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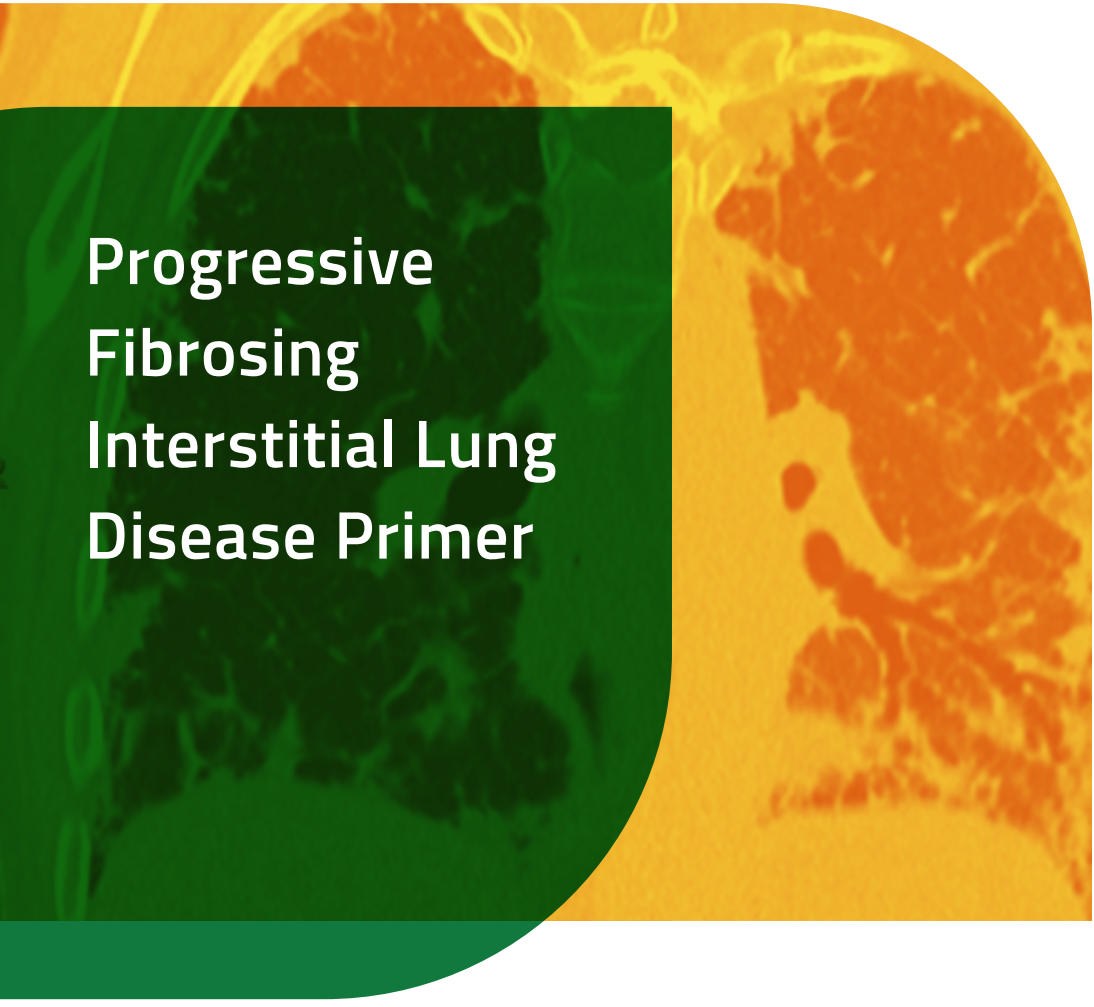

Progressive Fibrosing Interstitial Lung Disease Primer

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List of abbreviations and acronyms

6MWD: 6 minute walk distance
ANA: Antinuclear antibody
CTD: Connective tissue disease
DKC1: Dyskerin coding
DLCO: Diffusion capacity of lung for carbon monoxide
FEV1: Forced expiratory volume in 1 second
FPF: Familial pulmonary fibrosis
FVC: Forced vital capacity
GERD: Gastroesophageal reflux disease
HP: Hypersensitivity pneumonitis
HRCT: High-resolution computed tomography
IIP: Idiopathic interstitial pneumonia
ILD: Interstitial lung disease
iNSIP: Idiopathic non-specific interstitial pneumonia
IPAF: Interstitial pneumonia with autoimmune features
IPF: Idiopathic pulmonary fibrosis
IV: Intravenous
MCTD: Mixed connective tissue disease
MMF: Mycophenolate mofetil
NSIP: Non-specific interstitial pneumonia
PF-ILD: Progressive fibrosing interstitial lung disease
PFT: Pulmonary function test
PH: Pulmonary hypertension
PPFE: Pleuroparenchymal fibroelastosis
PROM: Patient reported outcome measure
RA: Rheumatoid arthritis
RV: Residual volume
SFTPA2: Surfactant protein-A2
SFTPC: Surfactant protein-C
SSc: Systemic sclerosis
TERC: Telomerase RNA component
TERT: Telomerase reverse transcriptase
TLC: Total lung capacity
UIP: Usual interstitial pneumonia

Definition and epidemiology

Definition

- **Progressive fibrosing interstitial lung diseases (PF-ILDs) are a diverse group of ILDs that share a similar disease behavior, are characterized by a progressive disease course, and overlapping genetic, pathophysiological, and clinical features (1).**
- **Features of PF-ILD include progressive fibrosis on high-resolution CT (HRCT) scan, lung function decline resulting in respiratory failure, progressive symptom worsening, and early mortality (1).**
- **Idiopathic pulmonary fibrosis (IPF), the "prototype" PF-ILD of unknown etiology, is often characterized by usual interstitial pneumonia (UIP) pattern on HRCT with or without biopsy and may lead to respiratory failure and death within 3-4 years.**
- **The PF-ILD phenotype may be found in numerous ILD subtypes such as familial pulmonary fibrosis (FPF), fibrotic hypersensitivity pneumonitis (HP), idiopathic non-specific interstitial pneumonia (iNSIP), unclassifiable interstitial pneumonia, sarcoidosis, connective tissue diseases associated ILDs (CTD-ILD) such as rheumatoid arthritis (RA-ILD), mixed connective tissue disease (MCTD-ILD) and systemic sclerosis (SSc-ILD), and pleuro-parenchymal fibroelastosis (PPFE); all with a lesser proportion than IPF.**

Clinical presentation

- **Common features of PF-ILD include exertional and progressive dyspnea, dry cough, finger clubbing, and velcro-like crackles on physical exam; fatigue is common in later stages of PF-ILD (2).**
- **Patients often present with additional clinical features typical of the underlying ILD subtype (1, 2):**
  - IPF is a lung-limited, male predominant disease.
  - Patients with FPF have a positive family history of ILD.
  - iNSIP is more common in women in 60s.
  - Although RA is female predominant, RA-ILD is male predominant. It is also often associated with morning stiffness, symmetric erosive arthritis, synovitis, and rheumatoid nodules.
  - SSc-ILD is female predominant often with skin thickening, Raynaud's phenomenon, GERD, and sometimes pulmonary arterial hypertension.
  - Sarcoidosis is more common in Black patients and often associated with extrapulmonary manifestations.
  - HP is frequently associated with history of antigen exposure.

Incidence/prevalence (3)

- **ILD prevalence is estimated at ~74 cases per 100,000 in the USA and ~76 cases per 100,000 in Europe.**
- **The most common ILDs are sarcoidosis, CTD-ILD and IPF, with prevalence of 30.2, 12.1 and 8.3 per 100,000. Respectively; prevalence varies widely between age ranges.**
- **Almost 13-40% of all non-IPF ILD cases will develop a progressive fibrosing phenotype, accounting for 28 patients in the USA and 20 patients in Europe per 100,000.**

Potential risk factors

- Male sex and older age are risk factors for development of IPF and RA-ILD; longer RA duration is a risk factor for developing RA-ILD (4, 5).
- Black race is a risk factor for progression of sarcoidosis.
- Smoking is a risk factor for development of IPF and RA-ILD (4, 5).
- Chronic microaspiration/GERD, farm exposure, hairdressing, metal dust, and vegetable/animal dust have been implicated in IPF pathogenesis.
- Continuous exposure to environmental antigens has been linked to the development and progression of HP; bird feathers, molds, organic dust, moldy hay, and synthetic compounds such as isocyanates are the most common offending antigens (6).
- Rapid FVC and DLCO decline, disease extent on HRCT, and the presence of honeycombing are universally poor prognostic markers in PF-ILD (1).

Genetic factors

- Up to 20% of patients with IPF have a family history of ILD, while 10% of relatives of patients with IPF will subsequently develop idiopathic interstitial pneumonia (7).
- Genetic syndromes such as Hermansky-Pudlak, dyskeratosis congenita, and short telomere syndromes are often associated with progressive pulmonary fibrosis (8).
- Short telomere syndromes may be indicated by the presence of clinical features such as cryptogenic cirrhosis, aplastic anemia, or premature graying (7).

- FPF, sporadic IPF, RA-ILD and HP have all been linked to telomerase complex related gene mutations (TERT, TERC, RTEL1, PARN) and associated telomere shortening; and are frequently characterized by rapid progression of IPF, worse post-transplant prognosis in ILD, and a greater burden of fibrosis and increased mortality in patients with fibrotic HP (8).
- The rs35705950 promoter polymorphism of the MUC5B gene, which encodes protein complexes in mucus involved in airway host defense and mucociliary clearance, has been described in up to 35% of sporadic IPF cases; and has also been associated with a higher incidence of RA-ILD, increased mortality and usual interstitial pattern (UIP) on imaging in RA-ILD (9), and higher extent of radiographic fibrosis in fibrotic HP.
- The major histocompatibility complex polymorphism HLA-DRB1 has been described in IPF, fibrotic HP, and CTD-ILD.
- The fibrosing phenotype of RA-ILD has been associated with several gene polymorphisms described in FPF and sporadic IPF, such as TERT, surfactant protein-coding genes SFTPC, SFTPA2, and dyskerin coding gene DKC1 (10).
- Careful family history should be obtained in all patients with PF-ILD; genetic testing and counseling might be offered for patients with suspected short telomere syndromes.

Diagnosis

- Progressive fibrosis occurs in a variety of ILD subtypes but currently lacks a standardized definition.
- However, in clinical practice, the progressive fibrosing phenotype may be identified using routinely acquired indicators and by applying clinical trial enrollment criteria.

Approach to diagnosis of ILDs (Refer to Figure 1)

- **Clinical findings culminating in a PF-ILD diagnosis include the presence of (1):**
  - **Symptoms**: commonly have worsening cough, dyspnea on exertion, poor exercise tolerance.
  - **Signs:** auscultatory fine crackles, disease-specific signs such as early gray hair in fibrosis associated with telomere dysfunction, inspiratory squeaks in hypersensitivity pneumonitis, joint and skin abnormalities in CTD.
  - **Serology:** elevated circulating autoantibodies may suggest underlying CTD.
  - **Radiology:** Chest high-resolution computed tomography (CT) characterized by architectural distortion with reticulation, traction bronchiectasis, or usual interstitial pneumonia (UIP) pattern (advanced pulmonary fibrosis); or non-UIP pattern often nonspecific interstitial pneumonia (varying ground-glass attenuation with superimposed reticulation). (Refer to Figures 2 & 3).
  - **Lung function testing:** forced vital capacity [FVC] decreased; the ratio of FEV1/FVC remained the same or increased; total lung capacity [TLC] decreased; residual volume [RV] decreased; diffusing capacity of the lung for carbon monoxide [DLCO] decreased; typically, consistent with a restrictive pattern.
  - **Additional procedures:** such as bronchoalveolar lavage, endobronchial ultrasonography with transbronchial needle aspiration for lymph node biopsy, transbronchial cryobiopsy, or thoracoscopic lung biopsy may be warranted after multidisciplinary discussion.

Multidisciplinary team discussion

- **This should be conducted among clinicians, radiologists, pathologists, and other health care providers to evaluate all available clinical, lung function, serologic, radiologic, and pathologic data to ensure early diagnosis and optimal management of the progressive fibrosing phenotype in patients with fibrotic ILD.**

Figure 1: Flowchart summarizing the approach to diagnosis of the progressive fibrosing interstitial lung disease (PF-ILD) phenotype in patients with fibrotic interstitial lung disease.

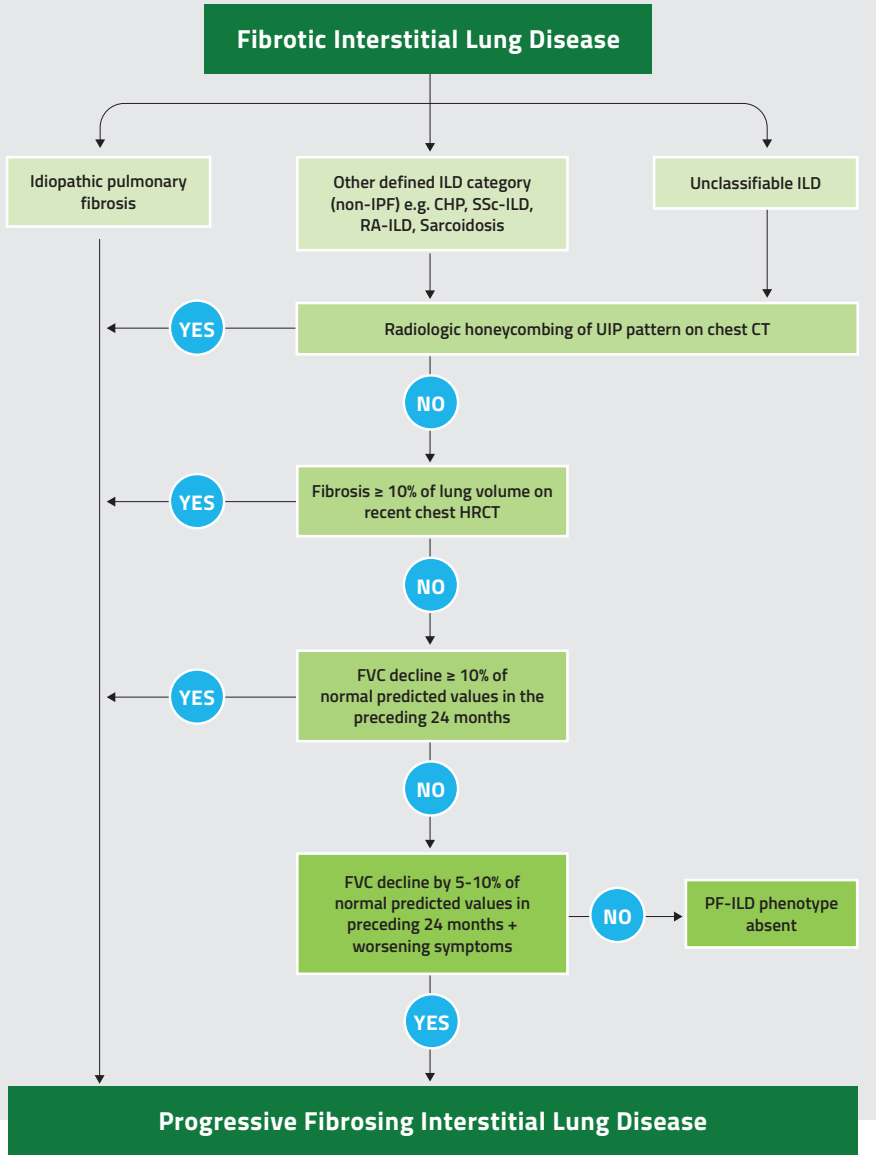


Figure 2: CT for NSIP with progressive fibrosing phenotype

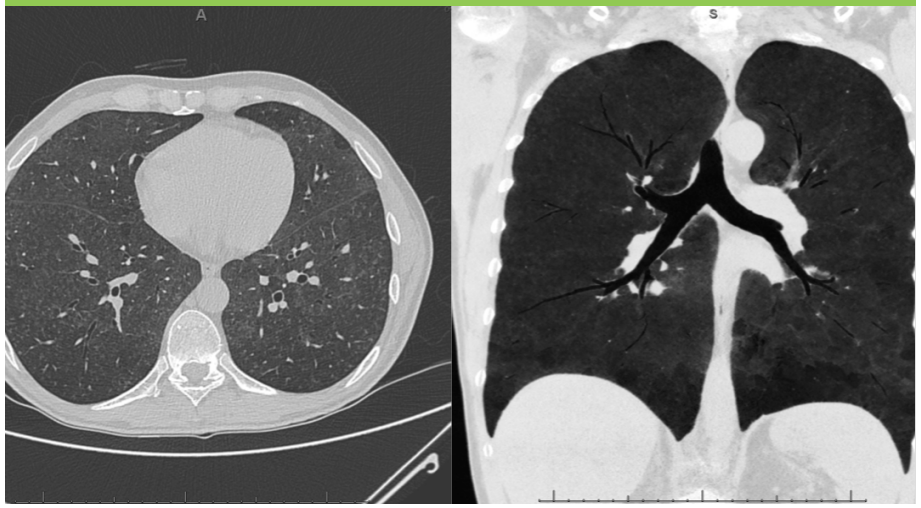
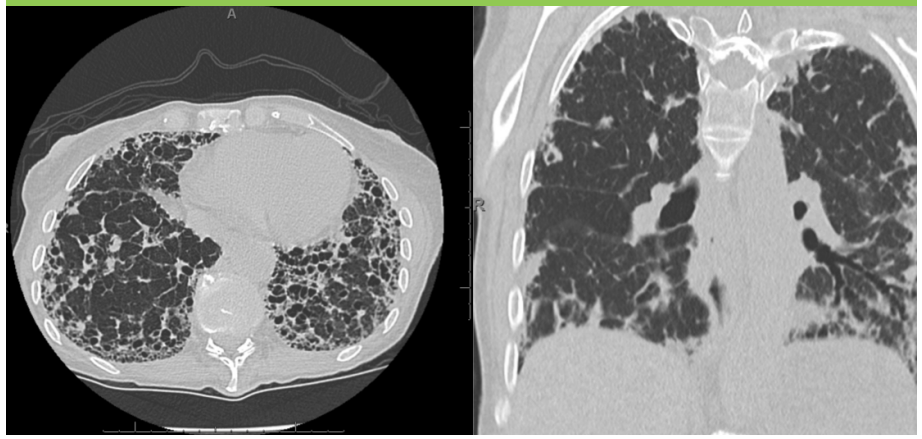


Figure 3: CT for UIP with progressive fibrosing phenotype



Population indicators identifying risk for the progressive fibrosing phenotype within specific fibrotic ILD subtypes

- **Idiopathic pulmonary fibrosis (IPF): ubiquitously presents with progressive disease and frequently affects males who present with honeycombing or a UIP pattern on chest CT, and FVC < 70% (1, 11).**
- **Other non-IPF ILDs often demonstrate a progressive fibrosing phenotype in the presence of:**
  - Scleroderma associated-ILD (SSc-ILD): Black race, male sex, features of diffuse cutaneous SSc within seven years of diagnosis, chest CT involvement exceeding 20%, decreased FVC & DLco, and anti–Scl-70 antibodies.
  - Rheumatoid-arthritis-ILD (RA-ILD): Older, male sex, chest CT involvement exceeding 20%, radiologic honeycombing or UIP pattern on chest CT and FVC < 70%.

Table 1: PF-ILD population indices and risk factors for progressive disease

PF-ILD	Age / gender / race	Imaging	Other	Lung function
IPF	Male, older age	Honeycombing, UIP		FVC < 70%
iNSIP	Female, older age		Fibrosing histology worse than cellular histology; UIP and HP overlap associated with worse prognosis. Presence of fibrotic features.	DLCO decline 15% or FVC decline 10% in 6-12 months
SSc-ILD	Male, Black	Chest CT > 20% involvement, honeycombing	Systemic sclerosis within 7 years of diagnosis, anti-Scl-70 positivity	FVC < 70% Low DLCO
RA-ILD	Male, older age	UIP pattern, honeycombing, chest CT > 20% involvement		Low FVC Low DLCO
HP	Older age	UIP pattern, honeycombing, fibrotic changes	Unknown antigen, continuous antigen exposure, smoking, absence of lymphocytes on BAL (30)	Low FVC Low DLCO
Sarcoidosis	Female, Black	Chest CT > 20% involvement, Scadding stage IV	Pulmonary hypertension predictor of mortality	Low FVC, low DLCO
Unclassifiable ILD	Male, older	Honeycombing, UIP pattern		Low FVC, low DLCO

- Sarcoidosis: Black race, female sex, pulmonary hypertension, chest CT involvement exceeding 20%.
- Fibrotic hypersensitivity pneumonitis: continuous exposure to inciting antigen, radiologic honeycombing, or UIP pattern on chest CT.
- Unclassifiable ILD: radiologic honeycombing on chest CT, progressively worsening lung function.

Diagnostic criteria based on clinical trials in PF-ILD

- **Any fibrotic ILD subtype with:**
  - Fibrosis exceeding 10% of lung volume on recent chest HRCT.
  - FVC decline ≥10% of the normal predicted values within the preceding 24 months.
  - FVC decline by 5% -10% of the normal predicted values within the preceding 24 months and with either worsening symptoms or worsening CT scan.
- **Unclassifiable-ILD with fibrosis ≥ 10% of lung volume on recent chest HRCT.**
- **DLCO, 6MWD test and other indicators of ILD progression have been used.**

Other risk factors for PF-ILD

- **CT Honeycombing (12).**
- **Histological pattern of usual interstitial pneumonia (13).**

Table 2: PF-ILD progression and mortality

PF-ILD	Progression	Mortality
IPF	Variable, but all eventually progress; progression can be rapid, slow (~ 21%) or mixed with periods of stability and periods of acute decline	70-80% mortality in 5 years
iNSIP	Variable; can improve or stabilize with treatment	20% mortality in 5 years
RA-ILD	Variable; UIP pattern associated with frequent hospitalizations and worst prognosis	39% mortality in 5 years
SSc-ILD	Variable; slow decline; rapid progression possible	34-46% mortality in 10 years for all patients with SSc; SSc-ILD responsible for 33% of scleroderma-related deaths
Sarcoidosis*	Usually responds to immunosuppression; chronic/ progressive in 10-30% of cases	Overall mortality 1-5%, higher in patients with PF-ILD
Fibrotic HP	May stabilize with immunosuppression and antigen avoidance	20-50% mortality in 10 years

* *Fibrotic forms of sarcoidosis may not respond optimally to immunosuppressive therapy. Treatment should therefore be geared towards addressing the increased rate of associated comorbidities that characterize advanced/fibrotic sarcoidosis such as pulmonary hypertension, mycetomas, hemoptysis, and bronchiectasis.*

Management of PF-ILD

Pharmacologic treatment of PF-ILD

- **First-line therapy in PF- ILD consists of treatment of the underlying disorder, if identifiable (14). This includes antigen removal (for HP) or use of immunosuppressive agents.**

Table 3: Clinical, radiologic, and histologic features of common PF-ILD subtypes

PF-ILD subtype	Clinical features	Imaging	Supporting findings	Histology
Idiopathic pulmonary fibrosis	Progressive respiratory failure, velcro-like crackles, age > 50, male predominance	Peripheral basal predominance, reticular pattern, traction bronchiectasis, honeycombing (UIP pattern)	Neutrophil-predominance on BAL	"UIP pattern"; architectural distortion, fibrosis, honeycombing, spatial temporal heterogeneity; areas of fibrosis alternating with areas of normal lung, fibroblastic foci
Idiopathic NSIP	Progressive respiratory failure, velcro-like crackles, age > 60, female predominance	Peripheral, basal, lower lung reticular pattern with subpleural sparing, ground glass opacities, traction bronchiectasis, irregular lines and consolidations (NSIP pattern)		Alveolar thickening, inflammatory cell infiltration, fibrosis, diffusely abnormal alveolar septa (NSIP pattern); honeycombing and fibroblastic foci can be seen
SSc-ILD	Skin thickening, pitting of fingertips, GERD, Raynaud's, teleangiectasia, pulmonary hypertension common	NSIP pattern most common, UIP pattern possible	Scl-70, anti-RNA polymerase III, anti-centromere Ab often positive; abnormal nail fold capillaroscopy	NSIP pattern most common
RA-ILD	Swelling and erosive arthritis of joints, synovitis, rheumatoid nodules	UIP, NSIP pattern most common	RF, CCP positive	Mixed pattern of fibrosis with both UIP and NSIP pattern; patchy fibrosis with loosely defined boundaries; lymphoid hyperplasia; rheumatoid nodules uncommon
Fibrotic hypersensitivity pneumonitis	History of antigen exposure, wheezing, symptoms may improve with decreased antigen exposure	"Probable UIP" pattern often seen; upper lobe predominance, ground glass opacities, centrilobular nodules, air trapping and mosaic attenuation. Presence of a UIP pattern with small airway disease implies a "compatible with HP" diagnosis while a lone UIP or probable UIP pattern confers an "indeterminate for HP" diagnosis.	Positive precipitins, lymphocytosis on BAL	Peribronchial interstitial pneumonia, giant cells, chronic bronchiolitis and poorly formed granulomas
Sarcoidosis	Systemic disease – can affect eyes, cardiac and CNS system, less frequently liver and GI tract; lymphadenopathy common	Upper lobe predominant, peribroncho-vascular distribution, reticulations and nodules that can coalesce, traction bronchiectasis, cysts and airway distortion; associated with different lung function profiles	Lymphocytosis on BAL	Well-formed, non-necrotizing granulomas that over time can confluence and coalesce; associated fibrosis; giant cells; can mimic UIP pattern
Unclassifiable fibrotic ILD	Median age 60-65, no specific diagnosis, absence of exposure or clear autoimmune features	UIP, NSIP pattern		UIP or NSIP pattern; atypical histological findings

- Some antifibrotic therapies may be considered next in the smaller proportion of patients who continue to progress despite appropriate first-line therapy (11, 14). However, not all antifibrotics have been tested or approved in each of these entities.
- For patients with IPF, treatment with antifibrotic drugs (pirfenidone or nintedanib) is recommended at the time of diagnosis (11, 15).

Figure 4: Pharmacologic management of PF-ILD

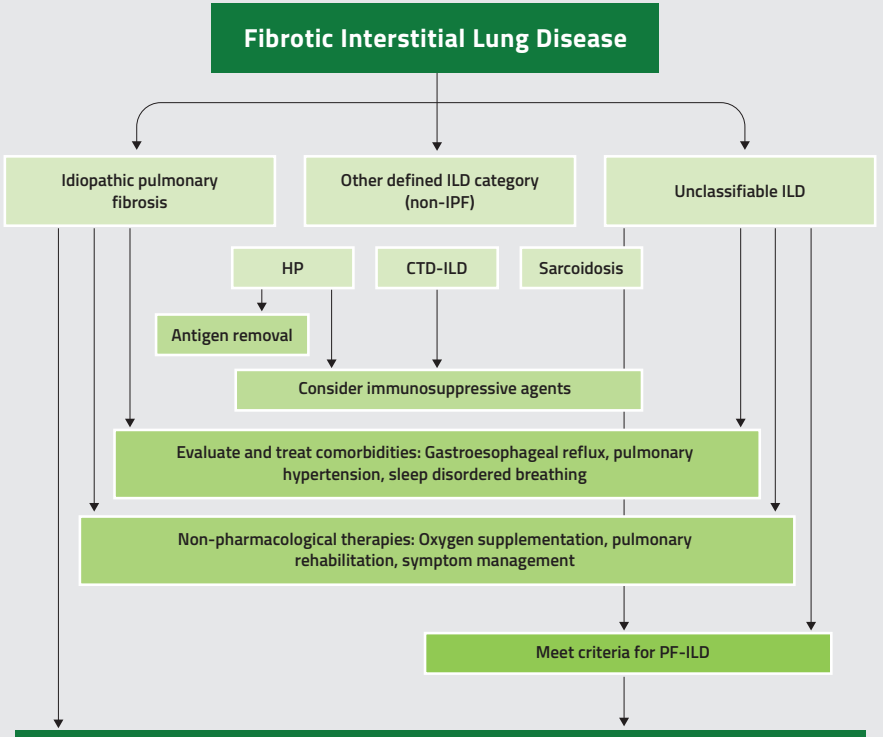


Figure 5: Comprehensive care of the PF-ILD patient

- Ground glass opacifications are usually considered to represent a higher degree of cellularity and suggest the disease is potentially more responsive to treatment with immunosuppression compared to the presence of UIP/ fibrotic disease where antifibrotic therapy may slow the rate of decline in FVC.
- Limited data is available on safety and interaction profile of antifibrotic agents in conjunction with immunosuppressive agents except for MMF.
- Refer to Figure 4 & 5.

Immunosuppressive agents

- There is limited evidence for corticosteroids and other immunosuppressive therapy in majority of the sub-group of PF-ILDs (with the exception of scleroderma) (16).
- However, if there is suspicion for inflammation-driven disease, corticosteroids and/or immunosuppressive drugs are generally used as first line therapy based on uncontrolled studies or anecdotal data (17, 18).
- Prophylaxis against pneumocystis jirovecii is recommended in patients receiving any immunosuppressive agent and corticosteroids equivalent to or greater than prednisone 20mg daily or two (or more) immunosuppressive agents.
- Refer to Table 4 for details on drug dosing, safety monitoring and common adverse effects.

Antifibrotic agents

- For patients with IPF, treatment with antifibrotic drugs (pirfenidone or nintedanib) is recommended at the time of diagnosis.
- Given common pathological pathways of aberrant complex interplay leading to a progressive, fibrotic phenotype, irrespective of the underlying disorder, antifibrotic drugs may alter disease course in non-IPF PF-ILDs.
- Antifibrotic drugs may reduce FVC decline in SSc-ILD and other PF-ILDs (20,21).
- Refer to Table 5 for details on drug dosing, safety monitoring and common adverse effects.

Table 4: Immunosuppressive therapies sometimes considered in PF-ILD*

Immunosuppressive drugs	Mechanism of action	RCTs	Dosage	Safety monitoring	Common side effects/ toxicity
Corticosteroids		None	Variable		
Mycophenolic acid	Inhibits proliferation of T and B lymphocytes	Scleroderma Lung Study II	Mycophenolic mofetil: start 500mg BID, titrate weekly to 1- 1.5gm BID mycophenolic acid: 360mg BID, titrate weekly to 720mg or 1080 mg BID	CBC weekly for first month, then monthly x 3 months, then quarterly	Leucopenia most common fatigue, nausea/ vomiting, constipation Serious: gastric ulcers and intestinal perforation; very low likelihood of lymphoma
Azathioprine	Inhibits purine synthesis, thus reducing DNA and RNA production and subsequent reduction in synthesis of white blood cells	None	Start 50mg daily, titrate to 150mg daily	CBC and hepatic function every 2 weeks for first month, then monthly x 3 months, then quarterly. Consider TPMT test.	Gastrointestinal intolerance and fatigue Elevated transaminases Leucopenia Opportunistic infections
Cyclophosphamide	Alkylating agent, causes cross-linking of strands of DNA and RNA, and inhibition of protein synthesis	Scleroderma Lung Study I and II	1-2 mg/kg/d po or 500-1,000 mg IV pulse every 4 weeks	CBC, renal function, and urinalysis at baseline, then twice monthly.	Hemorrhagic cystitis, neutropenia, opportunistic infections, and bladder cancer
Rituximab	Monoclonal antibody that targets CD20-positive B-lymphocytes	None	1gm IV twice at an interval of 2 weeks; mostly 6 monthly	Pre-infusion: hepatitis panel, CBC, TB quantiferon	Acute pneumonitis, infusion reaction, opportunistic infections
Tocilizumab	Monoclonal antibody to inhibit Interleukin-6 activity	FocuSSced trial (SSc-ILD)	162 mg Subcutaneous weekly	Pre-treatment: TB quantiferon CBC and hepatic function every 4 weeks for 6 months, then quarterly	Infections: tuberculosis, fungal and other opportunistic
Tacrolimus (typically in conjunction with other agents)	Inhibits calcineurin and subsequent downstream effect is reduction in T-cell proliferation	None	Start 1mg BID; titrate to maintain trough level of 5-10 ng/mL	CBC, serum electrolytes, renal function, hepatic function, glucose level, and BP weekly for first month, every 2 weeks for second month, then monthly	GI intolerance Renal toxicity, Infections and CNS side effects
Intravenous Immunoglobulin	Neutralization of pathogenic antibodies,alteration of immune cell effector function, inhibits inflammatory cytokines and chemokines	None	Typically 1gram/kg but can vary based on age and underlying conditions	None	Anaphylaxis, headache, chills or flushing Rare: DVT, stroke, acute kidney injury, aseptic meningitis

*Data are limited and approval by regulatory agencies might be lacking.

Table 5: Antifibrotic therapies tested in PF-ILD trials

Antifibrotic drugs	Mechanism of action	RCTs	Dosage	Safety monitoring	Common side effects/ toxicity
Nintedanib	Tyrosine Kinase Inhibitor	IPF: INPULSIS SSc-ILD: SENSCIS PF-ILD: INBUILD	150mg twice daily	CBC and hepatic function monthly x 3 months, then quarterly	Most common: Diarrhea Fatigue Elevated transaminases
Pirfenidone	Antifibrotic via multiple mechanisms	IPF: CAPACITY and ASCEND Trials SLS III (NCT03221257) Unclassifiable ILD	267mg thrice daily, titrated to 801mg thrice daily	CBC and hepatic function monthly x 3 months, then quarterly	Gastrointestinal intolerance and fatigue Elevated transaminases Photosensitivity

Management of comorbidities

Gastroesophageal reflux disease (GERD)

- Anti-acid treatment conditionally recommended in IPF patients with symptomatic GERD.
- Small increases in lower respiratory tract infection associated with anti-GERD therapy have been reported and should be taken into consideration.

Pulmonary hypertension (PH)

- Echocardiography is not accurate in estimating pulmonary hemodynamics in patients with fibrotic lung disease and should not be relied upon to assess presence and severity of PH.

- Right heart catheterization is required to confirm presence of PH.
- Inhaled active trepostinil increased 6MWD and can be considered for patients with PH and ILD.

Sleep disordered breathing

- Patients with ILD commonly exhibit abnormal sleep architecture and increased sleep fragmentation on polysomnography (23, 24).
- Screening and early referral to sleep center for diagnosis and treatment of obstructive sleep apnea should be considered (24).

Lung cancer

- The incidence of lung cancer is significantly higher among patients with ILD.
- Per U.S. Preventive Services Task Force recommendations, screening CT scans yearly in patients aged 55-80 with a history of 30-pack year smoking and either currently smoking or have quit within the past 15 years is recommended (25). But there is no available data for these guidelines specific to ILD patients.

Depression

- Patients with PF-ILD should be routinely screened for anxiety and depression. Counseling and pharmacologic therapy may be beneficial.

Non-pharmacologic treatment of PF-ILD

Pulmonary rehabilitation

- Pulmonary rehabilitation has been clearly demonstrated to improve exercise capacity and quality of life in patients with chronic respiratory disease (26).
- It is implemented by an interdisciplinary team including physicians, nurses, respiratory therapists, physical and occupational therapists, psychologists, behavioral specialists, nutritionists and social workers (26).
- Pulmonary rehabilitation involves exercise training (e.g. strength training, inspiratory muscle training) and self-management (e.g. goal setting, addressing motivational issues) (26).
- Anticipated barriers to participation in pulmonary rehabilitation includes distance from patient's location and reimbursement for attendance.
- Several telerehabilitation models have shown promise and can be considered among patients with internet access. Cost-effectiveness and insurance reimbursements for such sessions remain a challenge.

Oxygen supplementation

- Oxygen therapy is used to treat hypoxia and prevent development (or slow progression) of hypoxia-induced pulmonary hypertension and cardiovascular morbidity (27).
- 6MWD test is a valuable clinical tool to determine if a patient requires oxygen therapy and has been shown to be reproducible in ILD patients.

- Positive impact of oxygen therapy includes improved exercise tolerance and anxiety relief.
- Barriers to adherence include self-consciousness when using domiciliary oxygen therapy, fear of dependence on oxygen therapy and practical challenges involving portability of oxygen cylinders and concentrators.

Palliative care

- The goal of palliative care is improvement in the patients' quality of life throughout their disease course and should be offered alongside other non-pharmacological and pharmacological therapies for ILD.
- This includes patient-centered management, caregiver-centered management, disease stabilizing care and advanced care planning.
- The Needs Assessment Tool: Progressive disease in ILD can be used as a communication and decision tool to help clinicians evaluate patients' well-being, assess caregivers' needs and prompt referral to specialty palliative care.
- Chronic cough is highly debilitating in patients with PF-ILD and management includes addressing the underlying etiology (e.g. asthma, eosinophilic bronchitis, GERD), and utilizing appropriate medications, if available such as benzonatate, over-the-counter cough suppressants, chronic opioids and thalidomide(28).
- Severe dyspnea may be treated with chronic opioids with careful monitoring.

Patient-reported outcome measures (PROM)

- "Patient centered" approach involves focus on the physical and emotional well-being and quality of life (QoL) among patients with PF-ILD.
- King's Brief ILD health status questionnaire and symptom-specific PROMs including Leicester Cough Questionnaire, modified Medical Research Council (mMRC), St. George's Respiratory Questionnaire© (SGRQ) have not been validated but can be extrapolated to PF-ILD based on reports in IPF and chronic obstructive lung disease.
- Living with IPF (L-IPF) questionnaire, an IPF specific PROM takes into consideration several symptoms and their impact on quality of life among these patients.

Lung transplantation

- Lung transplantation is an option in select patients, although extrapulmonary disease or severe comorbidities may disqualify some patients, especially those with certain CTDs, from consideration as candidates for transplantation.

Management of acute exacerbations

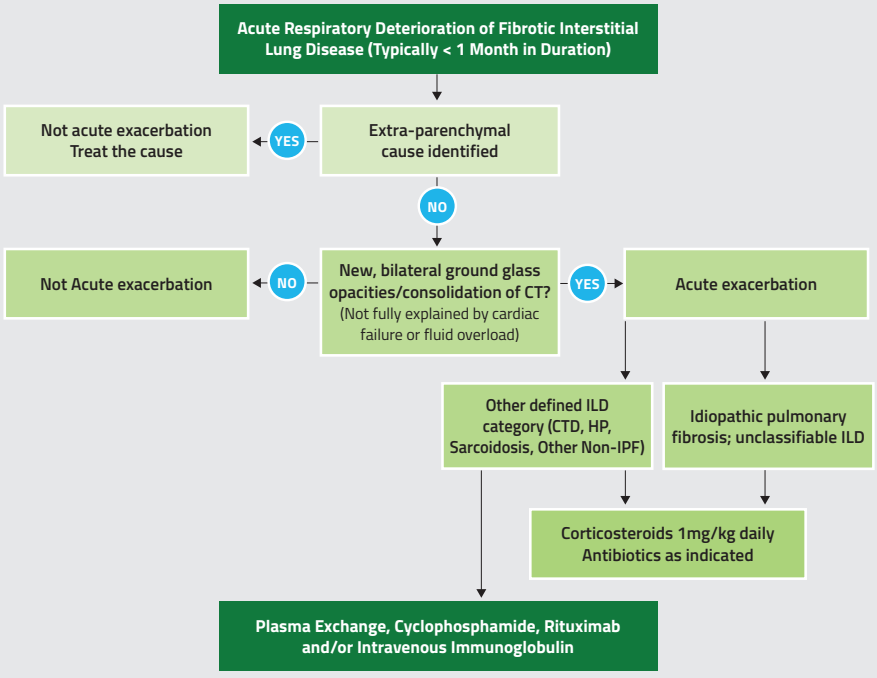
- Proposed definition for acute exacerbations include clinically significant respiratory deterioration, typically < 1 month in duration, with CT chest findings of new bilateral ground glass opacities or consolidation superimposed with pattern consistent with fibrosing ILDs (31).
- Bronchoscopy can be considered in patients with high suspicion of opportunistic infections, diffuse alveolar hemorrhage or eosinophilic pneumonia.
- Non-invasive techniques including high-flow oxygen (29) and positive pressure ventilation to improve gas exchange abnormalities in patients who fail conventional oxygen therapy (31).

- Evidence based guidelines make a weak recommendation against the utilization of mechanical ventilation in the majority of the patients with Acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) but if utilized, ventilatory strategy with low tidal volume should be considered among the select patients.
- Patients with acute exacerbations are universally treated with antimicrobial agents.
- Limited studies suggest that corticosteroids may confer benefit in acute exacerbations of IIP and CTD-ILD.
- Therapeutic plasma exchange to rapidly reduce circulating autoantibodies, immunosuppression with cyclophosphamide or rituximab and intravenous immunoglobulin to mitigate autoantibody rebound for a sustained clinical response, particularly in CTD-ILDs are suggested based on uncontrolled studies and can be considered.
- Refer to Figure 6.

Monitoring the clinical course of disease

- Though not formally investigated, disease progression is usually monitored over periods of 3-6 months with clinic visits to discuss symptom burden, PFTs, 6MWD, and oxygen saturation at rest and with exertion. HRCT is often repeated every 6-12 months.
- For patients manifesting acute respiratory worsening, the possibility of acute exacerbation of underlying ILD should be considered and prompt evaluation for alternative etiologies of acute worsening such as pulmonary embolism, pneumothorax, respiratory infection or aspiration should ensue.

Figure 6: Management of acute exacerbation of PF-ILD*



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Summary and conclusions

- Progressive fibrosing ILD represents a phenotype that may occur in many cases of ILD.
- Many factors likely determine the course of ILD progression including inciting injurious mechanisms and underlying genetic predisposition.
- While the definition of PF-ILD still resides from clinical trial inclusion and exclusion criteria, further study is needed to ascertain better and potentially molecular definitions.
- Anti-fibrotic therapies targeting the shared aspects of fibrosis across ILDs have proven a viable treatment option.
- Standard ILD therapies remain a cornerstone despite the more rapid course of disease supporting regular monitoring and interventions as appropriate.

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