JAMA | Review

Interstitial Lung Disease
A Review

Toby M. Maher, MD, MSc, PhD

IMPORTANCE Interstitial lung disease (ILD) consists of a group of pulmonary disorders characterized by inflammation and/or fibrosis of the lung parenchyma associated with progressive dyspnea that frequently results in end-stage respiratory failure. In the US, ILD affects approximately 650 000 people and causes approximately 25 000 to 30 000 deaths per year.

OBSERVATIONS The most common forms of ILD are idiopathic pulmonary fibrosis (IPF), which accounts for approximately one-third of all cases of ILD, hypersensitivity pneumonitis, accounting for 15% of ILD cases, and connective tissue disease (CTD), accounting for 25% of ILD cases. ILD typically presents with dyspnea on exertion. Approximately 30% of patients with ILD report cough. Thoracic computed tomography is approximately 91% sensitive and 71% specific for diagnosing subtypes of ILDs such as IPF. Physiologic assessment provides important prognostic information. A 5% decline in forced vital capacity (FVC) over 12 months is associated with an approximately 2-fold increase in mortality compared with no change in FVC. Antifibrotic therapy with nintedanib or pirfenidone slows annual FVC decline by approximately 44% to 57% in individuals with IPF, scleroderma associated ILD, and in those with progressive pulmonary fibrosis of any cause. For connective tissue disease–associated ILD, immunomodulatory therapy, such as tocilizumab, rituximab, and mycophenolate mofetil, may slow decline or even improve FVC at 12-month follow-up. Structured exercise therapy reduces symptoms and improves 6-minute walk test distance in individuals with dyspnea. Oxygen reduces symptoms and improves quality of life in individuals with ILD who desaturate below 88% on a 6-minute walk test. Lung transplant may improve symptoms and resolve respiratory failure in patients with end-stage ILD. After lung transplant, patients with ILD have a median survival of 5.2 to 6.7 years compared with a median survival of less than 2 years in patients with advanced ILD who do not undergo lung transplant. Up to 85% of individuals with end-stage fibrotic ILD develop pulmonary hypertension. In these patients, treatment with inhaled treprostinil improves walking distance and respiratory symptoms.

CONCLUSIONS AND RELEVANCE Interstitial lung disease typically presents with dyspnea on exertion and can progress to respiratory failure. First-line therapy includes nintedanib or pirfenidone for IPF and mycophenolate mofetil for ILD due to connective tissue disease. Lung transplant should be considered for patients with advanced ILD. In patients with ILD, exercise training improves 6-minute walk test distance and quality of life.

JAMA. 2024;331(19):1655-1665. doi:10.1001/jama.2024.3669
Published online April 22, 2024.

Multimedia

CME at jamacmelookup.com

Author Affiliations: University of Southern California, Los Angeles; National Heart and Lung Institute, Imperial College, London, UK.

Corresponding Author: Toby M. Maher, MD, MSc, PhD, University of Southern California, 1510 San Pablo St, Ste 514, Los Angeles, CA 90033 (tobymahe@usc.edu).

Section Editor: Kristin Walter, MD, Deputy Editor.

Interstitial lung disease (ILD) is characterized by inflammation and/or fibrosis within the alveolar interstitium of the lung. Approximately 30% to 40% of people with ILD develop progressive pulmonary fibrosis, which typically causes respiratory failure and is associated with a median survival of approximately 2.5 to 3.5 years.[1] In the US, ILD affects approximately 650 000 people and IPF affects approximately 198 000 people resulting in 26 000 deaths per year.[2] This review summarizes current evidence regarding the diagnosis and treatment of ILD.

Methods

A search of PubMed was performed for English-language studies on the epidemiology, pathophysiology, diagnosis, treatment, and prognosis of ILD published from January 1, 2010, to January 15, 2024. The reference lists of selected articles were manually inspected for other relevant articles. A total of 10 728 articles were retrieved. Of 728 articles identified, 115 were included, consisting of

38 clinical trials, 7 review articles, 7 meta-analyses, 22 longitudinal observational studies, 34 cross-sectional studies, and 7 guidelines, scientific statements, or consensus documents.

Classification and Nomenclature in ILD

ILDs are subcategorized based on etiology and include connective tissue disease–associated ILD (CTD-ILD), hypersensitivity pneumonitis, drug-induced ILD, postinfectious ILD, and the idiopathic interstitial pneumonias. These conditions, which have similar clinical features, are defined by distinct histopathologic appearances and prognoses (**Figure 1**).[3] The most common ILDs are idiopathic pulmonary fibrosis (IPF) (accounting for >30% of ILD), hypersensitivity pneumonitis (accounting for approximately 15% of ILD), and connective tissue disease (CTD) (accounting for approximately 25% of ILD).[1] Other ILDs include drug-induced ILD and postinfectious ILD (eg, post COVID-19).

Although different types of ILD have distinct pathophysiology, clinical manifestations, and prognoses, all forms of ILD can cause irreversible pulmonary fibrosis. Once established, pulmonary fibrosis may progress even when the underlying cause of the ILD has been treated or removed. The phrase *progressive pulmonary fibrosis* (PPF) refers to the disease behavior in a subset of people with ILD that can be more accurately defined and treated based on worsening fibrosis rather than the initial etiology.[4] People with CTD-ILD who meet criteria for PPF have a median survival of approximately 4 years compared with a median survival of 8 to 10 years for all patients with CTD-ILD.[5]

Epidemiology

In 2019, the Global Burden of Disease study estimated that approximately 654 841 patients in the US had ILD, consistent with an estimated prevalence of 179.7 per 100 000 in males and 218.9 per 100 000 in females. These figures represented an approximately 19% increase from 2010.[2] The prevalence of ILD increases with age and is highest in individuals aged 80 to 84 years.[2] The mean age at diagnosis is approximately 67 to 72 years.[6]

The incidence of IPF in adults is approximately 3 to 9 per 100 000[7] and, in contrast with ILD overall, is more common in males than females, with a sex prevalence ratio of approximately 3:1. In a US population identified from a Veterans Affairs database, the incidence of IPF increased from 73 per 100 000 person-years in 2010 to 210 cases per 100 000 person-years in 2019.[8] This increasing incidence has been reported in other cohorts but the reasons for the increase remain unclear.[9] Case-control studies reported that exposure to wood dusts,[10] metal dusts,[10,11] cigarette smoking,[12] and urban pollution[13] were associated with higher risk of IPF.

Hypersensitivity pneumonitis is a form of ILD that is precipitated by inhalation of specific antigens, most commonly avian proteins and mold or fungal spores. Prevalence rates for hypersensitivity pneumonitis in the US ranged from 1.67 to 2.71 per 100 000 with prevalence increasing with age.[14] Unlike IPF, the prevalence of hypersensitivity pneumonitis is approximately equal in men and women.[14]

The prevalence of CTD-ILD varies by underlying disease. Approximately 65% of all patients with systemic sclerosis and 80% of individuals with diffuse cutaneous systemic sclerosis develop ILD.[15] An estimated 36% to 45% of individuals with idiopathic inflammatory myopathy (a group of disorders including polymyositis, dermatomyositis, and antisynthetase syndrome) develop ILD but the incidence is as high as 80% in individuals with specific antisynthetase antibodies.[16,17] Approximately 52% to 67% of patients with mixed connective tissue disease, 11% to 27% of people with Sjogren syndrome, 1.5% to 5% of people with rheumatoid arthritis, and approximately 1% to 2% of patients with SLE develop ILD.[18]

The gender, age, and lung physiology (GAP) index integrates information from FVC and diffusion capacity of the lungs for carbon monoxide (DLCO) (together with age and sex) in patients with fibrotic ILD to estimate survival based on 3 stages of severity.[19] GAP stage 1, accounting for approximately 50% of patients with IPF at diagnosis, is associated with a 1-year mortality of 5.6% and a 3-year mortality of 16.3%. Approximately 10% of newly diagnosed patients have GAP stage 3, which is associated with a 1-year mortality of 39.2% and a 3-year mortality of 76.8%.[19]

IPF and other ILDs with pulmonary fibrosis are associated with disease-related complications including pulmonary hypertension and lung cancer. Approximately one-third of patients newly diagnosed with fibrotic ILD have evidence of obstructive sleep apnea on polysomnography.[20] There is no evidence to date that treating the obstructive sleep apnea alters prognosis.[21] Approximately 14% of individuals newly diagnosed with IPF have pulmonary hypertension,[22] and this number increases to approximately 86% in individuals with pulmonary fibrosis awaiting lung transplant.[23,24] The incidence of lung cancer in people with ILD is approximately 25.2 cases per 1000 person-years, a rate at least 3 times higher than people without ILD matched for age and smoking history.[25,26] Individuals with pulmonary fibrosis are susceptible to acute exacerbations, characterized by rapidly worsening dyspnea over several days to several weeks.[27] In these patients, computed tomography (CT) imaging of the lungs demonstrates widespread ground glass change, reflecting the development of acute lung injury and diffuse alveolar damage (Figure 1). In patients with IPF, the 1-year incidence of acute exacerbations is approximately 14.2% and the 3-year incidence of acute exacerbations is approximately 20.7%.[28] Acute exacerbations of IPF are associated with very poor outcomes with an estimated median survival of 2.2 months.[28,29]

Pathophysiology

IPF develops due to an abnormal wound healing response in genetically susceptible individuals following repeated alveolar epithelial injury.[30] Approximately 2% to 5% of individuals with fibrotic ILD have other family members with ILD.[31] Genome-wide association studies have identified several genes associated with increased risk for familial and sporadic IPF and other fibrotic ILDs; these include polymorphisms in genes related to host immunity, telomere maintenance, epithelial integrity, and cell division.[20,32,33].

Hypersensitivity pneumonitis is characterized by an immune-mediated granulomatous response to inhaled antigen.[34] The biological pathways that cause fibrosis in fibrotic hypersensitivity pneumonitis appear similar to those responsible for IPF, and the genetic

Figure 1. Classification and Description of the Most Commonly Encountered Interstitial Lung Diseases

Classification of interstitial lung disease (ILD)

Autoimmune ILD: rheumatoid arthritis, systemic sclerosis, idiopathic inflammatory myopathy (IIM), systemic lupus erythematosus, Sjogren syndrome, and mixed connective tissue disease–associated ILD

Idiopathic interstitial pneumonia: idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (iNSIP), organizing pneumonia (OP), and acute interstitial pneumonia (AIP)

Hypersensitivity pneumonitis (HP): fibrotic HP and nonfibrotic HP

Drug-induced ILD

Infection-related ILD

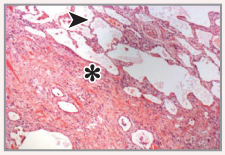
Unclassifiable ILD

Features of commonly encountered ILD histologic patterns

Usual interstitial pneumonia (UIP)

IPF, rheumatoid-ILD, asbestosis, scleroderma-ILD, HP, sarcoidosis

Poor prognosis: untreated median survival is approximately 3-4 y from diagnosis

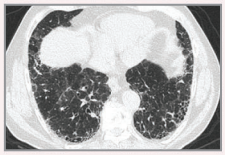


Patchy fibrosis with spatial and temporal heterogeneity

Predominantly subpleural distribution of fibrosis

Honeycomb cysts lined by hyperplastic epithelium

Scattered fibroblastic foci

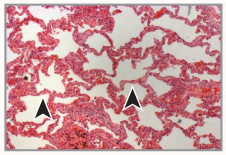


Subpleural basal reticulation and honeycombing with associated traction bronchiectasis

Nonspecific interstitial pneumonia (NSIP)

iNSIP, scleroderma-ILD, rheumatoid-ILD, drug-induced ILD, smoking-induced ILD

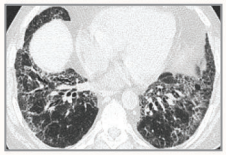
Intermediate prognosis: untreated median survival is approximately 8-10 y from diagnosis



Inflammation and/or fibrosis within the alveolar wall

Relative preservation of the lung architecture

Homogeneous distribution of change across the lung



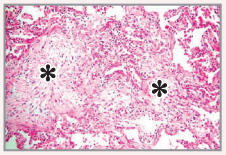
Predominantly basal ground glass attenuation with fine reticulation and traction bronchiectasis

Subpleural sparing

Organizing pneumonia

COP, IIM associated ILD, drug-induced ILD, rheumatoid-ILD, vasculitis

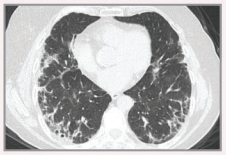
Good prognosis: often responds well to immunomodulatory therapy; however, some individuals with secondary OP progress to pulmonary fibrosis



Patchy filling of alveolar ducts and alveoli with loosely formed fibrous connective tissue (Masson bodies)

Mild associated inflammatory cell infiltrate

Preservation of alveolar architecture



Patchy consolidation

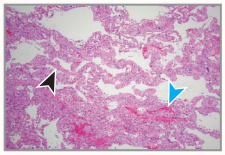
Cryptogenic disease is often unifocal while autoimmune disease tends to be multifocal

Atoll sign (central ground glass opacity with surrounding ring of consolidation)

Diffuse alveolar damage (DAD)

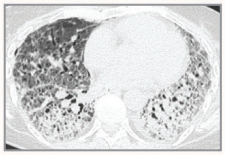
ARDS, AIP, IIM (especially MDA5+) associated ILD, acute exacerbations of existing ILD

Very poor prognosis: median survival is 2.2 mo



Exudative phase shows alveolar edema, hyaline membranes, denudation of alveolar basement membrane

Organizing phase shows loosely formed fibrosis within alveolar septae and hyperplasia of type II alveolar epithelium



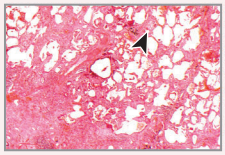
Exudative phase shows widespread patchy, dependent ground glass change

Organizing phase shows widespread consolidation in a dependent distribution with traction bronchiectasis and often cystic destruction of the lung

Hypersensitivity pneumonitis

Good prognosis: nonfibrotic HP, frequently resolves without significant sequelae

Intermediate prognosis: fibrotic HP

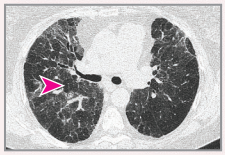


Airway-centered and interstitial lymphocytic inflammation

Poorly formed nonnecrotizing airway-centered granulomata

If present, fibrosis tends to be airway centered

In some cases, fibrosis may show features consistent with UIP or NSIP



Nonfibrotic (acute) disease shows centrilobular nodules, patchy ground glass, and mosaic attenuation

Fibrotic (chronic) disease shows peribronchovascular fibrosis in an upper or midzone distribution with associated mosaic attenuation and traction bronchiectasis

ARDS indicates acute respiratory distress syndrome; COP, cryptogenic organizing pneumonia; and MDA5+, antimelanoma differentiation–associated gene 5. The UIP histology highlights temporal and spatial heterogeneity with areas of normal alveoli interspersed by dense fibrosis. The black arrowhead highlights the normal alveoli in the UIP histology image. In addition there are fibroblastic foci (black star) and microcystic honeycomb airspaces lined by hyperplastic epithelium. The radiographic image shows bilateral basal and subpleural honeycomb change. The NSIP histology shows widespread alveolar wall thickening and fibrosis (black arrowheads) but overall preservation of the normal alveolar architecture. The radiographic imaging, obtained from a female with scleroderma, shows bilateral basal ground glass change and reticulation with traction bronchiectasis. The organizing pneumonia histology highlights the loosely formed intra-alveolar granulation tissue (Masson bodies; black stars) within a region of otherwise normal alveolar architecture. The computed tomography (CT) scan, from a patient with Jo-1 positive dermatomyositis, illustrates multifocal consolidation typical of connective tissue disease–associated organizing pneumonia. In diffuse alveolar damage there is evidence of hyaline membranes (black arrowhead), sloughing of epithelium from the basement membrane, and intra-alveolar hemorrhage (blue arrowhead). The corresponding CT shows dependent consolidation bilaterally (in a patient experiencing an acute exacerbation of IPF). The histology of fibrotic hypersensitivity pneumonitis shows airway-centered fibrosis with a loosely formed airway-centered granuloma (black arrowhead). The CT shows airway-centered fibrosis with evidence of mosaic attenuation (pink arrowhead).

polymorphisms associated with development of fibrotic hypersensitivity pneumonitis are indistinguishable from those of IPF.[35]

The biological pathways by which connective tissue disorders, such as scleroderma and rheumatoid arthritis, result in ILD are poorly understood. In scleroderma and idiopathic inflammatory myopathy, specific autoantibodies are associated with development of ILD.[36] In rheumatoid arthritis, the genetic profile of individuals who develop ILD is similar to that associated with IPF.[37]

Drugs and infection may also precipitate ILD.[38] Bleomycin, amiodarone, nitrofurantoin, and cancer immunotherapies such as immune checkpoint inhibitors are the most common drugs associated with development of ILD.[39-41] Residual interstitial lung abnormalities were identified in up to 11% of individuals hospitalized with severe COVID-19 infection.[42] Mechanisms underlying post–COVID-19 ILD are not fully understood. Interstitial infiltrates associated with COVID-19 typically resolve without treatment. However, some individuals with COVID-19 have developed progressive pulmonary fibrosis.[43] Other coronaviruses, including MERS and SARS,[44] were also associated with development of ILD.[45]

Clinical Presentation

Dyspnea is the primary symptom of ILD, which typically first manifests during strenuous exertion. As ILD progresses, individuals often report a gradual deterioration in exercise capacity. In advanced disease, resting hypoxemia is common. The onset and progression of dyspnea varies by ILD. Individuals with organizing pneumonia or diffuse alveolar damage (acute interstitial pneumonitis) present with acute or subacute onset dyspnea over days to a few weeks. Individuals with IPF or rheumatoid-associated ILD typically report onset of symptoms over a period of weeks to months, while those with scleroderma ILD and chronic hypersensitivity pneumonitis typically report more indolent symptom onset over many months.

Approximately 30% to 50% of patients with IPF report a cough that impairs quality of life.[46] As ILD progresses, patients often report fatigue and weight loss. Unintended weight loss in patients with ILD is associated with a poor prognosis. A greater than 5% decrease in weight at any time over the course of disease is associated with a 2.5-fold increase in risk of mortality.[47,48]

Most patients with ILD due to CTD are diagnosed with CTD before developing respiratory symptoms related to ILD. However, ILD can be the first manifestation of systemic autoimmune disease in a small proportion of individuals. This occurs most commonly in individuals with idiopathic inflammatory myopathy, for whom ILD precedes signs and symptoms of myopathy in 7.2% to 37.5% of patients.[49] Therefore, clinicians should inquire about systemic symptoms in individuals presenting with ILD.[50] History taking should evaluate exposure to potential precipitating factors for hypersensitivity pneumonitis, drugs known to cause ILD, or occupational exposures associated with the development of pneumoconioses such as silicosis or asbestosis.[4]

Assessment and Diagnosis

At presentation, approximately 7% to 42% of individuals with pulmonary fibrosis have digital clubbing.[51] On chest auscultation, 93% of patients with IPF and 73% of those with non-IPF ILD have fine Velcro-like crepitations at the lung bases.[52] Those with hypersensitivity pneumonitis may have high-pitched end-inspiratory squawks on lung auscultation. Signs of CTD such as active arthritis, skin thickening (or mechanic's hands), and Gottron papules may be present on physical examination. Patients with end-stage fibrotic ILD may have evidence of cyanosis or clinical findings of pulmonary hypertension such as a loud second pulmonary heart sound, S_3 or S_4 (a gallop rhythm), elevated jugular venous pressure, and peripheral edema.

Compared with CT scan, the sensitivity of chest radiography for ILD is 63% and specificity is 93%.[53] Serologic testing for autoantibodies (including antinuclear antibody, an extended myositis panel, antineutrophil cytoplasmic antibodies, and rheumatoid factor or anticyclic citrullinated peptide antibodies) and serum-specific IgG antibodies (precipitins) can suggest CTD or hypersensitivity pneumonitis as potential diagnoses. However, the sensitivity of precipitins for hypersensitivity pneumonitis is only approximately 57% to 64%.[54]

Thoracic CT is the primary diagnostic test for identifying and diagnosing ILD with approximately 91% sensitivity and 71% specificity for subtypes of ILDs.[4] Different forms of ILD typically have distinct appearances on CT (Figure 1). These appearances are associated with the various histopathologic patterns related to ILD classification (Figure 1). However, neither CT imaging nor histopathology alone are diagnostic for specific ILDs. Histopathologic characteristics are not unique to any specific ILD diagnosis and overlap exists between different histopathologic and radiologic findings.[55] This is especially true for the 4 most common histopathologic patterns: usual interstitial pneumonia, nonspecific interstitial pneumonia, organizing pneumonia, and diffuse alveolar damage. The accepted approach to ILD diagnosis is multidisciplinary assessment with a team consisting of pulmonologists, radiologists, and, where necessary, pathologists and rheumatologists.[56] This diagnostic approach (**Figure 2**) underscores the importance of integrating clinical information with imaging and, where appropriate, histology.

While lung biopsy was previously important for accurate ILD diagnosis, more recently, thoracic CT has replaced lung biopsy, primarily due[4] to improvements in CT imaging. Lung biopsy, particularly surgical lung biopsy, is associated with a mortality rate of 1% to 2%.[57] Currently, less than 10% of patients with ILD undergo lung biopsy.[58] In many centers, bronchoscopic transbronchial cryobiopsy, an endoscopic procedure that involves rapid freezing of lung tissue prior to biopsy, has replaced video-assisted thoracic surgical (VATS) biopsy for obtaining lung tissue samples. Bronchoscopic transbronchial cryobiopsy can be performed as a minimally invasive procedure with a lower complication rate than VATS surgery and has a similar level of diagnostic accuracy.[59] In a systematic review of published studies, cryobiopsy was associated with adverse effects of bleeding in 30% of patients and pneumothorax in 8% of patients. Serious adverse effects, including mortality were rare.[60] In 69 patients with ILD, multidisciplinary team assessment based on cryobiopsy yielded a diagnosis with a high degree of confidence in 60% of patients compared with 73% for a surgical VATS biopsy.[59] Even after detailed clinical assessment that includes lung biopsy, up to 15% of individuals have ILD that is unclassifiable.[61] The most common reasons for an unclassifiable diagnosis are clinical features that are not specific for a single diagnosis or inconsistent results from

different diagnostic tests. In some patients with unclassifiable ILD, the diagnosis becomes clearer when new clinical signs and symptoms develop over time.

When a diagnosis of ILD is suspected or made, pulmonary function testing (including forced vital capacity [FVC] and DLCO) should be obtained to assess disease severity. Patients with ILD typically present with a restrictive pattern on spirometry. At baseline, the degree of FVC and DLCO impairment is associated with both short-term and medium-term prognosis.[62] A 5% or greater loss of FVC over 3, 6, or 12 months is associated with poorer prognosis compared with a loss of FVC less than 5%, in patients with IPF, systemic sclerosis–associated ILD, and all other fibrotic ILDs.[5,62-65]

Treatment

The treatment of ILD has evolved over the last decade with the discovery and US Food and Drug Administration (FDA) approval of antifibrotic drugs for IPF and other forms of PPF, specific therapies for scleroderma-associated ILD, and treatment for ILD-associated pulmonary hypertension (**Table**).

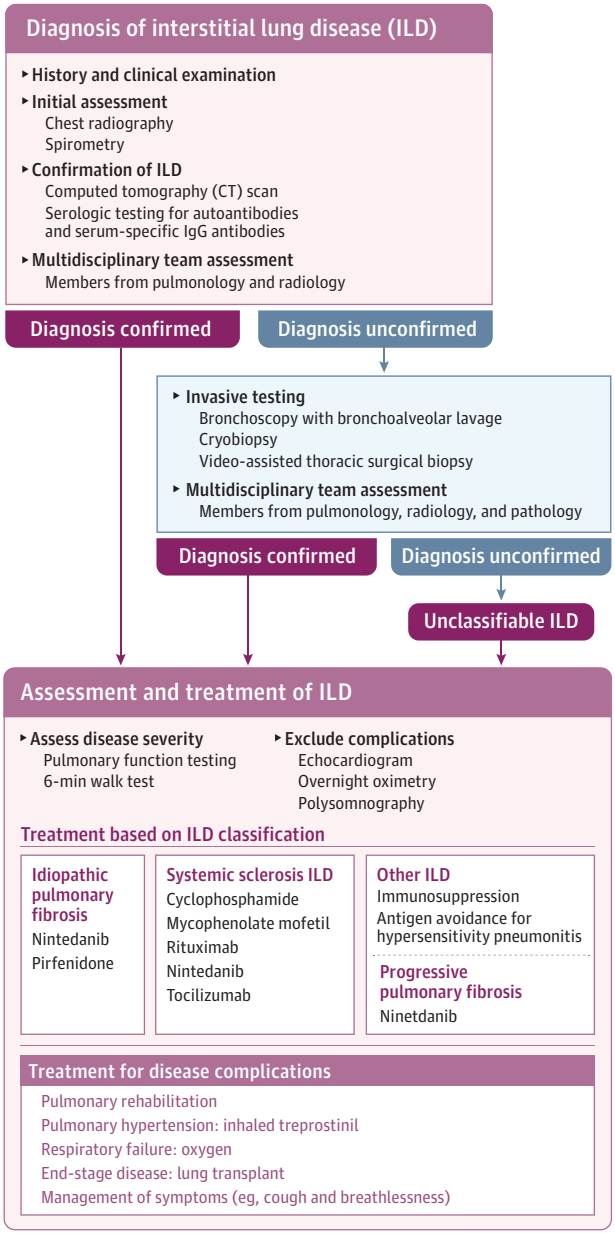
Antifibrotic Therapy

Pirfenidone is an orally administered small molecule pyridine-derivative with anti-inflammatory, antioxidant, and antifibrotic properties.[66] In the ASCEND clinical trial of 555 patients with IPF randomized to pirfenidone or placebo, pirfenidone reduced FVC decline at 52-week follow-up (235 mL decline vs 428 mL decline, consistent with a relative difference of 45.1%).[67] The most common adverse effects associated with pirfenidone compared with placebo were photosensitive rash (29.2% vs 9.0%), nausea (35.5% vs 15.1%), and anorexia (12.4% vs 4.3%).[68] In a pooled analysis that included 1247 patients, 22 patients (3.5%) who received pirfenidone had died by week 72 compared with 42 patients (6.7%) who received placebo (hazard ratio: 0.52; 95% CI, 0.31-0.87).[68]

In the RELIEF clinical trial of 127 patients with progressive pulmonary fibrosis, pirfenidone slowed FVC decline compared with placebo by 3.53% (95% CI, 0.21-6.86)[69] (absolute rates not provided). In a clinical trial of 253 patients with unclassifiable ILD randomized to either pirfenidone or placebo for 6 months, pirfenidone reduced FVC decline compared with placebo (17.8 mL decline vs 113.0 mL decline; between-group difference: 95.3 mL; 95% CI, 35.9-154.6 mL).[70] A clinical trial of pirfenidone in rheumatoid arthritis ILD was stopped early due to slow recruitment after enrolling 123 patients. In the pirfenidone group, 7 of 63 patients (11%) met the composite primary end point of greater than 10% FVC decline or death at 52-weeks compared with 9 of 60 placebo patients (15%) (odds ratio, 0.67; 95% CI, 0.22-2.03).[71] The rate of FVC decline in the pirfenidone group was 66 mL compared with 146 mL decline in the placebo group (P = .01).

Nintedanib is an oral small molecule multi–tyrosine kinase inhibitor. In a prespecified analysis of combined data from 2 parallel randomized clinical trials (RCTs), INPULSIS-1 and INPULSIS-2, 1066 patients were randomized to nintedanib or placebo. At 52-week follow-up, FVC decline was significantly less in the nintedanib group (114.7 mL compared with 239.9 mL [mean difference: 125.3 mL; 95% CI, 77.7-172.8 mL; P = .001]).[72] In INPULSIS-1, diarrhea occurred in 61.5% of patients randomized to nintedanib and in 18.6% of patients randomized to placebo. Corresponding rates of diarrhea in INPULSIS-2 were 63.2% in patients randomized to nintedanib and 18.3% in patients randomized to placebo. In the SENSCIS RCT of 579 patients with systemic sclerosis–associated ILD (including 48.5% receiving mycophenolate mofetil),[73] nintedanib reduced FVC decline compared with placebo (−52.4 mL vs −93.3 mL; difference: 41.0 mL; 95% CI, 2.9-79 mL). In a post hoc analysis, patients with the greatest reduction in annual FVC decline were receiving the combination of nintedanib and mycophenolate mofetil.[74] In the INBUILD RCT of 663 patients with PPF due to a cause other than IPF, nintedanib significantly reduced FVC decline compared with placebo, (−80.8 mL compared with −187.8 mL; difference of 107 mL;

Figure 2. Schematic for the Diagnosis, Assessment, and Treatment of Individuals With Interstitial Lung Disease



This algorithm has not been validated.

Table. Drugs Used for the Treatment of Interstitial Lung Disease

Drug name	Dose	Mechanism of action	Indication	Efficacy	Adverse effects associated with drug (%)
Nintedanib	150 mg twice daily reduced to 100 mg twice daily if adverse effects	Multi-tyrosine kinase inhibitor that inhibits >12 growth factor receptors at therapeutic concentrations	IPF; PPF; scleroderma-ILD	Slowed 52-week FVC decline by between 44% and 57% compared with placebo	Diarrhea (62); nausea (24); weight loss (9.5)
Pirfenidone	801 mg 3 times daily reducing to 534 mg 3 times daily if adverse effects	Exact mechanism unknown; acts to downregulate TGF-β, TNF, and other inflammatory cytokines	IPF	Slowed 52-week FVC decline by 45.1% compared with placebo	Nausea/bloating (35.5); weight loss (12.4); photosensitive rash (29.2)
Mycophenolate mofetil	Up to 1500 mg twice daily	An inhibitor of inosine-5′-monophosphate dehydrogenase (MPA); inhibition of MPA depletes guanosine nucleotides preferentially in T and B lymphocytes halting their proliferation	Not FDA approved for any ILD indication but recommended in guidelines for scleroderma ILD	2.8% Improvement in adjusted % predicted FVC over 24 mo	Anemia (11); infection (7)
Cyclophosphamide	Oral: 2 mg/kg daily; intravenous: 600 mg/m^2 body surface area every 3 to 4 weeks for a total of 6 doses; lifetime cumulative exposure should be limited to <20 g	An alkylating agent that prevents replication of proliferating cells, especially bone marrow–derived leukocytes	Not approved for any ILD indication but recommended in guidelines for scleroderma ILD	Improved 52-week % predicted FVC by 2.53%	Leukopenia (24); headache (11); infusion reactions (14); infection (8)
Rituximab	1000 mg intravenously repeated twice at an interval of 2 weeks; regimen can be repeated every 6 mo if necessary	An anti CD-20 monoclonal antibody that acts to deplete B cells	Not approved for any ILD indication but recommended in guidelines for scleroderma ILD	Improved FVC by 97 mL at 24 weeks compared with baseline	Infusion reactions (12); infection (10)
Tocilizumab	162 mg subcutaneously every week	An anti-interleukin 6 monoclonal antibody	Scleroderma-ILD	4.2% Difference (95% CI, 2.0 - 6.4) in % predicted FVC at week 48 compared with placebo	Injection-site reactions (8)
Treprostinil	By nebulization, >9 breaths per session 4 times per day	A synthetic prostacyclin analogue that exerts a vasodilatory effect on the pulmonary (and systemic) vascular beds	ILD-associated pulmonary hypertension	Improved 6-min walk test by 31.1 m at 16 weeks compared with placebo group	Cough (44); headache (28)

Abbreviations: AIP, acute interstitial pneumonia; ARDS, acute respiratory distress syndrome; FDA, US Food and Drug Administration; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; PF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PPF, progressive pulmonary fibrosis; RA, rheumatoid arthritis; TGF-β, transforming growth factor—β; TNF, tumor necrosis factor.

95% CI, 65.4-148.5 mL). A prespecified subgroup analysis showed a consistent effect of nintedanib in patients with PPF irrespective of specific ILD diagnosis.[75] In a pooled analysis of patients in RCTs of nintedanib, a Weibull distribution analysis estimated a mean survival for nintedanib treated patients of 11.6 years (95% CI, 9.6-14.1 years) compared with 3.7 years (95% CI, 2.5-5.4 years) for placebo.[76]

Immunomodulatory Therapy

In the FaSScinate and FocuSSced RCTs of individuals with diffuse cutaneous systemic sclerosis and active inflammation (defined as arthritis, raised platelets, or raised C-reactive protein),[77,78] tocilizumab did not significantly improve the primary outcome of 48-week change in modified Rodnan Skin Score. Neither study required the presence of ILD. In both studies, the secondary end point of 48-week change in FVC suggested a benefit of therapy that was ultimately sufficient for the FDA to approve tocilizumab as a treatment for scleroderma-ILD in the US. In the FaSScinate study of 87 patients, tocilizumab reduced FVC decline compared with placebo at 48-week follow-up (117 mL decline compared with 237 mL decline; mean difference 120 mL; 95% CI, −23 to 262[77]). In the FocuSSced trial of 210 patients, tocilizumab reduced % predicted FVC decline at 48-week follow-up (4.6% compared with 0.4%; difference 4.2%; 95% CI, 2.0%-6.4%).[78]

The scleroderma lung study 1 randomized patients with systemic sclerosis–associated ILD to either oral cyclophosphamide or placebo.[79] At 12 months, cyclophosphamide significantly improved % predicted FVC compared with placebo (difference: 2.53%; 95 CI, 0.28%-5.79%). The scleroderma lung study 2 RCT compared oral mycophenolate mofetil 1.5 g twice daily to oral cyclophosphamide in individuals with systemic sclerosis–associated ILD and found no difference in % predicted FVC between groups; the 24-month baseline-adjusted % predicted FVC improved by 2.19% in the oral mycophenolate mofetil group compared with 2.88% in the cyclophosphamide group (a difference between groups of −0.7; 95% CI, −3.1 to 1.7).[80] Fewer patients in the oral mycophenolate mofetil group discontinued treatment at 12 months (29.0% vs 43.8%). In the DESIRES multicenter RCT, 56 patients in Japan with scleroderma and a modified Rodnan Skin Score greater than 10 were randomized to rituximab (375 mg/m^2) or placebo for 24 weeks.[81] At 24-week follow-up, rituximab significantly reduced the modified Rodnan Skin Score (primary outcome) compared with placebo by 6.3 compared with 2.14, a difference of −8.44 (95% CI,

−11.0 to −5.88). Among participants with an FVC less than 80% at baseline, rituximab improved % predicted FVC at 24 weeks compared with placebo (0.09% vs −2.87%; a difference of 2.96%; 95% CI, 0.08-5.84).

In contrast, the PANTHER clinical trial randomized patients to the antioxidant N-acetyl cysteine alone, a combination of N-acetyl cysteine, prednisone, and azathioprine, or placebo. The study planned to recruit 390 patients but was stopped after approximately 50% of data were collected due to an excess of adverse events associated with the combination of prednisone, azathioprine, and N-acetyl cysteine. Mortality was 10.4% in the combination therapy group (N = 77) compared with 1.3% in the placebo group (n = 78). There were 23 hospitalizations in the combination group compared with 7 in the placebo group.[82] These results highlight the potential risk of immunosuppressive therapy for individuals with fibrotic lung disease. Other drugs tested in RCTs for patients with IPF that did not report improved outcomes compared with placebo include warfarin, imatinib, γ-interferon, anti-IL13 antibodies, endothelin antagonists, prophylactic antibiotics, and autotaxin inhibitors.[22,83-89]

Few clinical trials have been performed for patients with ILD due to diseases other than IPF and systemic sclerosis–associated ILD. In the RECITAL randomized double-blind, double-dummy clinical trial, rituximab was compared with cyclophosphamide in 101 individuals with ILD due to systemic sclerosis, mixed connective tissue disease, or idiopathic inflammatory myositis.[90] Rituximab was not significantly better than cyclophosphamide for the primary outcome of change in FVC at 24 weeks. However, both drugs increased FVC (cyclophosphamide by a mean [SD] of 99 [329] mL and rituximab by a mean [SD] of 97 [234] mL) and improved quality of life, according to the King's Brief ILD Questionnaire (K-BILD) at 24 and 48 weeks. Although corticosteroids and immunosuppressant therapies such as azathioprine and mycophenolate mofetil are frequently prescribed to treat hypersensitivity pneumonitis and rheumatoid arthritis ILD, none have been tested in RCTs in either disease. Although evidence-based pharmacotherapies are lacking for hypersensitivity pneumonitis, avoiding an identified inciting cause (such as birds or mold) may improve the condition.[91] For rheumatoid arthritis ILD, observational data suggested that rituximab, abatacept, and tofacitinib were associated with the best pulmonary outcomes, including a lower incidence of ILD and fewer respiratory hospitalizations.[92,93]

Transplant

Lung transplant is a therapeutic option for individuals with end-stage lung diseases including ILD. However, access to transplant is limited by organ availability. Furthermore, advanced age and comorbidities such as cardiovascular disease, diabetes, and right heart dysfunction exclude transplant as a therapeutic option in many patients with ILD. Nonetheless, the proportion of all lung transplants performed for ILD in the US has increased over the last decade. In 2018, ILD accounted for 60.0% of all lung transplants performed in the US compared with only 20.4% in 2006.[94,95] In the 2019 report of the International Society for Heart and Lung Transplantation, median survival following lung transplant for idiopathic interstitial pneumonias (including IPF) was 5.2 years compared with 6.7 years for all other ILDs.[96] Median survival was 6.2 years for all lung transplant recipients.[95]

Pulmonary Hypertension

Few treatments improve outcomes in patients with ILD and pulmonary hypertension.[22,97-101] In the INCREASE RCT of 326 patients with ILD and pulmonary hypertension, the inhaled prostacyclin analogue, treprostinil, increased 6-minute walk test distance at 16 weeks by a mean (SD) of 21.08 (5.12) m from baseline compared with a mean (SD) decline of −10.04 (5.12) m for placebo (mean difference: 31.1 m; 95% CI, 16.9 to 44.4 m). The most common adverse events were transient cough (43.6%), headache (27.6%), throat irritation (12.3%), and oropharyngeal pain (11.0%).

Pulmonary Rehabilitation

Pulmonary rehabilitation, consisting of a structured program of education and endurance training for 8 to 12 weeks, is an effective therapy for improving exercise capacity and reducing symptoms in individuals with chronic lung disease. A 2021 Cochrane meta-analysis of 16 studies that included 675 people reported that in individuals with symptomatic breathlessness due to ILD, pulmonary rehabilitation was associated with an improvement in 6-minute walk test distance of 40.1 m (95% CI, 32.7-47.4 m) compared with control.[102] Pulmonary rehabilitation was associated with improved symptoms of dyspnea and improvement in health-related quality of life.[102]

Supportive and Symptom-Based Therapy

Patients with chronic lung disease should be vaccinated for pneumococcus, COVID-19, respiratory syncytial virus, and influenza. However, no RCTs have been performed in this specific patient population to assess a potential protective effect of these vaccines against either acute exacerbations or mortality. People currently smoking cigarettes should be helped to quit smoking.

Ambulatory and continuous oxygen therapy are important treatments for patients with advanced ILD. In the prospective AMBOX trial, an open-label, 2-week crossover study that compared ambulatory oxygen (at a flow rate determined by oxygen need during a 6-minute walk test) to room air (administered using matching, but nonblinded, equipment to the oxygen) in 84 individuals with fibrotic ILD and evidence of oxygen desaturation below 88% on a 6-minute walk test, oxygen was associated with a clinically meaningful improvement in quality of life measured using the K-BILD (difference between trial periods, 3.7; 95% CI, 1.8-5.6).[103] The effect of oxygen therapy on development of pulmonary hypertension or mortality has not been assessed in an RCT. However, 24-hour oxygen therapy is appropriate for patients with ILD who have resting oxygen saturations consistently less than 90%.

Cough and dyspnea are common in patients with fibrotic ILD, and both symptoms impair quality of life.[46,104] Neither pirfenidone nor nintedanib has been shown in RCTs to affect cough or the perception of breathlessness. Short-acting opiates improve breathlessness in patients with end-stage lung disease.[105] Nalbuphine, an opioid agonist-antagonist, reduced objective cough frequency compared with placebo (75.1% vs 22.6%, a mean difference of

52.5%) in a 22-day crossover trial of 41 patients with IPF.[106] Morphine reduced awake cough frequency by 39.4% compared with placebo (95% CI, −54.4 to −19.4%) in a 2-week crossover study.[107] The most frequent adverse effect was constipation (21%).[106-108] Benzodiazepines can improve acute dyspnea and panic episodes in individuals with end-stage disease, however, RCT evidence is mixed regarding the benefit of this class of drugs.[109] A qualitative study of handheld fans suggested that these devices may provide relief from dyspnea.[109]

End-of-life planning and access to palliative care services are important for individuals with ILD and respiratory failure. Advanced directives provide patients with control over their treatments and outcomes as their disease progresses. For individuals with end-stage disease for whom lung transplant is not an option, intubation and mechanical ventilation should be avoided because they are associated with poor outcomes.

Guideline Recommendations

Current American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax guidelines strongly recommend nintedanib or pirfenidone for IPF.[8] These guidelines strongly recommend against azathioprine and high dose corticosteroids in individuals with IPF[4] and strongly recommend nintedanib and conditionally recommend pirfenidone for patients with PPF.[4] Referral of patients to a dedicated center with expertise in the diagnosis and management of ILD is recommended. American Thoracic Society scleroderma-ILD guidelines strongly recommend use of mycophenolate mofetil for patients with scleroderma and ILD. Tocilizumab, nintedanib, cyclophosphamide, rituximab, and the combination of mycophenolate and nintedanib are associated with conditional positive recommendations, however, no specific guideline recommendations have been proposed regarding the ordering of specific medications or the timing of combination therapy.[110] European Society of Cardiology and European Respiratory Society guidelines on pulmonary hypertension recommend that inhaled Treprostinil should be considered in individuals with PH associated with ILD.[111] The International Society for Heart and Lung Transplantation guidelines recommend that individuals with usual interstitial pneumonia due to any cause should be referred for lung transplant assessment at diagnosis.[112] For patients with other forms of ILD, referral for transplant assessment should occur when FVC is less than 80% predicted or DLCO less than 40% predicted or if there is evidence of PPF in the preceding 2 years.

Prognosis

Median survival for individuals with IPF is 3 to 3.5 years. Analysis of RCTs for pirfenidone and nintedanib, performed by the FDA, found that greater decline in FVC was associated with a higher risk of mortality.[113] In analyses of data combined from these clinical trials, 355 (31.4%) participants had an absolute FVC decline of between 5% and 10%; 24 (6.8%) died; and 157 (13.9%) had an FVC decline of between greater than 15% with 26 deaths (16.6%). Compared with individuals with a less than 5% FVC decline, the hazard ratio for death was 1.34 (95% CI, 0.75-2.4) for an FVC change of 5% to 10%, 2.20 (95% CI, 1.10-4.37) for an FVC decline of 10% to 15%, and 6.09 (95% CI, 31.4-11.80) for an FVC decline greater than 15%.[113] Slowing FVC decline with pirfenidone or nintedanib was associated with an improved life expectancy of approximately 1 to 2.5 years.[114-116] The effects of other therapies on survival in people with ILD remain unclear.

Limitations

This review has several limitations. First this was not a systematic review. A formal quality assessment of the literature was not performed. Second, included articles were limited to English language publications. Third, not all forms of ILD were discussed. Fourth, some relevant articles may have been missed.

Conclusions

Interstitial lung disease typically presents with dyspnea on exertion and can progress to respiratory failure. First-line therapy is nintedanib or pirfenidone for IPF and mycophenolate mofetil for ILD due to connective tissue disease. Lung transplant should be considered for patients with advanced ILD. In patients with ILD, exercise training improves 6-minute walk test distance and quality of life.

ARTICLE INFORMATION

Accepted for Publication: February 27, 2024.

Published Online: April 22, 2024. doi:10.1001/jama.2024.3669

Conflict of Interest Disclosures: Dr Maher reported receiving personal fees from Boehringer Ingelheim, Galapagos, Roche/Genentech, Pfizer, BMS, GSK, Sanofi-Aventis, Pliant, Trevi, Galecto, Merck, Astra Zeneca, CSL Behring, Vicore, Scleroderma Research Foundation, Qureight, and Veracyte outside the submitted work; in addition, Dr Maher had a patent for Itaconate for the treatment of tissue fibrosis pending application number PCT/GB2020/052218.

Funding/Support: Dr Maher is supported by an NIHR Clinician Scientist Fellowship (NIHR Ref: CS-2013-13-017) and British Lung Foundation Chair in Respiratory Research (C17-3).

Role of the Funder/Sponsor: The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

REFERENCES

1. Oldham JM, Lee CT, Wu Z, et al. Lung function trajectory in progressive fibrosing interstitial lung disease. *Eur Respir J*. 2022;59(6):2101396. doi:10.1183/13993003.01396-2021

2. Jeganathan N, Sathananthan M. The prevalence and burden of interstitial lung diseases in the USA. *ERJ Open Res*. 2021;8(1):00630-2021. doi:10.1183/23120541.00630-2021

3. Travis WD, Costabel U, Hansell DM, et al; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2013;188(6):733-748. doi:10.1164/rccm.201308-1483ST

4. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2022;205(9):e18-e47. doi:10.1164/rccm.202202-0399ST

5. Pugashetti JV, Adegunsoye A, Wu Z, et al. Validation of proposed criteria for progressive

pulmonary fibrosis. *Am J Respir Crit Care Med*. 2023;207(1):69-76. doi:10.1164/rccm.202201-0124OC

6. Zaman T, Moua T, Vittinghoff E, Ryu JH, Collard HR, Lee JS. Differences in clinical characteristics and outcomes between men and women with idiopathic pulmonary fibrosis: a multicenter retrospective cohort study. *Chest*. 2020;158(1):245-251. doi:10.1016/j.chest.2020.02.009

7. Maher TM, Bendstrup E, Dron L, et al. Global incidence and prevalence of idiopathic pulmonary fibrosis. *Respir Res*. 2021;22(1):197. doi:10.1186/s12931-021-01791-z

8. Kaul B, Lee JS, Zhang N, et al. Epidemiology of idiopathic pulmonary fibrosis among U.S. veterans, 2010-2019. *Ann Am Thorac Soc*. 2022;19(2):196-203. doi:10.1513/AnnalsATS.202103-295OC

9. Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J*. 2015;46(3):795-806. doi:10.1183/09031936.00185114

10. Hubbard R, Lewis S, Richards K, Johnston I, Britton J. Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis. *Lancet*. 1996;347(8997):284-289. doi:10.1016/S0140-6736(96)90465-1

11. Pauchet A, Chaussavoine A, Pairon JC, et al. Idiopathic pulmonary fibrosis: what do we know about the role of occupational and environmental determinants? a systematic literature review and meta-analysis. *J Toxicol Environ Health B Crit Rev*. 2022;25(7):372-392. doi:10.1080/10937404.2022.2131663

12. Abramson MJ, Murambadoro T, Alif SM, et al; Australian IPF Registry. Occupational and environmental risk factors for idiopathic pulmonary fibrosis in Australia: case-control study. *Thorax*. 2020;75(10):864-869. doi:10.1136/thoraxjnl-2019-214478

13. Conti S, Harari S, Caminati A, et al. The association between air pollution and the incidence of idiopathic pulmonary fibrosis in Northern Italy. *Eur Respir J*. 2018;51(1):1700397. doi:10.1183/13993003.00397-2017

14. Fernández Pérez ER, Kong AM, Raimundo K, Koelsch TL, Kulkarni R, Cole AL. Epidemiology of hypersensitivity pneumonitis among an insured population in the United States: a claims-based cohort analysis. *Ann Am Thorac Soc*. 2018;15(4):460-469. doi:10.1513/AnnalsATS.201704-288OC

15. Steele R, Hudson M, Lo E, Baron M; Canadian Scleroderma Research Group. Clinical decision rule to predict the presence of interstitial lung disease in systemic sclerosis. *Arthritis Care Res (Hoboken)*. 2012;64(4):519-524. doi:10.1002/acr.21583

16. Laporte A, Mariampillai K, Allenbach Y, et al. Idiopathic inflammatory myopathies: CT characteristics of interstitial lung disease and their association(s) with myositis-specific autoantibodies. *Eur Radiol*. 2022;32(5):3480-3489. doi:10.1007/s00330-021-08411-w

17. Hallowell RW, Danoff SK. Diagnosis and management of myositis-associated lung disease. *Chest*. 2023;163(6):1476-1491. doi:10.1016/j.chest.2023.01.031

18. Mageau A, Borie R, Crestani B, Timsit JF, Papo T, Sacre K. Epidemiology of interstitial lung disease in systemic lupus erythematosus in France: a nation-wide population-based study over 10 years. *Respirology*. 2022;27(8):630-634. doi:10.1111/resp.14268

19. Ley B, Ryerson CJ, Vittinghoff E, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann Intern Med*. 2012;156(10):684-691. doi:10.7326/0003-4819-156-10-201205150-00004

20. Peljto AL, Blumhagen RZ, Walts AD, et al. Idiopathic pulmonary fibrosis is associated with common genetic variants and limited rare variants. *Am J Respir Crit Care Med*. 2023;207(9):1194-1202. doi:10.1164/rccm.202207-1331OC

21. Myall KJ, West AG, Martinovic JL, et al. Nocturnal Hypoxemia Associates With Symptom Progression and Mortality in Patients With Progressive Fibrotic Interstitial Lung Disease. *Chest*. 2023;164(5):1232-1242. doi:10.1016/j.chest.2023.05.013

22. Raghu G, Behr J, Brown KK, et al; ARTEMIS-IPF Investigators. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. *Ann Intern Med*. 2013;158(9):641-649. doi:10.7326/0003-4819-158-9-201305070-00003

23. Raghu G, Nathan SD, Behr J, et al. Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. *Eur Respir J*. 2015;46(5):1370-1377. doi:10.1183/13993003.01537-2014

24. Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. *Eur Respir J*. 2015;46(4):1113-1130. doi:10.1183/13993003.02316-2014

25. Ozawa Y, Suda T, Naito T, et al. Cumulative incidence of and predictive factors for lung cancer in IPF. *Respirology*. 2009;14(5):723-728. doi:10.1111/j.1440-1843.2009.01547.x

26. Kato E, Takayanagi N, Takaku Y, et al. Incidence and predictive factors of lung cancer in patients with idiopathic pulmonary fibrosis. *ERJ Open Res*. 2018;4(1):00111-2016. doi:10.1183/23120541.00111-2016

27. Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. an international working group report. *Am J Respir Crit Care Med*. 2016;194(3):265-275. doi:10.1164/rccm.201604-0801CI

28. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur Respir J*. 2011;37(2):356-363. doi:10.1183/09031936.00159709

29. Salonen J, Purokivi M, Bloigu R, Kaarteenaho R. Prognosis and causes of death of patients with acute exacerbation of fibrosing interstitial lung diseases. *BMJ Open Respir Res*. 2020;7(1):e000563. doi:10.1136/bmjresp-2020-000563

30. Pardo A, Selman M. The interplay of the genetic architecture, aging, and environmental factors in the pathogenesis of idiopathic pulmonary fibrosis. *Am J Respir Cell Mol Biol*. 2021;64(2):163-172. doi:10.1165/rcmb.2020-0373PS

31. Hunninghake GM, Quesada-Arias LD, Carmichael NE, et al. Interstitial lung disease in relatives of patients with pulmonary fibrosis. *Am J Respir Crit Care Med*. 2020;201(10):1240-1248. doi:10.1164/rccm.201908-1571OC

32. Allen RJ, Guillen-Guio B, Oldham JM, et al. Genome-wide association study of susceptibility to idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2020;201(5):564-574. doi:10.1164/rccm.201905-1017OC

33. Fingerlin TE, Murphy E, Zhang W, et al. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. *Nat Genet*. 2013;45(6):613-620. doi:10.1038/ng.2609

34. Barnes H, Troy L, Lee CT, Sperling A, Strek M, Glaspole I. Hypersensitivity pneumonitis: current concepts in pathogenesis, diagnosis, and treatment. *Allergy*. 2022;77(2):442-453. doi:10.1111/all.15017

35. Furusawa H, Peljto AL, Walts AD, et al. Common idiopathic pulmonary fibrosis risk variants are associated with hypersensitivity pneumonitis. *Thorax*. 2022;77(5):508-510. doi:10.1136/thoraxjnl-2021-217693

36. Kuwana M, Gil-Vila A, Selva-O'Callaghan A. Role of autoantibodies in the diagnosis and prognosis of interstitial lung disease in autoimmune rheumatic disorders. *Ther Adv Musculoskelet Dis*. Published online July 27, 2021. doi:10.1177/1759720X211032457

37. Juge PA, Lee JS, Ebstein E, et al. MUC5B promoter variant and rheumatoid arthritis with interstitial lung disease. *N Engl J Med*. 2018;379(23):2209-2219. doi:10.1056/NEJMoa1801562

38. Molyneaux PL, Maher TM. The role of infection in the pathogenesis of idiopathic pulmonary fibrosis. *Eur Respir Rev*. 2013;22(129):376-381. doi:10.1183/09059180.00000713

39. Skeoch S, Weatherley N, Swift AJ, et al. Drug-induced interstitial lung disease: a systematic review. *J Clin Med*. 2018;7(10):356. doi:10.3390/jcm7100356

40. Delaunay M, Cadranel J, Lusque A, et al. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. *Eur Respir J*. 2017;50(2):1700050. doi:10.1183/13993003.00050-2017

41. Okada N, Matsuoka R, Sakurada T, et al. Risk factors of immune checkpoint inhibitor-related interstitial lung disease in patients with lung cancer: a single-institution retrospective study. *Sci Rep*. 2020;10(1):13773. doi:10.1038/s41598-020-70743-2

42. Stewart I, Jacob J, George PM, et al. Residual lung abnormalities after COVID-19 hospitalization: interim analysis of the UKILD post-COVID-19 study. *Am J Respir Crit Care Med*. 2023;207(6):693-703. doi:10.1164/rccm.202203-0564OC

43. Roach A, Chikwe J, Catarino P, et al. Lung transplantation for COVID-19-related respiratory failure in the United States. *N Engl J Med*. 2022;386(12):1187-1188. doi:10.1056/NEJMc2117024

44. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology*. 2010;15(3):543-550. doi:10.1111/j.1440-1843.2010.01720.x

45. Zhang P, Li J, Liu H, et al. Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. *Bone Res*. 2020;8:8. doi:10.1038/s41413-020-0084-5

46. Saunders P, Wu Z, Fahy WA, et al. The burden and impact of cough in patients with idiopathic pulmonary fibrosis: an analysis of the prospective observational PROFILE study. *Ann Am Thorac Soc*.

2023;20(9):1267-1273. doi:10.1513/AnnalsATS.202302-174OC

47. Pugashetti J, Graham J, Boctor N, et al. Weight loss as a predictor of mortality in patients with interstitial lung disease. *Eur Respir J*. 2018;52(3):1801289. doi:10.1183/13993003.01289-2018

48. Kreuter M, Bendstrup E, Jouneau S, et al. Weight loss and outcomes in subjects with progressive pulmonary fibrosis: data from the INBUILD trial. *Respir Res*. 2023;24(1):71. doi:10.1186/s12931-023-02371-z

49. Hallowell RW, Paik JJ. Myositis-associated interstitial lung disease: a comprehensive approach to diagnosis and management. *Clin Exp Rheumatol*. 2022;40(2):373-383. doi:10.55563/clinexprheumatol/brvl1v

50. Gaubitz M. Epidemiology of connective tissue disorders. *Rheumatology (Oxford)*. 2006;45(suppl 3):iii3-iii4. doi:10.1093/rheumatology/kel282

51. van Manen MJG, Vermeer LC, Moor CC, et al. Clubbing in patients with fibrotic interstitial lung diseases. *Respir Med*. 2017;132:226-231. doi:10.1016/j.rmed.2017.10.021

52. Moran-Mendoza O, Ritchie T, Aldhaheri S. Fine crackles on chest auscultation in the early diagnosis of idiopathic pulmonary fibrosis: a prospective cohort study. *BMJ Open Respir Res*. 2021;8(1):e000815. doi:10.1136/bmjresp-2020-000815

53. Ghodrati S, Pugashetti JV, Kadoch MA, Ghasemiesfe A, Oldham JM. Diagnostic accuracy of chest radiography for detecting fibrotic interstitial lung disease. *Ann Am Thorac Soc*. 2022;19(11):1934-1937. doi:10.1513/AnnalsATS.202112-1377RL

54. Szturmowicz M, Garczewska B, Jędrych ME, et al. The value of serum precipitins against specific antigens in patients diagnosed with hypersensitivity pneumonitis - retrospective study. *Cent Eur J Immunol*. 2019;44(4):390-394. doi:10.5114/ceji.2019.92791

55. Flaherty KR, Travis WD, Colby TV, et al. Histopathologic variability in usual and nonspecific interstitial pneumonias. *Am J Respir Crit Care Med*. 2001;164(9):1722-1727. doi:10.1164/ajrccm.164.9.2103074

56. Flaherty KR, King TE Jr, Raghu G, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med*. 2004;170(8):904-910. doi:10.1164/rccm.200402-147OC

57. Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000 to 2011. *Am J Respir Crit Care Med*. 2016;193(10):1161-1167. doi:10.1164/rccm.201508-1632OC

58. Cottin V. Lung biopsy in interstitial lung disease: balancing the risk of surgery and diagnostic uncertainty. *Eur Respir J*. 2016;48(5):1274-1277. doi:10.1183/13993003.01633-2016

59. Troy LK, Grainge C, Corte TJ, et al; Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease alliance (COLDICE) Investigators. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med*. 2020;8(2):171-181. doi:10.1016/S2213-2600(19)30342-X

60. Kheir F, Uribe Becerra JP, Bissell B, et al. Transbronchial lung cryobiopsy in patients with interstitial lung disease: a systematic review. *Ann Am Thorac Soc*. 2022;19(7):1193-1202. doi:10.1513/AnnalsATS.202102-198OC

61. Ryerson CJ, Urbania TH, Richeldi L, et al. Prevalence and prognosis of unclassifiable interstitial lung disease. *Eur Respir J*. 2013;42(3):750-757. doi:10.1183/09031936.00131912

62. Maher TM, Stowasser S, Voss F, et al. Decline in forced vital capacity as a surrogate for mortality in patients with pulmonary fibrosis. *Respirology*. 2023;28(12):1147-1153. doi:10.1111/resp.14579

63. Goh NS, Hoyles RK, Denton CP, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol*. 2017;69(8):1670-1678. doi:10.1002/art.40130

64. Russell AM, Adamali H, Molyneaux PL, et al. Daily home spirometry: an effective tool for detecting progression in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2016;194(8):989-997. doi:10.1164/rccm.201511-2152OC

65. Zappala CJ, Latsi PI, Nicholson AG, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. *Eur Respir J*. 2010;35(4):830-836. doi:10.1183/09031936.00155108

66. Maher TM. Pirfenidone in idiopathic pulmonary fibrosis. *Drugs Today (Barc)*. 2010;46(7):473-482. doi:10.1358/dot.2010.46.7.1488336

67. King TE Jr, Bradford WZ, Castro-Bernardini S, et al; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2083-2092. doi:10.1056/NEJMoa1402582

68. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. *Eur Respir J*. 2016;47(1):243-253. doi:10.1183/13993003.00026-2015

69. Behr J, Prasse A, Kreuter M, et al; RELIEF investigators. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med*. 2021;9(5):476-486. doi:10.1016/S2213-2600(20)30554-3

70. Maher TM, Corte TJ, Fischer A, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med*. 2020;8(2):147-157. doi:10.1016/S2213-2600(19)30341-8

71. Solomon JJ, Danoff SK, Woodhead FA, et al; TRAIL1 Network Investigators. Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Respir Med*. 2023;11(1):87-96. doi:10.1016/S2213-2600(22)00260-0

72. Richeldi L, du Bois RM, Raghu G, et al; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2071-2082. doi:10.1056/NEJMoa1402584

73. Distler O, Highland KB, Gahlemann M, et al; SENSCIS Trial Investigators. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med*. 2019;380(26):2518-2528. doi:10.1056/NEJMoa1903076

74. Highland KB, Distler O, Kuwana M, et al; SENSCIS trial investigators. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. *Lancet Respir Med*. 2021;9(1):96-106. doi:10.1016/S2213-2600(20)30330-1

75. Wells AU, Flaherty KR, Brown KK, et al; INBUILD trial investigators. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med*. 2020;8(5):453-460. doi:10.1016/S2213-2600(20)30036-9

76. Lancaster L, Crestani B, Hernandez P, et al. Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials. *BMJ Open Respir Res*. 2019;6(1):e000397. doi:10.1136/bmjresp-2018-000397

77. Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. *Lancet*. 2016;387(10038):2630-2640. doi:10.1016/S0140-6736(16)00232-4

78. Khanna D, Lin CJF, Furst DE, et al; focuSSced investigators. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2020;8(10):963-974. doi:10.1016/S2213-2600(20)30318-0

79. Tashkin DP, Elashoff R, Clements PJ, et al; Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med*. 2006;354(25):2655-2666. doi:10.1056/NEJMoa055120

80. Tashkin DP, Roth MD, Clements PJ, et al; Sclerodema Lung Study II Investigators. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med*. 2016;4(9):708-719. doi:10.1016/S2213-2600(16)30152-7

81. Ebata S, Yoshizaki A, Oba K, et al. Safety and efficacy of rituximab in systemic sclerosis (DESIRES): a double-blind, investigator-initiated, randomised, placebo-controlled trial. *Lancet Rheumatol*. 2021;3(7):e489-e497. doi:10.1016/S2665-9913(21)00107-7

82. Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ; Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med*. 2012;366(21):1968-1977. doi:10.1056/NEJMoa1113354

83. Noth I, Anstrom KJ, Calvert SB, et al; Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet). A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2012;186(1):88-95. doi:10.1164/rccm.201202-0314OC

84. Daniels CE, Lasky JA, Limper AH, Mieras K, Gabor E, Schroeder DR; Imatinib-IPF Study Investigators. Imatinib treatment for idiopathic pulmonary fibrosis: randomized placebo-controlled

trial results. *Am J Respir Crit Care Med*. 2010;181(6):604-610. doi:10.1164/rccm.200906-0964OC

85. King TE Jr, Albera C, Bradford WZ, et al; INSPIRE Study Group. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2009;374(9685):222-228. doi:10.1016/S0140-6736(09)60551-1

86. Maher TM, Costabel U, Glassberg MK, et al. Phase 2 trial to assess lebrikizumab in patients with idiopathic pulmonary fibrosis. *Eur Respir J*. 2021;57(2):1902442. doi:10.1183/13993003.02442-2019

87. Maher TM, Ford P, Brown KK, et al; ISABELA 1 and 2 Investigators. Ziritaxestat, a novel autotaxin inhibitor, and lung function in idiopathic pulmonary fibrosis: the ISABELA 1 and 2 randomized clinical trials. *JAMA*. 2023;329(18):1567-1578. doi:10.1001/jama.2023.5355

88. Wilson AM, Clark AB, Cahn T, et al; EME-TIPAC team. Effect of co-trimoxazole (trimethoprim-sulfamethoxazole) vs placebo on death, lung transplant, or hospital admission in patients with moderate and severe idiopathic pulmonary fibrosis: the EME-TIPAC randomized clinical trial. *JAMA*. 2020;324(22):2282-2291. doi:10.1001/jama.2020.22960

89. Martinez FJ, Yow E, Flaherty KR, et al; CleanUP-IPF Investigators of the Pulmonary Trials Cooperative. Effect of antimicrobial therapy on respiratory hospitalization or death in adults with idiopathic pulmonary fibrosis: the CleanUP-IPF randomized clinical trial. *JAMA*. 2021;325(18):1841-1851. doi:10.1001/jama.2021.4956

90. Maher TM, Tudor VA, Saunders P, et al; RECITAL Investigators. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. *Lancet Respir Med*. 2023;11(1):45-54. doi:10.1016/S2213-2600(22)00359-9

91. Raghu G, Remy-Jardin M, Ryerson CJ, et al. Diagnosis of hypersensitivity pneumonitis in adults: an official ATS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2020;202(3):e36-e69. doi:10.1164/rccm.202005-2032ST

92. Curtis JR, Sarsour K, Napalkov P, Costa LA, Schulman KL. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor α agents, a retrospective cohort study. *Arthritis Res Ther*. 2015;17:319. doi:10.1186/s13075-015-0835-7

93. Baker MC, Liu Y, Lu R, Lin J, Melehani J, Robinson WH. Incidence of interstitial lung disease in patients with rheumatoid arthritis treated with biologic and targeted synthetic disease-modifying antirheumatic drugs. *JAMA Netw Open*. 2023;6(3):e233640. doi:10.1001/jamanetworkopen.2023.3640

94. Valapour M, Lehr CJ, Skeans MA, et al. OPTN/SRTR 2018 annual data report: lung. *Am J Transplant*. 2020;20(suppl s1):427-508. doi:10.1111/ajt.15677

95. Bos S, Vos R, Van Raemdonck DE, Verleden GM. Survival in adult lung transplantation: where are we in 2020? *Curr Opin Organ Transplant*. 2020;25(3):268-273. doi:10.1097/MOT.0000000000000753

96. Chambers DC, Cherikh WS, Harhay MO, et al; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult lung and heart-lung transplantation Report-2019; Focus theme: Donor and recipient size match. *J Heart Lung Transplant*. 2019;38(10):1042-1055. doi:10.1016/j.healun.2019.08.001

97. Corte TJ, Keir GJ, Dimopoulos K, et al; BPHIT Study Group. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *Am J Respir Crit Care Med*. 2014;190(2):208-217. doi:10.1164/rccm.201403-0446OC

98. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW; Idiopathic Pulmonary Fibrosis Clinical Research Network. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med*. 2010;363(7):620-628. doi:10.1056/NEJMoa1002110

99. Behr J, Kolb M, Song JW, et al. Nintedanib and sildenafil in patients with idiopathic pulmonary fibrosis and right heart dysfunction. a prespecified subgroup analysis of a double-blind randomized clinical trial (INSTAGE). *Am J Respir Crit Care Med*. 2019;200(12):1505-1512. doi:10.1164/rccm.201903-0488OC

100. Behr J, Nathan SD, Wuyts WA, et al. Efficacy and safety of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med*. 2021;9(1):85-95. doi:10.1016/S2213-2600(20)30356-8

101. Nathan SD, Behr J, Collard HR, et al. Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study. *Lancet Respir Med*. 2019;7(9):780-790. doi:10.1016/S2213-2600(19)30250-4

102. Dowman L, Hill CJ, May A, Holland AE. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev*. 2021;2(2):CD006322.

103. Visca D, Mori L, Tsipouri V, et al. Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial. *Lancet Respir Med*. 2018;6(10):759-770. doi:10.1016/S2213-2600(18)30289-3

104. Wu Z, Smith DJF, Yazbeck L, et al. Cough severity visual analogue scale assesses cough burden and predicts survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2024. doi:10.1164/rccm.202311-2169LE

105. Hui D, Bruera E. Use of short-acting opioids in the management of breathlessness: an evidence-based review. *Curr Opin Support Palliat Care*. 2020;14(3):167-176. doi:10.1097/SPC.0000000000000509

106. Maher TM, Avram C, Bortey E, et al. Nalbuphine tablets for cough in patients with idiopathic pulmonary fibrosis. *NEJM Evid*. 2023;2(8):a2300083. doi:10.1056/EVIDoa2300083

107. Wu Z, Spencer LG, Banya W, et al. Morphine for treatment of cough in idiopathic pulmonary fibrosis (PACIFY COUGH): a prospective, multicentre, randomised, double-blind, placebo-controlled, two-way crossover trial. *Lancet Respir Med*. 2024;S2213-2600(23)00432-0. doi:10.1016/S2213-2600(23)00432-0

108. Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. *Am J Respir Crit Care Med*. 2007;175(4):312-315. doi:10.1164/rccm.200607-892OC

109. Luckett T, Phillips J, Johnson MJ, et al. Contributions of a hand-held fan to self-management of chronic breathlessness. *Eur Respir J*. 2017;50(2):1700262. doi:10.1183/13993003.00262-2017

110. Raghu G, Montesi SB, Silver RM, et al. Treatment of systemic sclerosis-associated interstitial lung disease: evidence-based recommendations: an official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2023.

111. Humbert M, Kovacs G, Hoeper MM, et al; ESC/ERS Scientific Document Group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2023;61(1):2200879. doi:10.1183/13993003.00879-2022

112. Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: an update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2021;40(11):1349-1379. doi:10.1016/j.healun.2021.07.005

113. Paterniti MO, Bi Y, Rekić D, Wang Y, Karimi-Shah BA, Chowdhury BA. Acute exacerbation and decline in forced vital capacity are associated with increased mortality in idiopathic pulmonary fibrosis. *Ann Am Thorac Soc*. 2017;14(9):1395-1402. doi:10.1513/AnnalsATS.201606-458OC

114. Fisher M, Nathan SD, Hill C, et al. Predicting life expectancy for pirfenidone in idiopathic pulmonary fibrosis. *J Manag Care Spec Pharm*. 2017;23(3-b)(suppl):S17-S24. doi:10.18553/jmcp.2017.23.3-b.s17

115. Jo HE, Glaspole I, Grainge C, et al. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. *Eur Respir J*. 2017;49(2):1601592. doi:10.1183/13993003.01592-2016

116. Dempsey TM, Thao V, Helfinstine DA Jr, Chang YH, Sangaralingham L, Limper AH. Real-world cohort evaluation of the impact of the antifibrotics in patients with idiopathic pulmonary fibrosis. *Eur Respir J*. 2023;62(4):2301299. doi:10.1183/13993003.01299-2023