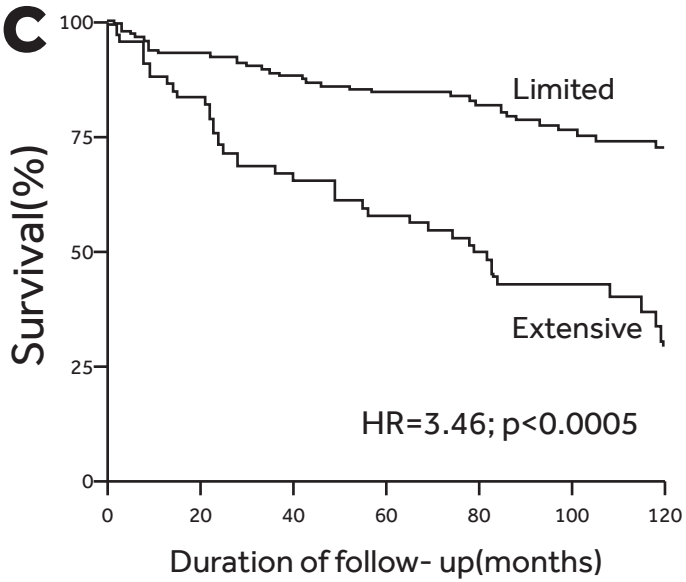
Systemic Sclerosis–Associated ILD (SSc-ILD)

SSc-ILD is a leading cause of morbidity and mortality in systemic sclerosis. Baseline HRCT screening is recommended for all patients with systemic sclerosis. Disease phenotype may be inflammatory early and fibrotic later; NSIP is common, although UIP may be present in a substantial proportion. Assessment should also address pulmonary hypertension, gastro-esophageal reflux, and aspiration.

Limited SSc-ILD

- Limited disease in SSc-ILD is defined as less than 20% fibrosis on HRCT and FVC greater than 70%, according to the Goh scoring system.
- In limited disease, close monitoring with serial PFTs and clinical assessment is typically sufficient, without the need for immunosuppressive or antifibrotic therapy. [25]





Extensive SSc-ILD

- Extensive disease is defined as more than 20% HRCT involvement with FVC less than 70% [25,26]
- In extensive disease, or when ILD is accompanied by significant extrapulmonary manifestations, immunosuppressive therapy with mycophenolate (MMF) is recommended (start 500 mg twice daily and increase to 1–1.5 g twice daily), with regular monitoring of full blood count, liver function tests, and renal function tests. [26]
- Cyclophosphamide can also be used as initial therapy, but MMF is preferred due to better safety profile.
- Tocilizumab (162 mg subcutaneous weekly) can also be given in SSc-ILD for patients with early diffuse cutaneous systemic sclerosis, particularly when there are elevated inflammatory markers or recent progression of skin fibrosis. Its main role is stabilization of FVC, with additional benefits on skin fibrosis and fatigue, and an overall tolerable safety profile. [27]

Isolated Fibrotic SSc-ILD with no extrapulmonary involvement

- If there is ≥ 10 % fibrosis on HRCT and no significant extrapulmonary involvement, antifibrotic therapy is recommended with Nintedenib (150 mg twice daily).[28]

High Risk SSc-ILD or Progressive ILD

If the patient is at high risk of complications, the ILD is progressive, or there is severe multi-organ involvement, the following options should be considered:

- Add-on therapy with an additional immunosuppressant.
- Add-on therapy with Nintedenib in combination with mycophenolate mofetil (MMF) in cases of progressive pulmonary fibrosis.
- Add-on therapy with Rituximab can be used (500–1000 mg IV, repeated after 2 weeks, then every 24 weeks) for refractory disease.
- Lung Transplant referral should be considered. [26]

Note: Glucocorticoids are not recommended for routine use in SSc-ILD.

Supportive care considerations in SSc-ILD

Manage gastro-esophageal reflux aggressively [18], optimize nutrition, encourage pulmonary rehabilitation, and assess for group I pulmonary hypertension when symptoms are disproportionate to ILD severity [19]. Consider early discussion regarding long-term oxygen therapy and referral for lung transplantation assessment in progressive severe disease.

Rheumatoid Arthritis–Associated ILD (UIP)

RA-ILD is common in older male patients and in those with long-standing seropositive disease. UIP-pattern disease occurs frequently and is associated with higher risk of progression and poorer prognosis.

Asymptomatic or Mild RA-ILD

- For asymptomatic patients, or those with mild RA-ILD (mild dyspnea or cough and FVC ≥ 70%), clinical follow-up with PFT surveillance is recommended rather than initiating anti-inflammatory or antifibrotic therapy. [14]

RA-ILD with presence of active arthritis

- In patients with RA-ILD and active inflammatory arthritis, management should follow a treat-to-target strategy for RA, aiming for remission or low disease activity. Practical options mycophenolate mofetil, azathioprine, glucocorticoids (short-term when needed), and RA-directed biologic/targeted agents such as abatacept, rituximab, tocilizumab, and JAK inhibitors; [29,30]

Well Controlled Arthritis with Severe or Progressive ILD

- If the arthritis is well controlled but the ILD is progressive or severe, guidelines recommend addition of another immunosuppressant. [30]

Well Controlled Arthritis with Progressive Pulmonary Fibrosis

If RA-ILD develops a progressive pulmonary fibrosis phenotype, the following treatment options are recommended:

- Add-on Nintedanib (150 mg twice daily) in combination with an immunosuppressant. [13•]
- Nintedenib monotherapy (150 mg twice daily).
- Pirfenidone, titrated as follows: 267 mg three times daily for 1 week, then 534 mg three times daily for 1 week, then 801 mg three times daily (total 2403 mg/day). [31]

Idiopathic Inflammatory Myopathy–Associated ILD (IIM-ILD)

Idiopathic inflammatory myopathies (IIMs) were traditionally classified into polymyositis, dermatomyositis, and inclusion body myositis. However, newer recognized subsets include immune-mediated necrotizing myopathy and anti-synthetase syndrome. ILD occurs in approximately 35–45% of patients with IIM and is a major contributor to morbidity [32]. The most common ILD pattern in IIM is NSIP; other frequent patterns include organizing pneumonia (OP) and NSIP/OP overlap, while less common patterns include UIP, acute interstitial pneumonia (AIP), and lymphocytic interstitial pneumonia (LIP). Anti-MDA5 positivity is associated with rapidly progressive ILD and high early mortality and requires urgent recognition and aggressive management. [33]

Asymptomatic/Early IIM-ILD

In asymptomatic patients, or those with minimal exertional dyspnea, with less than 10% HRCT involvement, FVC >75% and/or DLCO >65%, and no oxygen requirement, pharmacological therapy is not indicated; clinical follow-up with monitoring is recommended. [34]

First Line Treatment in IIM-ILD

Glucocorticoids are the mainstay of induction treatment in IIM-ILD.

- The recommended regimen is prednisolone 1 mg/kg/day (maximum 60 mg/day). After 1 month, taper to 40 mg/day, then continue a gradual taper until 20 mg/day is reached, followed by a reduction of 2.5 mg every 2 weeks, with a total treatment duration of 4–6 months. [14]

Indications for adding an immunosuppressant include: [14]

1. Clinical or physiological worsening on glucocorticoids, defined as a decline in FVC >10% or DLCO >15%.

2. Inability to taper glucocorticoids without relapse or deterioration.

3. Rapidly progressive ILD, particularly anti-MDA5–positive disease or anti-synthetase syndrome.

4. Glucocorticoid intolerance or contraindication.

The options for immunosuppressive therapy in symptomatic IIM-ILD include azathioprine, mycophenolate mofetil (MMF), rituximab, and calcineurin inhibitors (CNIs).

Progressive or Severe IIM-ILD

- In patients with high risk of ILD progression or severe multi-organ involvement, combination of immunosuppressants is indicated.
- A practical approach is induction with high-dose glucocorticoids plus a rapid-acting agent such as cyclophosphamide, rituximab, intravenous immunoglobulin (IVIG), tofacitinib, or tacrolimus, followed by transition to mycophenolate mofetil (MMF) for maintenance after clinical stabilization, typically after 3–6 months. [35-41]

IIM-ILD with Progressive Pulmonary Fibrosis

- Combination therapy with an immunosuppressant plus Nintedanib should be considered in progressive pulmonary fibrosis [13]

Rapidly Progressive IIM-ILD (Over weeks to few months)

- Initiate combination therapy with high-dose glucocorticoids plus cyclophosphamide or rituximab, together with a calcineurin inhibitor (CNI) (e.g., Tacrolimus: 0.075 mg/kg twice daily) [35-41]
- **IVIG, JAK** inhibitors (e.g., Tofacitinib 5 mg twice daily) and plasmapheresis may also be considered in rapidly progressive ILD over weeks or few months. [38,40]
- Consider referral for lung transplant.

Other CTD-ILDs (SjD, SLE, MCTD associated ILD)

- SjD-ILD and SLE-ILD and are less common than systemic sclerosis but remain important causes of CTD-ILD.
- The most frequent HRCT pattern across these CTD-ILDs is NSIP, while organizing pneumonia (OP) can occur, and lymphocytic interstitial pneumonia (LIP) is most closely associated with Sjogren disease.
- Although disease behavior varies by diagnosis and phenotype, the overall clinical approach and treatment framework are broadly similar across these CTD-ILDs, using the same principles of severity assessment, monitoring for progression, and stepwise escalation when indicated.
- **MCTD and Overlap phenotypes** should be managed according to the dominant clinical and radiological phenotype, with particular attention to systemic sclerosis features (risk of renal crisis with high-dose steroids) and myositis features (risk of rapid progression).
  Asymptomatic/Mild CTD-ILD

Asymptomatic/Mild CTD-ILD

- In asymptomatic patients, or those with minimal symptoms and burden of disease based on HRCT and PFTs only require monitoring of symptoms, HRCT and PFTs at 6–12-month intervals [41]

First Line Treatment in CTD-ILD

As NSIP is the most frequent pattern, management broadly follows the approach used for idiopathic NSIP, alongside active treatment of the underlying CTD. [42,43]

- Prednisolone is initiated at 0.5–1 mg/kg/day (maximum 60 mg/day), then tapered after 4–6 weeks according to clinical and physiological response, with continuation of a low maintenance dose for at least 6 months.
- In patients who do not respond adequately to systemic steroids, require prolonged therapy, or develop steroid-related adverse effects, a steroid-sparing immunosuppressant should be added.
- Azathioprine or mycophenolate mofetil (MMF) may be used in stable disease (azathioprine 1–2 mg/kg/day; MMF start 500 mg twice daily and increase to 1–1.5 g twice daily, as tolerated).

Progressive or Severe CTD-ILD

If ILD is severe, or there is a high risk of progression, the following options should be considered:

- Addition of another immunosuppressant, for example combination therapy with azathioprine and MMF. [44]
- Rituximab (1 g IV, repeat after 2 weeks, then every 24 weeks) or cyclophosphamide (500–750 mg IV, repeated every 4 weeks for 6 months) should be reserved for refractory disease that has not responded to prednisolone in combination with azathioprine or MMF. [43]
- Consider referral for lung transplant consideration

CTD-ILD with progressive pulmonary fibrosis

If CTD-ILD develops a progressive pulmonary fibrosis phenotype, the following treatment options are recommended:

- Add-on Nintedanib (150 mg twice daily) in combination with an immunosuppressant.
- Nintedanib monotherapy (150 mg twice daily). [13]

Adjunctive Therapies in all CTD-ILDs

1. Supplemental oxygen should be prescribed for resting hypoxemia, and ambulatory oxygen should be provided for patients with exertional desaturation. [15]

2. In patients with chronic refractory dyspnea, opioids and benzodiazepines can be used for symptom relief. Simple measures, including hand-held fans and breathing exercises, can also reduce the sensation of breathlessness. [16]

3. Gabapentin can be considered for chronic cough in CTD-ILD. [17]

4. Pulmonary rehabilitation should be offered to suitable patients with CTD-ILD to improve exercise tolerance, functional status, and symptom control. [16]

5. Patients should be guided about vaccination specially who are on immunosuppressant therapy (Influenza Vaccine, Pneumococcal Vaccine and COVID-19 Vaccine)

Management of Comorbidities

1. Gastro-esophageal reflux disease (GERD): GERD is common in CTD-ILD, particularly in systemic sclerosis–associated ILD. Proton pump inhibitors should be prescribed in all patients with systemic sclerosis–associated ILD. [18]

2. Pulmonary arterial hypertension (PAH): Group 1 PAH is an important and relatively frequent complication of CTDs, particularly systemic sclerosis and mixed connective tissue disease. Patients should be assessed for PAH when clinically suspected, as selected patients may benefit from pulmonary hypertension–specific therapies. [19]

Prevention & Management of Long-Term Glucocorticoid Complications

1. Use the lowest possible effective dose for the shortest duration; introduce steroid-sparing therapy early when prolonged treatment is anticipated.

2. Screen for and manage steroid-induced hyperglycemia/diabetes; monitor fasting/random glucose and adjust antidiabetic therapy as needed.

3. Monitor and treat hypertension and fluid retention; advise salt restriction and optimize antihypertensive therapy.

4. Prevent glucocorticoid-induced osteoporosis: ensure adequate calcium and vitamin D, assess fracture risk, and prescribe bisphosphonates when Prednisolone is taken at the doses of ≥7.5 mg/day for ≥3 months. [20]

5. Reduce infection risk: review vaccination status (influenza, pneumococcal as appropriate), counsel on early reporting of infection symptoms, and consider Pneumocystis jirovecii prophylaxis in patients receiving high-dose steroids (Prednisone ≥ 20 mg/day or equivalent for ≥4 weeks). [21]

6. Monitor for gastrointestinal toxicity; prescribe gastroprotection when indicated, especially in patients who are taking concomitant NSAIDs or anticoagulants.

7. Perform regular eye assessment for cataract and glaucoma.

8. Counsel regarding weight gain, mood changes, sleep disturbance, and myopathy; advise diet, exercise, and timely dose reduction when feasible.

9. Monitor for adrenal suppression; taper gradually after prolonged use and provide stress-dose guidance for intercurrent illness/surgery when required.

Lung Transplant

Lung transplantation can be considered in carefully selected patients with severe or progressive CTD-ILD, and post-transplant outcomes in suitable candidates are comparable to those in other restrictive lung diseases.

Prognosis and Counselling

CTD-ILD generally has a better prognosis than idiopathic pulmonary fibrosis, largely because NSIP is more common in CTD-ILD [8]. Prognosis varies with age, the underlying CTD, and the ILD pattern and severity. UIP in CTD-ILD often behaves better than idiopathic UIP [22]; however, RA-ILD with a UIP pattern can have outcomes similar to IPF[7]. Poor prognostic features include extensive traction bronchiectasis and honeycombing on HRCT, and the presence of pulmonary hypertension. Rapidly progressive ILD in amyopathic dermatomyositis, particularly with anti-MDA5 positivity, carries a very poor prognosis (90-day survival ~67% and 6-month survival ~40.8%) [23]. Despite appropriate treatment, approximately 9–12% of patients with CTD-ILD progress to end-stage respiratory failure [24]. In Pakistan, counselling should explicitly address practical limitations, including delayed presentation, restricted access to specialist ILD services, limited availability and high cost of biologics/antifibrotics, and the need for reliable laboratory monitoring during immunosuppression

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Chapter 06:
Rare Interstitial Lung Diseases (rILDs)

1) Scope and purpose

This chapter provides practical, locally adapted guidance for recognizing, diagnosing, and managing rare interstitial lung diseases (rILDs) in Pakistan.

It emphasizes conditions with high clinical yield or distinctive action points in our setting: Lymphangioleiomyomatosis (LAM), Pulmonary Langerhans Cell Histiocytosis (PLCH), Pulmonary Alveolar Proteinosis (PAP), and idiopathic eosinophilic pneumonias (ICEP/IAEP); plus, high value mimics (Birt–Hogg–Dubé, LIP/Sjögren related, amyloidosis, exposure related ILDs). The recommendations align with the 2025 ERS/ATS interstitial pneumonia (IP) classification update and the 2022 ATS/ERS/JRS/ALAT IPF PPF guideline where relevant. [1,3]

Why now? Pakistan's exposure profile (biomass fuels, silica/stone crushing, agricultural molds), infectious background (TB, parasites), drug access variability, and procedural capacity (BAL widely available; cryobiopsy/WLL in selected centers) require contextualized pathways that integrate HRCT **first triage, BAL driven differentiation, and selective biopsy/advanced testing**. [2,4,9]

2) Classification anchors and cross cutting principles

2.1. Updated classification (ERS/ATS 2025)

- Pattern first approach across idiopathic and secondary IPs; major biopsy/radiology patterns: UIP, NSIP, and Bronchiolocentric Interstitial Pneumonia (BIP); alveolar filling disorders as a parallel concept. New terminology includes Alveolar Macrophage Pneumonia (AMP) for DIP and idiopathic DAD for AIP. Diagnostic confidence levels are embedded. [1]
- This favors MDT based synthesis (history–HRCT–BAL–pathology) — crucial when surgical tissue is limited. [1]

2.2. Progressive pulmonary fibrosis (PPF) across non IPF ILDs (ATS/ERS/JRS/ALAT 2022)

- **PPF is defined by ≥2 of:**
  1. Worsening symptoms
  2. Physiologic decline (e.g., absolute FVC or DLCO drop)
  3. Radiologic progression within 1 year. Consider antifibrotics (e.g., nintedanib) and transplant evaluation per local feasibility. [2,3]

3) HRCT in ILD — general guidance for Pakistan

Acquisition & protocol: thin section volumetric HRCT (≤1.0–1.5 mm) at full inspiration, reconstructions in axial and coronal planes; prone views if dependent atelectasis suspected; expiratory series when mosaic/air trapping or small airway disease is a concern. Use consistent parameters across follow up scans. [4,10]

Interpretation (pattern first): document reticulation/traction, ground glass opacities (GGO), consolidation, nodules (centrilobular/perilymphatic/random), cysts (size, wall, distribution), mosaic attenuation/air trapping, and honeycombing; map distribution (upper vs lower; peripheral vs peribronchovascular) and ancillary signs (pleura, lymph nodes, pulmonary artery). Integrate with clinical context in MDT using the 2025 classification lexicon.[1,4]
Structured reporting: specify (i) principal pattern (UIP/NSIP/BIP; alveolar filling), (ii) distribution, (iii) ancillary signs, (iv) differential with confidence, and (v) recommended next steps (BAL, cryobiopsy, serology). Track PPF year to year. [1-3]

4) Investigation tiers (resource adapted)

- **Tier 1** (available everywhere): CBC with eosinophils; LFT/renal; TB rule out (smear/NAAT if indicated); stool ova & parasites based on exposure; baseline autoimmune screen if clinical clues; HRCT; BAL with cell differential (eosinophils, lymphocytes), PAS for PAP, Prussian blue if DAH suspected; full microbiology including TB/fungi/NTM.[2,4-9]
- **Tier 2** (regional/referral centers): **Transbronchial cryobiopsy** in MDT selected cases; VEGF D (for LAM) and anti GM CSF antibodies (for PAP) as send out tests; BRAF/MAPK testing in systemic/refractory LCH; **WLL** capability for PAP; antifibrotics access for PPF.[1-4,6-8]

Pakistan specific safety net: Always consider **TB** and parasitic diseases in eosinophilic or GGO predominant patterns before labeling "idiopathic"; review drug history (e.g., amiodarone, nitrofurantoin, MTX, checkpoint inhibitors).[2,4-9]

5) Entity by entity guidance

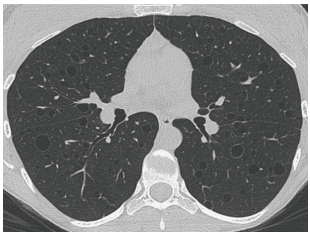
5.1. Lymphangioleiomyomatosis (LAM)

Who to suspect: Women 20–50yrs; recurrent pneumothorax, chylous effusions, renal angiomyolipomas, or TSC features. [4,6]
HRCT: Diffuse, uniform thin walled cysts (0.5–2 cm) with preserved lung volumes; not upper predominant. [4,6]
Investigations: VEGF D >800pg/mL is highly specific and decreases biopsy need, but sensitivity is imperfect and local access limited; where unavailable, combine HRCT + renal AML/TSC/chyle to reach a confident diagnosis; biopsy reserved for uncertainty. [4,6]
Histology: HMB45+, SMA+ LAM cells along lymphatics/vessels/airways. [4,6]

Management

- Sirolimus for progressive disease, chylous effusions, or large AMLs.
- Early surgical pleurodesis for pneumothorax (avoid talc if transplant likely);
- Counsel regarding pregnancy/estrogens; renal AML embolization if indicated.
- Transplant for end stage disease. [4,6]

Pakistan notes: Where VEGF D testing is not feasible, use the composite clinical–HRCT approach to minimize invasive procedures; definitive pleurodesis at the first pneumothorax.[4,6]



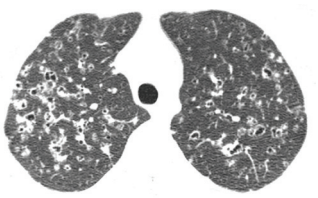
5.2. Pulmonary Langerhans Cell Histiocytosis (PLCH)

Who to suspect: Young smokers; cough, dyspnea, weight loss; spontaneous pneumothorax; bone pain/diabetes insipidus (multisystem). [4]
HRCT: Upper/mid zone small nodules cavitated nodules irregular/bizarre cysts with costophrenic sparing; cysts often persist/enlarge; smoking cessation can drive radiologic improvement. [4]
Investigations: BAL CD1a+ cells supportive; biopsy if atypical (especially "pure nodular" disease) or when infection/malignancy is in the differential. MAPK pathway mutations (e.g., BRAF V600E, MAP2K1, NRAS) in a subset—inform targeted options for systemic disease. [4]

Management:

- Smoking cessation is mandatory and prognostically meaningful.
- Steroids sometimes in inflammatory nodular phase.
- Cladribine in progressive cases.
- Selected targeted therapy (e.g., BRAF inhibitors) in mutation positive refractory disease.
- Pleurodesis for pneumothorax.
- Transplant if severe PH/end stage. [4]

Pakistan notes: Integrate **cessation programs** into ILD clinic workflow; reserve molecular testing for refractory/systemic disease due to cost/access. [4]



High-resolution CT through the upper lobes shows nodules and irregular air-density cysts, usually in the upper and mid-lung regions. These findings are characteristic of Langerhans cell histiocytosis in a patient with a history of smoking.
Image courtesy of Harold R. Collard, MD.

5.3. Pulmonary Alveolar Proteinosis (PAP)

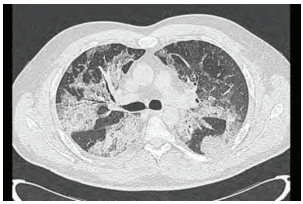
Who to suspect:
Exertional dyspnea/hypoxemia with "crazy paving" on HRCT; susceptibility to opportunistic infections. Autoimmune PAP (anti GM CSF) is most common; in Pakistan, consider secondary PAP (silica/metal fumes, hematologic malignancy). [4,7]

HRCT: GGO with interlobular septal thickening (crazy paving), typically diffuse/patchy. [4,7]
Investigations: BAL with milky return and PAS positive alveolar material confirms alveolar filling; anti GM CSF antibodies (if available) support autoimmune PAP. Exclude infections. [4,7]

Management:

- Whole Lung Lavage (WLL) is standard (10–20L/lung; often 1–2 sessions).
- Inhaled GM CSF can reduce relapses where available.
- Rituximab in selected autoantibody mediated cases.
- Treat triggers in secondary PAP (often poorer prognosis).
- Centralize WLL capability. [4,7]

Chest X-ray identifies diffuse opacities on the lung bases and HRCT presents subpleural ground glass and nodules in Pulmonary Alveolar Proteinosis.

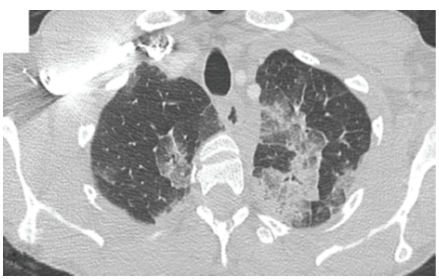


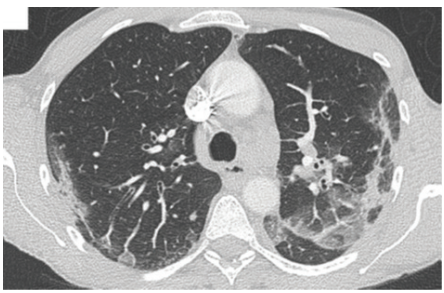
5.4. Idiopathic eosinophilic pneumonias (ICEP/IAEP)

ICEP (chronic): subacute cough/dyspnea, fever, weight loss; asthma/atopy common.
HRCT: peripheral, upper lobe predominant GGO/consolidation. Sometimes, it "resembles "photographic negative of edema. Peripheral eosinophilia frequent; BAL eosinophils >25–40%. [4, 8]
IAEP (acute): acute febrile hypoxemic illness, often weeks after initiating or resuming tobacco or inhalational exposures; peripheral eosinophilia usually absent; BAL eosinophils diagnostic (obtain before steroids if safe). HRCT: diffuse GGO/consolidation; small effusions in ~1/3. [4,8]

Management:

- Corticosteroids produce rapid responses.
- ICEP: prednisolone ~0.5mg/kg/day, taper 3–6months; relapse >50%—consider slower taper/ICS adjunct.
- IAEP: early high dose IV steroids taper; excellent prognosis if treated. Always exclude **TB, parasites, and drug causes first.** [4,8]





CT scan of a patient with idiopathic chronic eosinophilic pneumonia showing bilateral peripheral alveolar opacities with airspace consolidation and ground-glass opacities. a) Upper

6) High yield mimics to remember

- **Birt–Hogg–Dubé (BHD):** lower/peripheral lung cysts, recurrent pneumothorax; skin fibrofolliculomas; renal tumors. [4]
- **LIP (often with Sjögren's):** Diffuse GGO + thin walled cysts; lymphoma risk; immunomodulation per systemic disease. [4]
- **Amyloidosis:** Airway or interstitial pattern; confirm with Congo red birefringence; treat systemic disease. [4]
- **Exposure related:** Hard metal (cobalt/tungsten), chronic beryllium disease, silicosis variants—integrate exposure questionnaires & targeted testing (BeLPT where available). [4]

7) Quick Review

7.1. Diffuse cystic lung disease (young adult)

- **HRCT confirms true cysts** (not bullae/honeycombing); assess sex/age, smoking, pneumothorax, renal AML/skin lesions/family history.
- **Probable LAM if woman 20–50** with diffuse uniform cysts ± pneumothorax/chylothorax/renal AML/TSC aVEGF D if available; otherwise, clinical–HRCT diagnosis; sirolimus if progressive; pleurodesis early. [4,6]
- **Probable PLCH** if young smoker with upper/mid zone nodules bizarre cysts and costophrenic sparing smoking cessation; BAL CD1a+ supportive; biopsy if atypical. [4]
- **Consider BHD** if lower/peripheral cysts with skin/renal signs, genetic counseling where feasible. [4]
- **If uncertain:** MDT + exposures; cryobiopsy/Surgical biopsy when safe/indicated. [1,4]

7.2. "Crazy paving" on HRCT

- Suspect PAP; perform BAL (milky, PAS+ surfactant); anti GM CSF if available. Exclude infections. [4,7]
- If not PAP, evaluate DAH (Prussian blue), cardiac edema, AEP, lipoid pneumonia, and opportunistic infections. [4]
- PAP confirmed: WLL; inhaled GM CSF where available; treat triggers in secondary PAP; transplant referral for refractory cases. [4,7]

7.3. PPF pathway for non IPF fibrosing ILDs

- Monitor symptoms, FVC/DLCO, and HRCT at 6–12 months.
- If ≥2 of symptoms worse, physiology decline, or radiologic progression within 1 year PPF. [2,3]
- MDT consider antifibrotic therapy (e.g., nintedanib), clinical trials, transplant evaluation, and supportive care (pulmonary rehab, O_2) as appropriate. [2,3]

8) Implementation in Pakistan (checklist)

- **Structured history:** biomass, silica/stone cutting, metal fumes, birds/barns/humidifiers, TB contact, medications (amiodarone, nitrofurantoin, MTX, cancer immunotherapy), smoking (including naswar co use).[2,4,9]
- **MDT** standard for all suspected rILDs; referral pathways for cryobiopsy, WLL, antifibrotics, transplant. [1,3,7]

- **Lab send outs:** VEGF D (LAM) and anti GM CSF (PAP) selectively; molecular tests for refractory/systemic LCH.[4,6-8]
- **Smoking cessation** embedded in every PLCH/LAM clinic visit; pharmacotherapy + counseling. [4]
- **Data & quality:** contribute to a national rILD registry to quantify Pakistan's burden and outcomes; adopt pattern based HRCT reporting per 2025. [1]

Summary of Management: Similarities and Differences

- **Steroid Responsiveness:** Eosinophilic pneumonias (ICEP, IAEP) and Organizing Pneumonia (COP) are typically highly steroid-sensitive, with IAEP and COP showing dramatic clinical shifts within days. In contrast, fibrotic diseases like PPFE and advanced PLCH are largely refractory to immunosuppression.
- **Targeted Therapies:** Rare ILDs often require disease-specific molecules: mTOR inhibitors for LAM, somatostatin analogs for DIPNECH, and GM-CSF for PAP.
- **Antifibrotics:** Nintedanib has been shown to slow the rate of FVC decline across various progressive fibrotic ILDs (PF-ILD phenotype), including fibrotic HP, fibrotic NSIP, and certain CTD-ILDs, regardless of the underlying primary diagnosis.
- **Pakistan Perspective:** In Pakistan, a high index of suspicion is required for LAM (in young females) and PLCH (correlated with smoking prevalence). Diagnostic delays are frequent due to limited access to advanced serology (e.g., VEGF-D) and expert radiology.

This table is designed to serve as a high-yield diagnostic and management guide for clinicians dealing with the heterogeneous spectrum of rare Diffuse Parenchymal Lung Diseases (DPLDs) and eosinophilic conditions, emphasizing the critical role of multidisciplinary discussion (MDD) in differentiating these often-overlapping phenotypes.

Comparative Analysis of Rare Interstitial Lung Diseases and Eosinophilic Pneumonias

Disease Entity	Epidemiology & Prevalence	Causative Agent / Pathogenesis	Clinical Features & Associations	HRCT Characteristic Findings	Histological & Investigation Hallmarksrs	Treatment & Management
LAM (Lymphangioleiomyomatosis)	Almost exclusively women of reproductive age (20–40 yrs). Prevalence: 3.3-7 per million	Loss-of-function mutations in TSC1/TSC2 genes; mTOR pathway activation leading to smooth muscle-like "LAM cell" proliferation	Progressive dyspnea, recurrent pneumothorax (50–70%), chylous effusions. Associated with Tuberous Sclerosis Complex (TSC).	Numerous small, round, thin-walled cysts distributed uniformly; preserved lung volumes.	**Histology:** Spindle cells positive for HMB-45, actin, and desmin. **Inv:** Serum VEGF-D $\geq$ 800 pg/mL is diagnostic.	mTOR inhibitors (Sirolimus) to stabilize FEV1; pleurodesis for pneumothorax; lung transplant in end-stage.
PLCH (Pulmonary Langerhans Cell Histiocytosis	Young adult smokers (20–40 yrs). Rare: 1–2 per million.	Smoking-related; clonal proliferation of Langerhans cells, often driven by MAPK pathway mutations.	Nonproductive cough, dyspnea. Assoc: Bone lesions (<20%), diabetes insipidus (<5%).	Combination of nodules and bizarrely shaped cysts; upper/mid-zone predominance; costophrenic angle sparing.	**Histology:** Bronchiolocentric stellate nodules; cells positive for CD1a and Langerin. **Inv:** BAL CD1a+ cells >5%.	Mandatory smoking cessation (leads to 50% resolution); steroids for progressive disease; Cladribine in refractory cases.

PAP (Pulmonary Alveolar Proteinosis)	Mean age 39–43; male predominance. Prevalence: ~6.2 per million.	Defective surfactant clearance by alveolar macrophages; 90% are autoimmune (anti-GM-CSF antibodies).	Insidious dyspnea, dry cough. Assoc: Increased risk of opportunistic infections (Nocardia, Aspergillus).	Geographic ground-glass opacities with smooth septal thickening ("Crazy Paving" pattern).	**Histology:** Alveoli filled with granular, eosinophilic PAS-positive material. **Inv:** Milky/turbid BAL fluid.	Whole-lung lavage (WLL) is the gold standard; inhaled/SC GM-CSF augmentation; Rituximab for refractory aPAP.
PPFE (Pleuroparenchymal Fibroelastosis	Middle-aged to elderly; no sex predilection. Very rare (<1/100,000).	Unknown etiology; suggested chronic lung injury pattern. Assoc: BMT/Lung transplant (RAS), infections, or genetic factors (TERT).	Progressive dyspnea, weight loss, recurrent pneumothorax. Sign: Platythorax (flat chest).	Bi-apical pleural thickening; subpleural upper-lobe fibrosis; superior retraction of hila; volume loss.	**Histology:** Visceral pleural fibrosis with prominent intra-alveolar fibroelastosis (IAFE); elastic stain highlights "kinked" fibers.	No established medical therapy; supportive care; lung transplantation is the only definitive option.
PCH (Pulmonary Capillary Hemangiomatosis)	Rare; often presents in young adults.	Proliferation of capillaries within alveolar walls; leads to Group 1.5 Pulmonary Hypertension	Dyspnea, cough, hemoptysis. Clinical mimic: Often misdiagnosed as IPF or NSIP.	Enlarged main pulmonary artery; ill-defined ground-glass centrilobular nodules; right heart enlargement.	**Histology:** Proliferating capillaries causing thickened alveolar walls. **Inv:** RHC reveals pre-capillary PH.	Targeted PH therapies (cautiously to avoid pulmonary edema); lung transplantation
DIPNECH (Diffuse Idiopathic Neuroendocrine Cell Hyperplasia)	Almost exclusively in non-smoking middle-aged women.	Preneoplastic proliferation of neuroendocrine cells producing fibrogenic peptides; results in constrictive bronchiolitis.	Progressive exertional dyspnea, chronic non-productive cough. Assoc: Peripheral carcinoid tumors.	**Mosaic attenuation; air trapping on expiration; small nodules; bronchiectasis**	**Histology:** Linear/nodular hyperplasia of NE cells (Chromogranin+) with subepithelial fibrosis.	Somatostatin analogs (Octreotide) to improve symptoms; avoid harmful steroids if misdiagnosed as HP.
ICEP (Idiopathic Chronic Eosinophilic Pneumonia)	Women (2:1); mean age 45; 93% non-smokers. Rare (<3% of ILDs).	Idiopathic; associated with Th2-polarized immune response and IL-5 production.	Subacute cough, fever, night sweats, weight loss. Assoc: Prior asthma in 60–75%.	Bilateral, peripheral/subpleural "photographic negative of pulmonary edema" (consolidation/GGO).	**Histology:** Alveoli filled with eosinophils and macrophages**. Inv:** BAL eosinophils usually >40%.	Dramatic response to steroids (within 48h); long-term treatment (6-12 months) required; high relapse rate (>50%).

IAEP (Idiopathic Acute Eosinophilic Pneumonia)	Young adults (29 yrs); male predominance (2:1).	Often triggered by recent initiation of smoking or toxic dust inhalation.	Acute febrile illness (<7 days); ARDS-like respiratory failure. Assoc: No prior history of asthma.	Diffuse GGO; consolidation; interlobular septal thickening; bilateral pleural effusions (70-80%).	**Histology:** Acute lung injury (DAD) with eosinophilic infiltration. **Inv:** >25% BAL eosinophils; initial blood eosinophilia is often absent.	Rapid improvement with IV/oral steroids; relapse is unusual; near-complete recovery is the rule.
EGPA (Eosinophilic Granulomatosis with Polyangiitis)	Prevalence: 7.3–17.8 per million. Mean age ~50.	ANCA-associated small-vessel vasculitis (usually anti-MPO+); characterized by eosinophilic tissue damage.	Severe asthma, paranasal sinusitis. Assoc: Mononeuritis multiplex (70%), cardiac failure (31% of deaths).	Migratory peripheral infiltrates; nodules (some cavitary); bronchial wall thickening.	Histology: Necrotizing vasculitis, eosinophilic pneumonia, and extravascular granulomas.	Steroids + cyclophosphamide for severe (FFS $\geq$ 1) disease; Mepolizumab (anti-IL-5) for refractory cases.

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