Interstitial lung diseases

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Over 200 interstitial lung diseases, from ultra rare to relatively common, are recognised. Most interstitial lung diseases are characterised by inflammation or fibrosis within the interstitial space, the primary consequence of which is impaired gas exchange, resulting in breathlessness, diminished exercise tolerance, and decreased quality of life. Outcomes vary considerably for each of the different interstitial lung diseases. In some conditions, spontaneous reversibility or stabilisation can occur, but unfortunately in many people with interstitial lung disease, especially in those manifesting progressive pulmonary fibrosis, respiratory failure and death are a sad reality. Over the past 3 years, the field of interstitial lung disease has had important advances, with the approval of drugs to treat systemic sclerosis-associated interstitial lung disease, interstitial lung disease-associated pulmonary hypertension, and different forms of progressive pulmonary fibrosis. This Seminar provides an update on epidemiology, pathogenesis, presentation, diagnosis, disease course, and management of the interstitial lung diseases that are most frequently encountered in clinical practice. Furthermore, we describe how developments have led to a shift in the classification and treatment of interstitial lung diseases that exhibit progressive pulmonary fibrosis and summarise the latest practice-changing guidelines. We conclude with an outline of controversies, uncertainties, and future directions.

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Introduction

Interstitial lung disease is an umbrella term encompassing a broad spectrum of disorders, most, but not all, of which primarily affect the pulmonary interstitium.[1,2] Bounded on one side by the alveolar epithelium and on the other by the capillary endothelium, the interstitial space contains lymphatic vessels, occasional fibroblasts, and extracellular matrix proteins, such as collagen. In healthy people, the interstitium provides structural support to the alveolus but is only a few micrometres thick, thereby facilitating efficient gas exchange. Interstitial lung diseases are characterised by inflammation or fibrosis within the interstitial space, the primary consequence of which is impaired gas exchange, thus giving rise to breathlessness and, in many cases, respiratory failure and death.

It is estimated that more than 200 separate disorders can give rise to interstitial lung disease. These disorders range from ultra-rare disorders, such as lymphangioleiomyomatosis, to multisystem conditions, including systemic sclerosis or rheumatoid arthritis, where interstitial lung disease is a frequent disease manifestation, to more common diseases, such as idiopathic pulmonary fibrosis (responsible for 1% of all deaths in the UK).[3–8] Confusingly, some conditions that are characterised by alveolar filling rather than interstitial involvement (eg, pulmonary alveolar proteinosis) are included in the classification of interstitial lung disease, primarily because of overlapping clinical and radiological manifestations.[1,9]

The most common form of fibrotic interstitial lung disease, idiopathic pulmonary fibrosis, carries a poor prognosis with a median untreated life expectancy from diagnosis of 3–5 years.[6] However, other interstitial lung diseases, especially those that are characterised primarily by inflammation, such as non-fibrotic hypersensitivity pneumonitis and many forms of sarcoidosis, have good outcomes and usually respond well to therapy.[10–13] Over the past decade there have been considerable developments in understanding the pathogenesis of several of the interstitial lung diseases, resulting in notable advances in therapy and improvements in clinical outcome. These therapeutic advances have, in turn, driven a shift in the characterisation and treatment of the subset of interstitial lung diseases that have the potential to cause progressive pulmonary fibrosis. This Seminar provides an update on the interstitial lung diseases that are most often encountered in clinical practice, with a particular focus on epidemiology, pathogenesis, clinical presentation, diagnosis, and advances in therapy.

Classification and epidemiology of interstitial lung disease

Interstitial lung diseases can be broadly categorised into idiopathic, autoimmune-related, exposure-related (including iatrogenic), interstitial lung diseases with cysts or airspace filling, sarcoidosis, and orphan diseases (figure 1). Within these respective categories, onset of disease can vary from insidious to acute and

Search strategy and selection criteria

We searched the medical literature using MEDLINE and Embase for articles published between Oct 1, 2010, and Dec 31, 2021, with the medical subject heading terms "interstitial lung diseases " OR "interstitial pneumonia" OR "lung fibrosis" to identify pertinent articles. We included only publications published in English and selected those with findings that were, in our view, of the greatest importance, favouring randomised controlled trials, meta-analyses, systematic reviews, guidelines, consensus documents, and high-quality comprehensive reviews in view of the limit on the number of references. We predominantly selected publications from the past 3 years, but also included highly regarded older publications. We also included relevant publications that were identified via reference lists of articles that were identified by the search strategy or were otherwise identified by the authors. Further details on the search strategy can be found in the appendix (p 9).

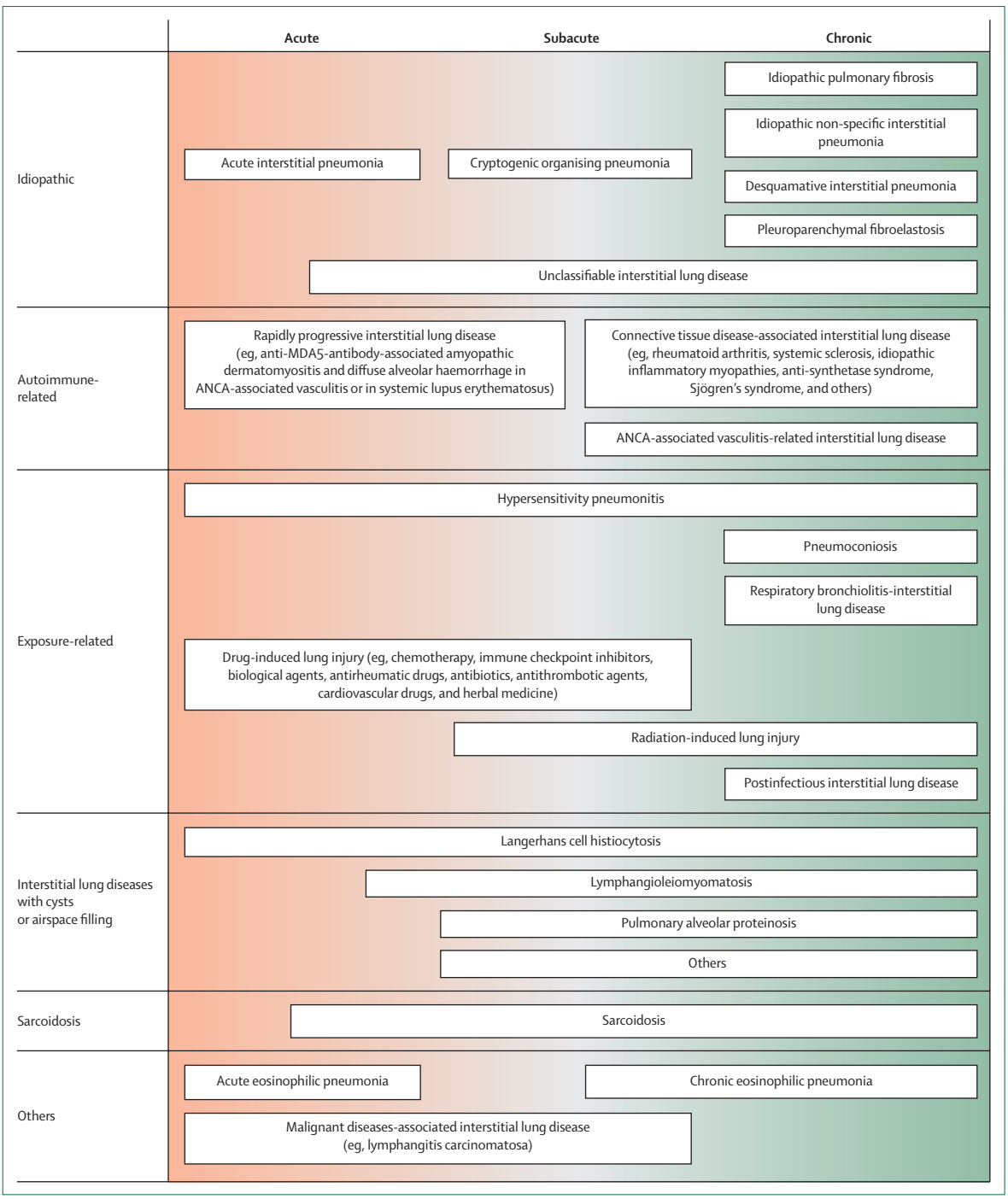


Figure 1: **Classification of interstitial lung diseases**
Interstitial lung disease can be broadly subgrouped into idiopathic, autoimmune-related, caused by external agents (eg, exposure or treatments, such as drugs or radiation), interstitial lung diseases with cysts or airspace filling, sarcoidosis, and orphan disorders. ANCA=anti-neutrophil cytoplasmic antibody.

life-threatening.[1] Diagnosis and classification are based on a combination of clinical, radiological, and sometimes pathological information. Idiopathic and secondary interstitial lung diseases share similar radiological–histopathological patterns, with the most frequently encountered patterns being usual interstitial pneumonia, non-specific interstitial pneumonia, and organising pneumonia (figure 2).[1,14] For example, a usual interstitial pneumonia pattern is a prerequisite to a diagnosis of idiopathic pulmonary fibrosis but is also

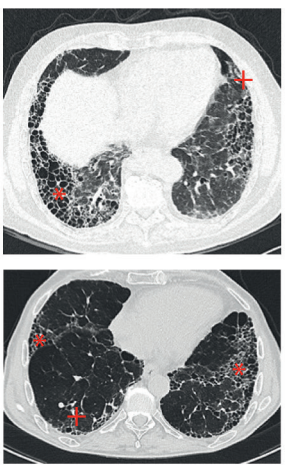
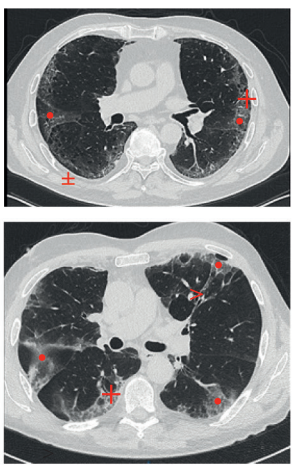
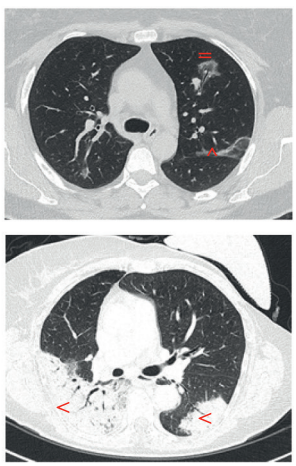
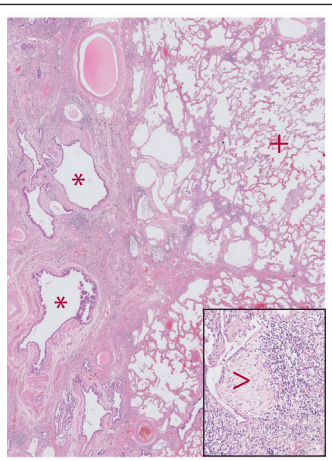
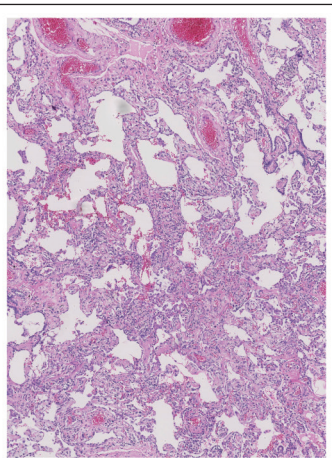
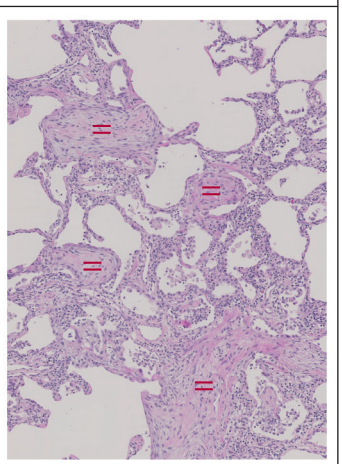
	Usual interstitial pneumonia	Non-specific interstitial pneumonia	Organising pneumonia
Typical image	 Honeycombing (*) with or without peripheral traction bronchiectasis (+), in a subpleural and basal predominant, often heterogeneous, distribution.	 Ground-glass opacities (•) with traction bronchiectasis (+), often peribronchovascular (>) predominance with subpleural sparing (±).	 Peripheral consolidation with air bronchograms (<), bronchocentric distribution, a perilobular pattern, reversed halo sign (=), and band-like consolidations (^) can also be seen.
Typical pathology	 Marked fibrosis, architectural distortion with or without honeycombing (*) in predominant subpleural or paraseptal distribution, presence of patchy involvement, and areas of preserved normal lung tissue (+). Presence of fibroblast foci (>) and absence of features suggesting an alternate diagnosis.	 Diffuse alveolar wall thickening by uniform fibrosis (pale pink) with preservation of the alveolar architecture and mild interstitial inflammation (purple).	 Patchy distribution, filling of the distal airways, and adjacent alveoli with fibromyxoid plugs (=) of granulation tissue with temporal uniformity. Relative preservation of the underlying pulmonary architecture. Mild to moderate interstitial inflammation can be present.
Seen in	Often: Idiopathic pulmonary fibrosis or rheumatoid arthritis-associated interstitial lung disease. Sometimes: Fibrotic hypersensitivity pneumonitis, systemic sclerosis-associated interstitial lung disease, sarcoidosis, or asbestosis.	Often: Connective tissue disease-associated interstitial lung disease especially systemic sclerosis-associated interstitial lung disease, exposure-related and treatment-related interstitial lung diseases, or idiopathic non-specific interstitial pneumonia. Sometimes: Hypersensitivity pneumonitis.	Often: Cryptogenic organising pneumonia, exposure-related and treatment-related interstitial lung disease, connective tissue disease-associated interstitial lung disease especially dermatomyositis-associated interstitial lung disease. Sometimes: Hypersensitivity pneumonitis, vasculitis, or as an epiphenomenon associated with malignancy.

Figure 2: **Most seen interstitial lung disease patterns**
The three most seen patterns in interstitial lung disease with examples of chest high-resolution CT and histological appearance and examples of diseases that often manifest these patterns.

seen in some individuals with rheumatoid arthritis-associated interstitial lung disease and some with fibrotic hypersensitivity pneumonitis (figure 2). A non-specific interstitial pneumonia pattern is most often seen in people with systemic sclerosis-associated interstitial lung disease and drug-induced interstitial

lung disease but, if no cause can be identified, is defined as idiopathic non-specific interstitial pneumonia. Integration of the clinical, radiological, and pathological information by multidisciplinary discussion is recommended to increase diagnostic confidence.[15] It should, however, be recognised that in 15–20% of people with fibrotic interstitial lung disease, classification according to current diagnostic criteria cannot be achieved, even following extensive investigation and multidisciplinary discussion. To avoid therapeutic nihilism, this group has been labelled in current disease guidelines as unclassifiable interstitial lung disease.[1]

Available epidemiological data show a wide variation in the incidence of interstitial lung diseases across age, gender, ethnicity, and geographical regions. Idiopathic pulmonary fibrosis is associated with older age (ie, >60 years) and male sex, with incidence estimates ranging from 0·9–9·3 cases per 100 000 people per year in Europe and North America to 3·5–13·0 cases per 100 000 people per year in Asia and South America.[16–18] In contrast to idiopathic pulmonary fibrosis, more than 50% of cases of idiopathic non-specific interstitial pneumonia and connective tissue disease-associated interstitial lung disease occur in middle-aged (ie, aged 40–60 years) or older-aged women.[19–21] Few studies have reported the incidence of other interstitial lung diseases. Most of the available estimates suggest that other interstitial lung diseases are individually less common than is idiopathic pulmonary fibrosis (ie, 0·8 cases per 100 000 people per year of idiopathic non-specific interstitial pneumonia, 2·7–4·3 cases per 100 000 people per year of connective tissue disease-associated interstitial lung diseases, 0·6–1·1 cases per 100 000 people per year of fibrotic hypersensitivity pneumonitis, and 4·9 cases per 100 000 people per year of sarcoidosis with interstitial lung disease).[17,20–22] The overall prevalence for interstitial lung disease is estimated at 6·3–76·0 cases per 100 000 people.[23] The interpretation of epidemiological data relating to interstitial lung disease is complicated by limitations in disease coding (with codes often mapping poorly to distinct disease entities), differences in study methods, and varying access to health care and use of electronic health records between territories.

Pathogenesis

Of all the internal organs, the lungs are uniquely exposed to the external environment. Adults inhale approximately 8000 L of air per day, which in turn interacts with an alveolar surface area of 75 m². Ambient air contains myriad microparticles, including pollutants, micro-organisms, and oxidants, all of which are capable of causing direct injury to the delicate structure of the alveolar epithelium. Consequently, the lung is protected by key components of both the innate and adaptive immune systems. The epithelial surface of the lung provides a physical barrier and has a pathogen-sensing capacity. Injury to the alveolar epithelium or dysregulation of the highly adapted lung immune response can result in a wide range of disorders. Most interstitial lung diseases are characterised by either inflammation or fibrosis, or a combination of these two mechanisms with initial inflammation progressing to fibrosis (figure 3). Several ultra-rare interstitial lung diseases have distinct disease mechanisms that are characterised by unique disease phenotypes. These varying mechanisms are important because they might foretell prognosis and inform choice of pharmacotherapy.

Inflammation

Inflammation in interstitial lung disease can be related to several causes, with the most common being autoimmune disease. In the best understood of the autoimmune diseases, rheumatoid arthritis, it is recognised that in genetically susceptible individuals, abnormal citrullination (ie, replacement of the amino acid arginine with citrulline) of structural cell proteins predisposes to the development of a range of autoantibodies through activation of the adaptive immune system.[24,25] The presence of autoantibodies, in turn, activates specialised macrophages and stromal cells, resulting in the release of a range of cytokines, including TNF, interleukin (IL)-1, IL-6, and prostaglandins. It is unclear whether interstitial lung disease arises in people with rheumatoid arthritis due to direct antibody-mediated injury of resident lung cells or through the paracrine effects of circulating cytokines and growth factors.[26] Other autoimmune diseases, such as systemic sclerosis and the idiopathic inflammatory myopathies, share similarities with the pathogenesis of rheumatoid arthritis but are characterised by a different repertoire of autoantibodies.[27] Notably, in people with systemic sclerosis and people with idiopathic inflammatory myopathies, the likelihood of interstitial lung disease occurring and the pattern in which it occurs (ie, organising pneumonia *vs* non-specific interstitial pneumonia *vs* usual interstitial pneumonia) are influenced by the presence of specific autoantibodies, suggesting that direct antibody-mediated injury is an important driver of the development of interstitial inflammation and subsequent fibrosis.[28]

The other common manifestation in people with inflammatory interstitial lung disease is granuloma formation.[29] Granulomata are formed by tightly aggregated macrophages, which often fuse to form large multinucleate cells.[30] Non-caseating granulomatous inflammation is the cardinal feature of the multisystem disorder, sarcoidosis, with over 90% of individuals having pulmonary involvement. The typical sarcoid granuloma contains $CD4^+$ T-helper cells and is surrounded by tightly packed regulatory T cells, fibroblasts, and B cells, suggesting that innate and adaptive immune activation contributes to development of the disease.[31]

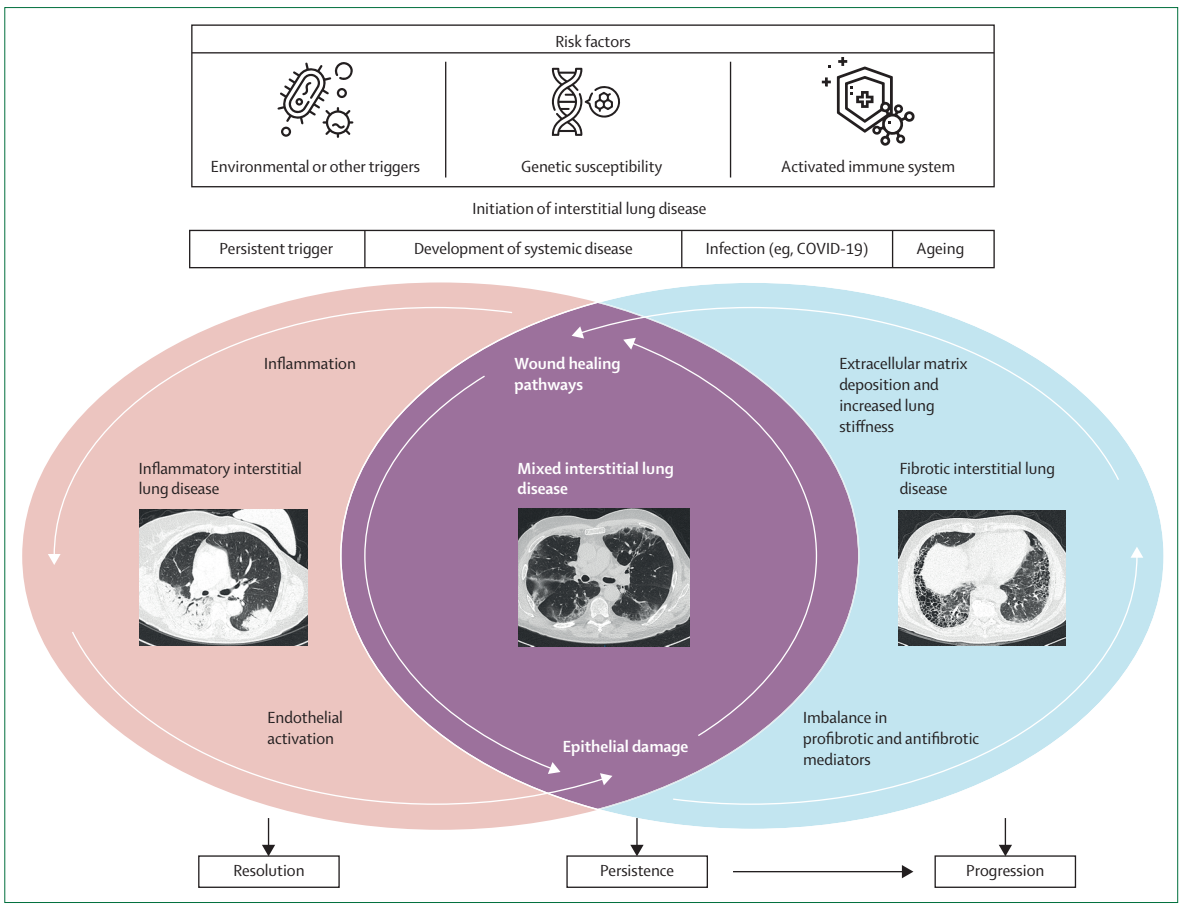


Figure 3: **Pathogenesis of interstitial lung diseases**
A schematic overview of the pathogenesis of a large group of interstitial lung diseases that are characterised by inflammation, fibrosis, or a combination of these two mechanisms, with initial inflammation having the potential to progress to fibrosis.

Hypersensitivity pneumonitis, a complex syndrome arising from repeated exposure to a wide range of potential antigens, is also characterised by granulomatous inflammation. The most common triggers include avian and fungal proteins. The non-fibrotic form of the disease is mediated by immune complex formation. The fibrotic form is characterised by alveolar and dendritic cells presenting antigens to T lymphocytes, which skew towards a T-helper-1 phenotype through polarisation by cytokines, such as IL-12 and IFN-γ.[10,32]

Fibrosis

The pathogenesis of pulmonary fibrosis is best understood in the context of idiopathic pulmonary fibrosis. In individuals with idiopathic pulmonary fibrosis, the development of fibrosis appears to hinge on a triad of factors: a lifetime of excessive epithelial damage due to exposure to inhaled injurious agents, ageing, and genetic susceptibility.[33] The combined effect of these events is to cause premature senescence of alveolar epithelial stem cells, resulting in an aberrant wound-healing response following subsequent epithelial injury.[34] Epithelial senescence results in a failure of proliferation and repopulation of the alveolar epithelium following injury with consequent denudation of the basement membrane.[35] Subsequently, a cascade of pathways involved in the normal wound-healing process is triggered, resulting in an imbalance of profibrotic and antifibrotic growth factors. These growth factors activate multiple cell types, including macrophages, epithelium, fibroblasts, and endothelium, resulting in the unopposed production of collagen and extracellular matrix.[36,37] The net effect of these changes is progressive architectural disruption of alveolar airspaces with consequent loss of surface area for gas exchange and aberrant remodelling of the pulmonary vasculature, favouring the development of secondary pulmonary hypertension. Changes to the composition of the extracellular matrix and increasing stiffness of the lung lead to further progression of fibrosis, suggesting that at a particular point of severity, pulmonary fibrosis can become self-perpetuating irrespective of the initial trigger (figure 3).[38,39]

The pathogenic mechanisms controlling the development of fibrosis are less studied in other forms of

	Common clinical findings	Serologic autoantibodies	Radiological and histopathological patterns
Systemic sclerosis	Raynaud's phenomenon, skin thickening, sclerodactyly, ulceration, calcinosis, telangiectasia, microstomia, xerostomia, and esophageal dilation	Anti-topoisomerase I (Scl-70), anti-Th/To, and anti-RNA polymerase III	Non-specific interstitial pneumonia and usual interstitial pneumonia
Rheumatoid arthritis	Inflammatory arthritis and polyarticular morning stiffness	Rheumatoid factor and anti-cyclic citrullinated peptide	Usual interstitial pneumonia, non-specific interstitial pneumonia, and organising pneumonia
Idiopathic inflammatory myositis	Gottron's sign, mechanic hands, shawl sign, and muscle weakness	Anti-aminoacyl tRNA synthetase (eg, Jo-1, PL-7, PL-12) and anti-MDA5	Non-specific interstitial pneumonia, organising pneumonia, diffuse alveolar damage, usual interstitial pneumonia
Sjögren's syndrome	Ocular or oral dryness, salivary gland swelling, and inflammatory arthritis	Anti-Sjögren-syndrome-related antigen A autoantibodies (anti-Ro)	Non-specific interstitial pneumonia, lymphocytic interstitial pneumonitis, organising pneumonia, usual interstitial pneumonia

In people with interstitial lung disease, different extrapulmonary features and serologic autoantibodies can provide clues to specific underlying connective tissue disease.

Table: **Main connective tissue diseases that can manifest interstitial lung disease**

fibrotic interstitial lung disease. However, although the proximate cause for onset of fibrosis might differ (ie, autoimmune injury of the alveolus *vs* environmental exposure), according to available evidence, the downstream pathways driving fibrogenesis overlap and might well be identical.[2]

Genetic associations with interstitial lung disease

It is recognised that many interstitial lung diseases have the potential to be familial. Furthermore, it has been shown in several family pedigrees that individual members of the same family can develop different forms of fibrotic interstitial lung disease.[40] Genetic studies performed in people with idiopathic pulmonary fibrosis and replicated in people with other fibrotic interstitial lung diseases have identified multiple single nucleotide polymorphisms that are associated with progressive fibrosis.[41–43] These single nucleotide polymorphisms range from rare polymorphisms conferring a high risk for development of pulmonary fibrosis to common polymorphisms with a much lower attributable risk (appendix p 1). Important pathways that are affected by these polymorphisms include those that are related to telomere length, surfactant biogenesis, cellular mitogenesis, and host defence.

See Online for appendix

Genes located within the MHC region coding a range of class II HLAs have been associated with the development of hypersensitivity pneumonitis and sarcoidosis.[44] Interestingly, in people with hypersensitivity pneumonitis and people with rheumatoid disease, the genetic determinants of the underlying inflammatory disease are independent from those that predict the development of pulmonary fibrosis, with the genes that are related to development of pulmonary fibrosis appearing to be the same as the risk alleles for development of idiopathic pulmonary fibrosis.[45,46]

Other mechanisms of interstitial lung disease pathogenesis

Orphan interstitial lung diseases tend to have distinct disease phenotypes. Insights derived from understanding the pathogenesis of these disorders have resulted in important treatment advances.

Lymphangioleiomyomatosis, a cystic lung disease affecting women, has been recognised to arise due to constitutive activation of mTOR signalling in smooth muscle cells expressing human melanoma black-45 (ie, lymphangioleiomyomatosis cells [also known as LAM cells]).[3] mTOR inhibitors have transformed outcomes for women with lymphangioleiomyomatosis.

Pulmonary alveolar proteinosis, an alveolar filling disease that is characterised by accumulation of lipid-laden macrophages, results from a failure of GM-CSF signalling to macrophages. This failure occurs either due to genetically driven loss of function of GM-CSF receptors or, more commonly, the occurrence of anti-GM-CSF antibodies. Treatment with GM-CSF replacement via nebulisation reduces disease-associated morbidity.[47]

Langerhans cell histiocytosis, a cystic lung disease that is caused by proliferation of a subset of dendritic cells, has been linked to somatic mutations in the *BRAF* and *MAPK* genes. This link has raised the possibility that treatment of individuals carrying these mutations with specific *BRAF* or *MAPK* inhibitors might be effective.[48]

Clinical presentation and diagnosis

The clinical presentation of interstitial lung diseases is non-specific. The most common symptoms are dyspnea, cough, and fatigue.[49–51] Some people might be symptomatic for many months or even years before diagnosis.[52,53] On physical examination, bibasilar Velcro-like crackles are heard in 60–79% of people with interstitial lung diseases.[49] Clubbing is common, but is also seen in other lung or heart diseases.[16,49] Extrapulmonary symptoms point to the possibility of interstitial lung disease being part of a systemic disorder. Early greying, signs of bone marrow failure, or liver cirrhosis can point towards telomeropathies and familial forms of interstitial lung disease. Skin, hand, joint, or muscle abnormalities can be an indication of an underlying connective tissue disease (table).[54] In the

assessment of individuals with confirmed connective tissue disease, there should be a high level of clinical suspicion for interstitial lung disease.[55] Early, asymptomatic interstitial lung diseases might be detected incidentally on CT or chest radiographs performed for other indications.[56]

A multidimensional approach is required to diagnose interstitial lung diseases, integrating clinical, radiological, physiological, and sometimes histological findings (figure 4). Carefully taking a clinical history and conducting a thorough examination are important first steps to confirm the presence of interstitial lung disease and to provide pointers towards diagnosis. Domiciliary or work-based exposure to organic antigens (eg, from birds or moulds), pneumotoxic drugs (eg, bleomycin, amiodarone, or nitrofurantoin), or dusts known to induce pneumoconiosis (eg, asbestos, silica, or coal dust) all point towards possible external causes for interstitial lung disease.[57] Testing pulmonary function often shows a restrictive pattern and reduced diffusion capacity, although normal lung function or an obstructive pattern can occasionally be seen. The identification of serum autoantibodies can facilitate diagnosis of underlying connective tissue disease.[54,58] Importantly, specific serological autoantibodies are associated with the occurrence and clinical course of interstitial lung diseases in people with connective tissue disease (table).[58] Chest x-ray can show signs of interstitial lung disease; however, subtle changes might be missed. High-resolution CT (HRCT) of the chest is the key diagnostic test in individuals with suspected interstitial lung disease. In more than two-thirds of people with interstitial lung disease, HRCT pattern, when combined with clinical findings, is sufficient to enable a diagnosis to be made (appendix pp 2–6).

The cellular analysis of bronchoalveolar lavage fluid can be useful when particular non-idiopathic pulmonary fibrosis interstitial lung diseases are suspected. Lymphocytosis on bronchoalveolar lavage is an important feature of hypersensitivity pneumonitis.[10,59] Eosinophilia on bronchoalveolar lavage supports the diagnosis of eosinophilic pneumonia or drug-induced lung injury.[59] Other bronchoalveolar lavage findings can be helpful in making specific diagnoses, such as pulmonary alveolar proteinosis or Langerhans cell histiocytosis, and in excluding infection and malignancy.[59]

In people for whom clinical, radiological, and bronchoscopic information fail to confirm a specific diagnosis following multidisciplinary discussion, histopathological assessment should be considered. Surgical lung biopsy, usually performed through video-assisted thoracic surgery, is the gold standard for identifying histopathological patterns of interstitial lung disease. However, the procedure carries important risks for postoperative complications, with a 30-day postprocedure mortality rate of 1·5–2·4%.[60,61] Surgical lung biopsy is, therefore, not always an appropriate procedure for patients to undergo; the risks and benefits of obtaining samples for histological assessment should be discussed both in the multidisciplinary discussion and with the patient. Transbronchial lung cryobiopsy has been developed as a less invasive method than surgical lung biopsy for obtaining biopsy samples in individuals with interstitial lung disease. Studies comparing transbronchial lung cryobiopsy with surgical lung biopsy suggest a lower incidence of complications but a similar level of diagnostic accuracy when histological findings are incorporated into the multidisciplinary discussion; thus, in centres with appropriate bronchoscopic and pathological expertise, transbronchial lung cryobiopsy represents a good alternative to surgical biopsy.[62–64] It is important to recognise that, given the overlap of

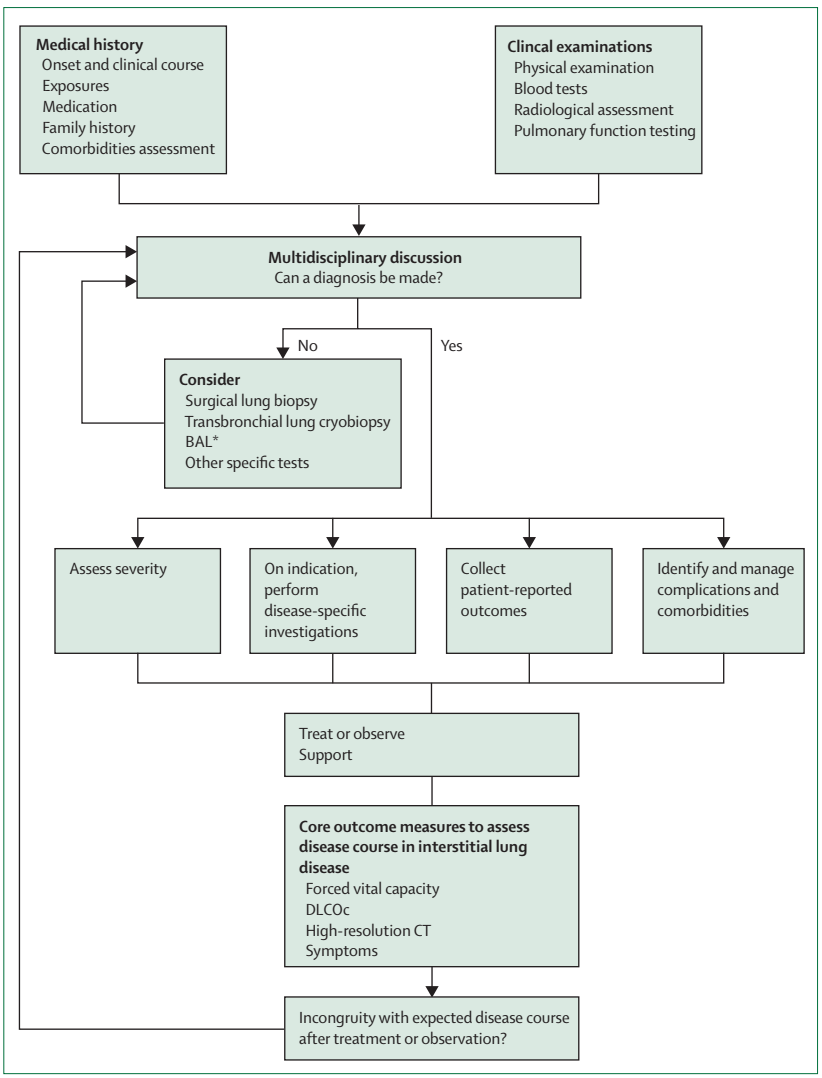


Figure 4: **Simplified interstitial lung disease diagnostic algorithm**
Multidisciplinary discussion is key to diagnosis. Lung function, often combined with symptoms and imaging, is the basis for assessing disease progression. BAL=bronchoalveolar lavage. DLCOc=diffusing capacity of the lung for carbon monoxide corrected for haemoglobin. *Alternatively BAL can be performed before multidisciplinary discussion.

histopathological lesions across interstitial lung diseases, biopsy is not in itself the diagnostic gold standard but should be integrated into multidisciplinary discussion of the diagnosis.[65]

Following diagnosis, evaluation of disease severity is important in predicting prognosis and determining treatment strategy. Various intrapulmonary or extrapulmonary comorbidities can affect clinical course and health-related quality of life in people with interstitial lung disease; the most common of these are pulmonary hypertension, lung cancer, gastro-oesophageal reflux disease, obstructive sleep apnoea, and cardiovascular disease.[66] Echocardiography and specific questionnaires can assist in the detection of pulmonary hypertension, gastro-oesophageal reflux disease, and obstructive sleep apnoea. Although no evidence-based guidance exists for the screening and management of these comorbidities in people with interstitial lung disease, early identification might improve clinical course and survival.[67]

Screening for interstitial lung disease

No guidelines exist on screening people who are at increased risk for interstitial lung disease. In people with systemic sclerosis, screening with HRCT is recommended in view of the high prevalence of interstitial lung disease.[68] In people with other connective tissue diseases, there is no consensus on when and which tests are suitable for screening, but physicians should maintain a high level of suspicion for interstitial lung disease when assessing these individuals.[55] Routinely asking about shortness of breath, cough, and exercise limitation and performing auscultation of the chest to detect crepitations should guide the decision to further assess for interstitial lung disease with HRCT and pulmonary function testing. In familial interstitial lung diseases, referral for genetic counselling and potential screening is generally offered to first-degree relatives of patients.[42,69,70]

Panel: Criteria for progressive pulmonary fibrosis* as defined in the 2022 guideline on progressive pulmonary fibrosis in adults

"In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation":[84]

- worsening of respiratory symptoms
- an absolute decline in forced vital capacity of at least 5% or an absolute decline in diffusing capacity for carbon monoxide (corrected for haemoglobin) of at least 10%
- radiological evidence of disease progression on high-resolution CT

ILD=interstitial lung disease. IPF=idiopathic pulmonary fibrosis. PPF=progressive pulmonary fibrosis. *Progressive pulmonary fibrosis is not a diagnosis but rather a disease behaviour definition that is associated with prognosis.

An increasing number of therapeutic agents, including chemotherapy, immune-checkpoint inhibitors, and biological agents, are associated with drug-induced lung injuries. When prescribing drugs at high risk of causing interstitial lung disease, pretreatment screening for interstitial lung disease with imaging is recommended, as pre-existing interstitial lung disease has been reported to increase pulmonary toxicity.[71–73]

Disease course in people with interstitial lung disease and defining progression of pulmonary fibrosis

The clinical course of the different interstitial lung diseases ranges from completely reversible to self-limiting to progressive, irreversible, and often fatal despite optimal management (appendix p 7).[1,2,74] Accurate diagnosis of people with interstitial lung disease is important because, in disease that is driven by exposure, removing the inciting cause can result in remission and sometimes cure.[75] Interstitial lung diseases with a non-specific interstitial pneumonia or organising pneumonia pattern frequently tend to reverse or stabilise with treatment.[1,2,76] In people with idiopathic pulmonary fibrosis, the clinical course is almost universally progressive. By contrast, in other interstitial lung diseases, 15–40% of individuals will ultimately manifest progressive pulmonary fibrosis, irrespective of specific diagnosis.[76–83] Progressive pulmonary fibrosis, which conveys substantial morbidity and mortality, has long been recognised as a major challenge across interstitial lung diseases. However, the outcomes of clinical trials have resulted in a shift from diagnosis-based treatments to disease behaviour-based treatments in people who start to show progressive pulmonary fibrosis, irrespective of their interstitial lung disease diagnosis. Three pivotal studies have sought to define criteria for identifying individuals with progression of non-idiopathic pulmonary fibrosis.[80–82] Although the approach taken in each trial was slightly different, the results have led to the development of a standardised definition for progressive pulmonary fibrosis (panel).[84] On the basis of a multidimensional assessment of symptoms, pulmonary function, and imaging, these studies identified people for whom the underlying interstitial lung disease progressed at a rate similar to that of idiopathic pulmonary fibrosis despite best treatment.

In individuals with interstitial lung disease, the extent and pattern of fibrosis on HRCT are associated with prognosis: a non-specific interstitial pneumonia pattern is associated with a more favourable prognosis, whereas a usual interstitial pneumonia pattern is associated with disease progression and a prognosis similar to idiopathic pulmonary fibrosis independent of the underlying cause for the interstitial lung disease.[85,86] Post-hoc analysis of the placebo group of a landmark trial in people with progressive fibrosing interstitial lung diseases other

than idiopathic pulmonary fibrosis showed that 108 (52·4%) of 206 of participants with a usual interstitial pneumonia pattern show a forced vital capacity (FVC) decline of 10% or more at 52 weeks, whereas fewer participants (54 [43·2%] of 125) with non-usual interstitial pneumonia fibrotic patterns on HRCT showed this decline.[86] Other risk factors for poor outcomes include lower lung function at baseline (ie, <75% predicted FVC), older age (ie, >60 years), need for oxygen supplementation, continued exposure to a causative agent, telomere dysfunction, loss of more than 10% FVC in the preceding year, and poor response of fibrotic interstitial lung disease to therapy.[14,70,75,87] In people with systemic sclerosis-associated interstitial lung disease, more than 10–20% of fibrosis on HRCT is associated with increased mortality, and similar findings have been reported in people with rheumatoid arthritis-associated interstitial lung disease.[88,89] Different (often disease-specific) composite predictor scores of outcomes and prognostic circulating biomarkers have been studied, although their broad clinical uptake is low because they are not readily available and their effects on decision making in practice have not been established.[90,91] Despite these observations, for an individual patient, anticipating progression of interstitial lung disease is challenging and is further complicated by unpredictable events, such as acute exacerbations, respiratory infections, and comorbidities.[67,92–95]

Management

An understanding of the underlying diagnosis and expected disease course is important because it dictates treatment expectations and choice of therapy (appendix p 7). Evidence-based treatment recommendations exist for only a few interstitial lung diseases and off-label use of treatments is common (figure 5). In this light, patient education and shared decision making that balance the potential risks and benefits of therapy are of extra importance. Some interstitial lung diseases, such as those associated with anti-neutrophil cytoplasmic antibody-associated vasculitis, systemic lupus erythematosus, and anti-MDA5 antibody-positive amyopathic dermatomyositis, can be life-threatening at presentation and demand immediate and aggressive treatment approaches.[96,97] At the other end of the spectrum, some interstitial lung diseases have a high chance of spontaneous resolution without pharmacotherapy, such as for some individuals with sarcoidosis or individuals with organising pneumonia or non-fibrotic hypersensitivity pneumonitis after removal of the causative agent.[12,75] In these individuals, observation is the preferred management approach. A multidisciplinary approach to treatment is required for people with interstitial lung diseases in the context of systemic diseases, such as connective tissue disease-associated interstitial lung disease or sarcoidosis, as the need for therapy can be driven by extrapulmonary manifestations of disease. Multidisciplinary supportive management is of particular importance in individuals with progressive interstitial lung diseases, such as idiopathic pulmonary fibrosis and other interstitial lung diseases that manifest progressive pulmonary fibrosis.[98,99] A poor prognosis and increasing symptom burden affect quality of life and often lead to a downward spiral of loss of physical functioning and autonomy and increased anxiety and depression.[99–102]

Pharmacological management

In the past decade, major advances have been made in the treatment of many interstitial lung diseases. Randomised controlled trials in participants with idiopathic pulmonary fibrosis have led to the development of antifibrotic drugs and have identified that immunosuppressive therapy is deleterious.[103–106] By contrast, interstitial lung diseases that are characterised by an inflammatory driver (eg, connective tissue disease-associated interstitial lung disease, hypersensitivity pneumonitis, and sarcoidosis) often benefit from immunosuppressive therapy or other disease-specific therapies (figure 5). For some interstitial lung diseases, such as pulmonary alveolar proteinosis and lymphangioleiomyomatosis, specific and often highly effective treatments are available. In view of the rarity of pulmonary alveolar proteinosis and lymphangioleiomyomatosis, consultation with an interstitial lung disease expert centre is recommended to guide treatment decisions.[9,47,107,108]

Although the use of different immunomodulatory agents is widespread, randomised controlled data are scarce and guideline recommendations are largely absent. Most evidence exists for the treatment of people with sarcoidosis and connective tissue disease-associated interstitial lung disease.[68,109,110]

In people with sarcoidosis, in case of a pulmonary treatment indication, first-line therapy with prednisone is generally recommended, followed by second-line management with methotrexate or azathioprine.[109,111] In people with refractory disease, anti-TNF therapy or experimental therapies, such as Janus kinase inhibitors, might be beneficial.[11,12,109,111,112] In people with systemic sclerosis-associated interstitial lung disease, both mycophenolate mofetil and cyclophosphamide have been shown to stabilise lung function over 52 weeks of treatment, with mycophenolate mofetil being better tolerated than cyclophosphamide.[113] The role of corticosteroids in systemic sclerosis-associated interstitial lung disease is controversial, and high doses (ie, >10 mg/day) should be avoided because of an increased risk of systemic sclerosis renal crisis.[114] In a study in people with systemic sclerosis, tocilizumab, an anti-IL-6 monoclonal antibody, did not show an effect on the primary endpoint of skin scores but had a positive effect on FVC decline and the extent of interstitial lung disease seen on HRCT, resulting in approval of the drug in the USA by the Food and Drug Administration as a treatment for systemic sclerosis-associated interstitial lung disease.[115] Trials of

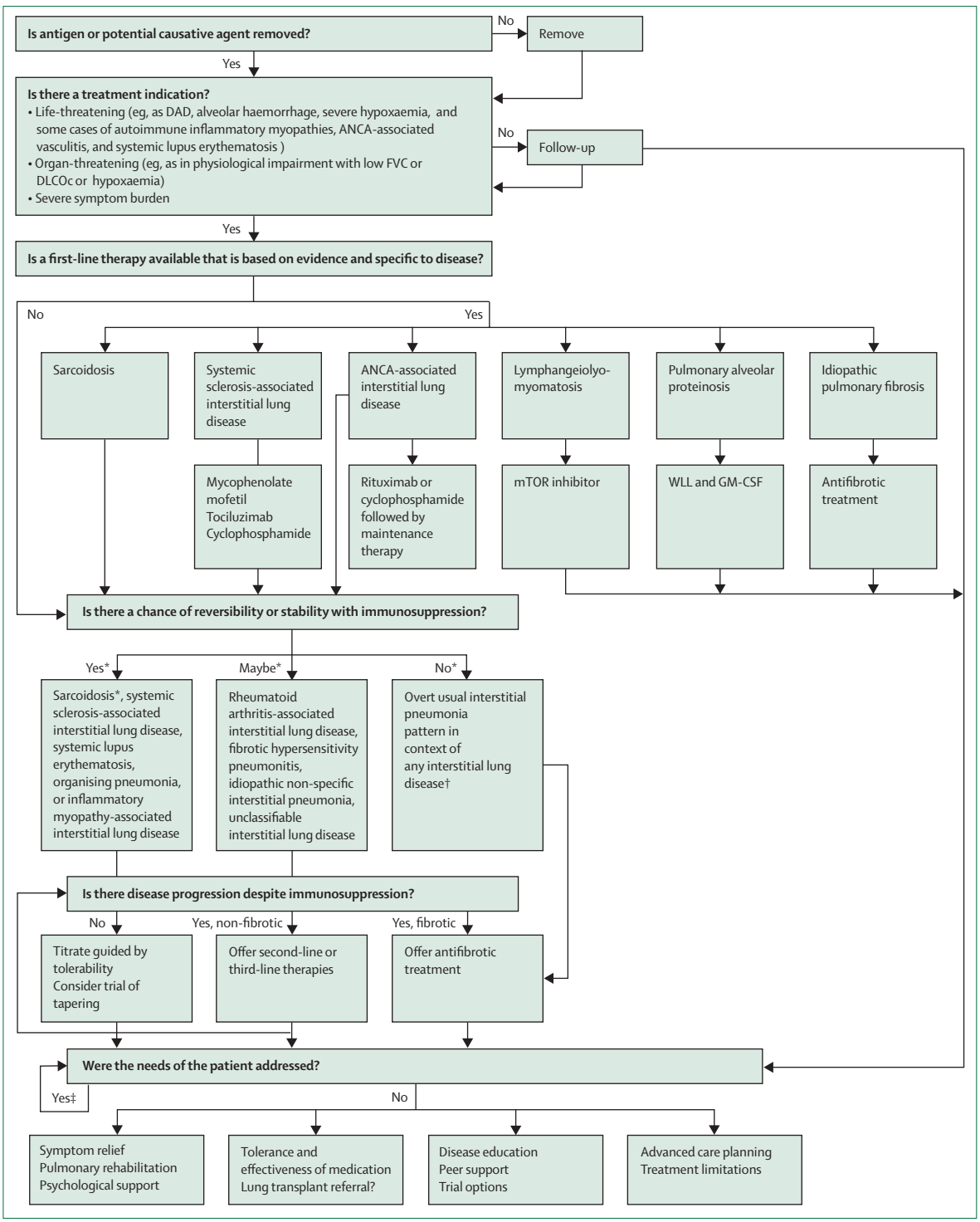


Figure 5: **Simplified treatment algorithm for the different interstitial lung diseases**
ANCA=anti-neutrophil cytoplasmic antibody. DAD=diffuse alveolar damage. DLCOc=diffusing capacity of the lung for carbon monoxide corrected for haemoglobin. FVC=forced vital capacity. mTOR inhibitor=inhibitor of the mechanistic target of rapamycin. WLL=whole lung lavage. *Discuss risks and benefits in case of off-label use with the patient. †No data yet exist on first-line treatment with antifibrotics in people with non-idiopathic pulmonary fibrosis. ‡Assessing patient needs is an iterative process throughout the disease course.

haematopoietic stem-cell transplantation showed a beneficial effect on FVC and survival compared with cyclophosphamide in a selected group of participants with systemic sclerosis with multiorgan involvement (including interstitial lung disease); however, treatment-related mortality was higher in the haematopoietic stem-cell transplantation group.[116,117]

Randomised controlled trial data do not exist for the treatment of people with rheumatoid arthritis-associated interstitial lung disease. Retrospective series have indicated some ameliorating effect on lung function decline of different immunosuppressive agents, such as cyclophosphamide, azathioprine, methotrexate, and rituximab.[5,118] Caution with immunosuppression in people with rheumatoid arthritis-associated interstitial lung disease is warranted, as usual interstitial pneumonia is the most frequently encountered pattern of fibrosis and, given data from individuals with idiopathic pulmonary fibrosis, there is a concern that immunosuppression in this context might even be harmful.[105] Despite previous data that methotrexate causes interstitial lung disease in people with rheumatoid arthritis, studies of general rheumatoid arthritis populations have shown that methotrexate use is not associated with any increased risk of rheumatoid arthritis-associated interstitial lung disease.[73,119] Idiopathic inflammatory myopathy-associated interstitial lung disease is characterised by progressive interstitial lung disease in most people. Expert recommendations include various immunosuppressive regimens.[27,120,121] Generally, treatment is started with oral prednisone followed by steroid sparing agents, such as azathioprine, mycophenolate mofetil, tacrolimus, or rituximab, and tapering of prednisone. Some people, such as those with amyopathic dermatomyositis with anti-MDA5 antibodies, can present with rapidly progressive and life-threatening disease, and initial treatment includes intravenous methylprednisolone or intravenous cyclophosphamide followed by, or sometimes combined with, steroid-sparing agents.[122,123] The role of plasmapheresis and intravenous immunoglobulin for people with idiopathic inflammatory myopathy-associated interstitial lung disease is not yet clear.[124]

For people with other connective tissue disease-associated interstitial lung diseases, such as systemic lupus erythematosus, Sjögren's syndrome, mixed connective tissue disease, and undifferentiated connective tissue disease, there is a scarcity of evidence-based treatments.[124] In clinical practice, most people are treated on the basis of severity and progression of interstitial lung disease (and other organ involvement), with therapeutic regimens extrapolated from other connective tissue diseases. Physicians should be alert for disease-specific pulmonary complications, such as lymphoma or amyloidosis in people with Sjögren's syndrome or pulmonary haemorrhage in people with systemic lupus erythematosus.

Hypersensitivity pneumonitis is the most common exposure-related interstitial lung disease. In the non-fibrotic form, observational and retrospective data report some benefits of corticosteroids, whereas in people with fibrotic hypersensitivity pneumonitis, some effect on diffusing capacity for carbon monoxide has been reported with mycophenolate mofetil and azathioprine, although without a survival benefit.[125,126] Mycophenolate mofetil and azathioprine use were associated with less adverse events than was prednisone.[127] Case series also report some effect of rituximab salvage therapy.[128] For the treatment of people with drug-induced interstitial lung diseases, corticosteroids are often the first choice if withdrawal of the causative agent is insufficient.[129] Developments in oncology have led to the first expert-based recommendations for the treatment of immune-checkpoint inhibitor toxicity and a call for more structured research on treatment options than currently exists.[130,131]

Acute exacerbations, characterised by acute lung injury and diffuse alveolar damage, are most reported in people with idiopathic pulmonary fibrosis, but can happen in people with any interstitial lung disease and are associated with 90-day mortality as high as 50%.[93,94] Treatment practices for acute exacerbation-associated interstitial lung diseases widely vary worldwide.[92] Corticosteroids are the most commonly administered therapy, although without convincing evidence to support this practice and with some data to support a non-corticosteroid management approach in acute exacerbation of idiopathic pulmonary fibrosis.[92,106,132] In a randomised placebo-controlled trial, the use of cyclophosphamide in participants with acute exacerbations of idiopathic pulmonary fibrosis led to increased mortality at 3 months.[133]

In clinical practice, idiopathic pulmonary fibrosis is irreversibly progressive from the moment of diagnosis; therefore, initiation of treatment should not be delayed. Antifibrotic therapy with either pirfenidone or nintedanib is recommended for people with idiopathic pulmonary fibrosis by international guidelines.[134] Both drugs slow down lung function decline, and post-hoc analysis and registry data indicate a protective effect against acute exacerbations and a survival benefit.[103,104,135,136] The most common adverse events are diarrhoea (nintedanib) and nausea (pirfenidone). Individuals should be counselled on potential phototoxicity with pirfenidone. Liver toxicity was seen in up to 7% of participants in the registrational studies for pirfenidone and nintedanib;[103,104] therefore, regular monitoring is recommended. In people with systemic sclerosis-associated interstitial lung disease, a positive effect of nintedanib on annual decline in FVC was identified.[137] In addition to being a treatment for people with idiopathic pulmonary fibrosis, nintedanib has been approved in multiple countries for the treatment of people with all forms of progressive pulmonary fibrosis. In a trial of nintedanib for people with progressive pulmonary fibrosis, nintedanib halved the rate of decline in FVC over

52 weeks.[81,138] In a study performed in people with progressive unclassifiable interstitial lung disease, pirfenidone slowed FVC decline.[80] A similar effect of pirfenidone was seen in a phase 2b study in people with fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis.[82] Importantly, in contrast to people with idiopathic pulmonary fibrosis, for whom antifibrotic drugs are offered at the time of diagnosis, in these studies people were included on the basis of disease progression in the preceding 6–24 months. By use of a multidimensional assessment of disease progression, these studies identified patient cohorts with a disease trajectory and response to therapy that was similar to that of people with idiopathic pulmonary fibrosis.

These results are shifting the treatment model for people with pulmonary fibrosis, whereby decisions to treat are now guided as much by disease behaviour as by CT or histological patterns. However, many uncertainties exist. Principal among these uncertainties is when and how best to integrate antifibrotic therapy with immunosuppressant therapies in diseases with an autoimmune or inflammatory cause. This decision is particularly challenging given the scarcity of clinical trial data and evidence-based guidelines to support the use of any specific therapy for the treatment of most interstitial lung diseases.

Lung transplantation and other treatments

In people with interstitial lung diseases that progress despite medical therapy, lung transplantation can be an option for a selected few. With the introduction of the lung allocation score in many countries, people with interstitial lung disease are prioritised for transplant because of more rapidly progressive disease behaviour than is shown with other lung transplant indications. Nevertheless, many people with interstitial lung disease will have coexisting conditions that might preclude them from being transplant candidates, and timely referral to a transplant service for careful assessment is important (appendix p 8).[139]

Bacterial burden and composition have been associated with disease progression in people with idiopathic pulmonary fibrosis, and respiratory infections are a potential trigger of acute exacerbations.[140,141] On the basis of this observation, broad-spectrum antibiotics are pragmatically used in the management of people with acute exacerbations of idiopathic pulmonary fibrosis, although again based on little evidence. Randomised controlled trials did not show any effect of long-term prophylactic antibiotics on disease progression, admissions to hospital for respiratory reasons, exacerbations, or death in people with idiopathic pulmonary fibrosis.[142,143]

Proton pump inhibitors, the most common treatment for gastro-oesophageal reflux disease, have been proposed as a treatment for preventing progression in people with idiopathic pulmonary fibrosis. Analyses of placebo groups from many trials suggest that proton pump inhibitors are not associated with reduced mortality or admissions to hospital in people with idiopathic pulmonary fibrosis. Therefore, the 2022 idiopathic pulmonary fibrosis guideline recommends not to use antacid medication to improve respiratory outcomes.[84] Pulmonary hypertension frequently complicates advanced fibrotic lung disease. A phase 3 trial showed a beneficial effect of inhaled treprostinil in treating people with pulmonary hypertension associated with fibrotic interstitial lung disease, resulting in an approval in the USA by the Food and Drug Administration for this indication.[144]

Supportive management, follow-up, and outcomes

Major unmet needs for people with interstitial lung disease include timely diagnosis, education, symptom relief, and improved access to palliative care.[145] Education and prevention are the first step in the treatment of people with interstitial lung disease. Removal and avoidance of potential causative agents in hypersensitivity pneumonitis and occupational and iatrogenic interstitial lung diseases are priorities, as are smoking and vaping cessation. Viral and pneumococcal vaccinations are recommended, especially in people with chronic interstitial lung diseases, because airway infections are potential triggers of exacerbations.[2,6] Individuals (especially those with fibrotic disease) also need to be counselled on other potential triggers for exacerbations, such as mechanical ventilation, chemotherapy, radiation therapy, or pulmonary surgery.[146] When familial interstitial lung disease is suspected, patients and their families should be offered genetical counseling.[42,69] Comorbidities, such as gastro-oesophageal reflux disease, sleep disorders, cardiovascular disease, diabetes, lung cancer, pulmonary hypertension, and psychological problems, are common in interstitial lung disease.[66,67,95] Identification and treatment of these comorbidities might improve quality of life and survival.

Pulmonary rehabilitation has been studied mostly in people with fibrotic or chronic interstitial lung diseases and improves quality of life and exercise capacity, especially if started when people are not yet severely impaired.[147,148] The beneficial effects of pulmonary rehabilitation in other diseases, such as connective tissue disease-associated interstitial lung disease, are less established, and the presence of extrapulmonary manifestations, such as joint, muscle, and skin involvement, might possibly need different approaches.[149] In people with interstitial lung disease and exertional hypoxaemia, ambulatory oxygen improves quality of life and dyspnea.[150] Expert opinion and clinical guidelines recommend supplemental oxygen for people with hypoxaemia at rest (ie, oxygen saturation by pulse oximetry ≤88%, PaO_2 ≤55 mm Hg, or PaO_2 of <60 mm Hg and cor pulmonale or polycythaemia), although structured research to support this recommendation is still scarce.[151,152]

As prognosis is poor for people with idiopathic pulmonary fibrosis and other interstitial lung diseases that manifest progressive pulmonary fibrosis, advanced

care and end-of-life planning are imperative but are challenging due to the unpredictable course in many interstitial lung diseases.[98,99]

Disease course, response to therapy, and potential adverse effects of therapy are often monitored at intervals of 3–6 months.[77] Lung function (measured by spirometry and diffusing capacity for carbon monoxide) and symptoms, often combined with imaging and a 6-min walking test, are key determinants of treatment response. Patient-reported outcome measures, including health-related quality of life, symptoms, functional status, and physiological status, are widely used in clinical trials but are infrequently used in clinical practice.[102,153] Blood monitoring is required for antifibrotic therapy and many immunosuppressants. If response to treatment is not in line with predefined aims or if side-effects occur, then the benefit–risk ratio of therapy should be re-evaluated, and potential treatment adjustments should be discussed with the patient.

Controversies, uncertainties, and future directions

There are a broad range of unmet needs affecting the diagnosis, treatment, and monitoring of individuals with interstitial lung disease. Fortunately, many of these needs are being addressed by current research.[154] Early diagnosis of individual interstitial lung diseases enables timely intervention, including elimination of disease triggers and tailored treatment aimed at disease reversal or stabilisation in advance of the development of irreversible fibrosis. Unfortunately, diagnostic and treatment delay are common for many reasons, including non-specific presentation (eg, cough, dyspnea, and fatigue are symptoms that are common to many respiratory diseases), absence of awareness of these rare diseases, patient delay (eg, belief that symptoms are due to age), and doctor delay (eg, difficulty in accessing specialised centres), and negatively affect prognosis, quality of life, and wellbeing for patients.[53] New techniques, such as molecular classifiers, exhaled breath analysis, and artificial intelligence-based image analysis, need further validation before generalised uptake but should facilitate earlier and more accurate diagnosis of individual interstitial lung diseases than is currently possible, especially outside expert centres.[155–157] Recognition of individuals who are at high risk of developing symptomatic interstitial lung disease, as has been shown with identification of interstitial lung abnormalities on screening with HRCT or in family members who are at high risk of interstitial lung disease, has opened up the possibility of secondary prevention of fibrosis.[158,159]

Novel insights into disease pathobiology and genetics have brought about the possibility of precision medicine for people with interstitial lung disease. For example, data for pharmacogenomic interactions show that telomerase gene mutations (resulting in short leucocyte telomere length) are related to detrimental responses to immunosuppression in people with idiopathic pulmonary fibrosis and fibrotic hypersensitivity pneumonitis.[160,161] The growth in availability of detailed genetic, transcriptomic, and proteomic data for individuals is providing the opportunity to identify molecular phenotypes, which span individual interstitial lung diseases, in much the same way as has been done in oncology. We envision future interstitial lung disease ontologies will be based on biological signatures that reflect either predominant pathobiological mechanisms, disease behaviour, or responses to therapy, rather than the current histopathological–radiological patterns. Results of trials showing that progressive fibrosis responds favourably to antifibrotic treatment, irrespective of the cause of underlying interstitial lung disease, could be seen as a move away from the need for precision medicine for people with interstitial lung disease.[80–82,138] The alternative view is that these trials show the importance of treating disease mechanisms (ie, fibrosis) over and above treating discrete clinical entities. An important challenge going forwards will be to identify those individuals with interstitial lung disease who will develop progressive pulmonary fibrosis in advance of them developing irreversible loss of functional lung tissue. A range of blood-based biomarkers have been identified that predict prognosis and, importantly, response to therapy in idiopathic pulmonary fibrosis.[90,91,162–164] The most promising of these biomarkers, including CA-125 (ie, the epitope of MUC16), C3M (ie, a cleavage fragment of matrix metalloprotease-degraded collagen III), and ProC6 (ie, a marker of collagen VI synthesis), have the potential to transform clinical trial design, improve assessment of treatment response in clinical practice, and, importantly, enable early identification of individuals at high risk of progressive fibrosis.[162,163]

In addition to the need for more effective and safer treatments than are available, a major day-to-day clinical challenge relates to the choice, timing, and duration of immunomodulatory therapy in people with presumed inflammatory-driven disease. Except for systemic sclerosis-associated interstitial lung disease, there is a scarcity of well designed, prospective randomised controlled trials of immunosuppressive therapy for different interstitial lung diseases. Trials of immunosuppressant drugs either used alone or in combination and, in individuals with fibrosis, administered concurrently or sequentially with antifibrotic treatments are urgently required. Trials are also needed to evaluate symptom-based therapies and to define optimal use of oxygen in people with advanced disease.

The growth of patient-led charities for interstitial lung disease has driven a transformation in research collaborations between researchers and individuals with interstitial lung disease, resulting in prioritisation of patient-centred care and research into patient-valued outcomes, such as cough, dyspnea, and quality of life.[153,165] New patient-reported outcome measures have been co-developed with patients.[102] Advances in digital health

now permit domiciliary assessments, such as home spirometry, accelerometry, and pulse-oximetry, thus offering the potential for personalised care close to home and for those who are far from expert centres.[166–168] Technological, logistical, and analytical challenges still exist; nevertheless, these novel methods of digital collaboration will facilitate broader-based clinical care and research, especially for rare diseases, such as interstitial lung diseases, for which patients have frequently had to travel long distances to access expert centres.[80,168]

Conclusion

The heterogeneous nature of the many different interstitial lung diseases makes accurately identifying and diagnosing specific disorders challenging, emphasising the importance of multidisciplinary discussion. Similarly, the differing causes and clinical courses that are associated with individual interstitial lung diseases make it impossible to generalise treatment approaches. Nonetheless, recognition of the relationship between progressive pulmonary fibrosis and increased morbidity and mortality in many forms of interstitial lung disease has resulted in the use of antifibrotic therapy to improve outcomes. Similarly, trials of immunomodulatory agents in people with systemic sclerosis-associated interstitial lung disease have emphasised the importance of such treatment approaches in people with inflammatory-mediated interstitial lung disease. Future research into novel therapies, symptom-based treatment, biomarker-directed care, and home-based disease monitoring should further reduce the considerable morbidity and mortality that are associated with interstitial lung disease.

Contributors

All authors conceived and wrote the Seminar.

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References

1 Travis WD, Costabel U, Hansell DM, et al. 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:** 733–48.
2 Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. *N Engl J Med* 2020; **383:** 958–68.
3 Harari S, Spagnolo P, Cocconcelli E, Luisi F, Cottin V. Recent advances in the pathobiology and clinical management of lymphangioleiomyomatosis. *Curr Opin Pulm Med* 2018; **24:** 469–76.
4 Khanna D, Tashkin DP, Denton CP, Renzoni EA, Desai SR, Varga J. Etiology, risk factors, and biomarkers in systemic sclerosis with interstitial lung disease. *Am J Respir Crit Care Med* 2020; **201:** 650–60.
5 McDermott GC, Doyle TJ, Sparks JA. Interstitial lung disease throughout the rheumatoid arthritis disease course. *Curr Opin Rheumatol* 2021; **33:** 284–91.
6 Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. *N Engl J Med* 2018; **378:** 1811–23.
7 Navaratnam V, Hubbard RB. The mortality burden of idiopathic pulmonary fibrosis in the United Kingdom. *Am J Respir Crit Care Med* 2019; **200:** 256–58.
8 Appleby J. UK deaths in 2020: how do they compare with previous years? *BMJ* 2021; **373:** n896.
9 Trapnell BC, Nakata K, Bonella F, et al. Pulmonary alveolar proteinosis. *Nat Rev Dis Primers* 2019; **5:** 16.
10 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:** e36–69.
11 Grunewald J, Grutters JC, Arkema EV, Saketkoo LA, Moller DR, Müller-Quernheim J. Sarcoidosis. *Nat Rev Dis Primers* 2019; **5:** 45.
12 Spagnolo P, Rossi G, Trisolini R, Sverzellati N, Baughman RP, Wells AU. Pulmonary sarcoidosis. *Lancet Respir Med* 2018; **6:** 389–402.
13 Costabel U, Miyazaki Y, Pardo A, et al. Hypersensitivity pneumonitis. *Nat Rev Dis Primers* 2020; **6:** 65.
14 Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; **183:** 788–824.
15 Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; **198:** e44–68.
16 Natsuizaka M, Chiba H, Kuronuma K, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. *Am J Respir Crit Care Med* 2014; **190:** 773–79.
17 Duchemann B, Annesi-Maesano I, Jacobe de Naurois C, et al. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. *Eur Respir J* 2017; **50:** 1602419.
18 Maher TM, Bendstrup E, Dron L, et al. Global incidence and prevalence of idiopathic pulmonary fibrosis. *Respir Res* 2021; **22:** 197.
19 Belloli EA, Beckford R, Hadley R, Flaherty KR. Idiopathic non-specific interstitial pneumonia. *Respirology* 2016; **21:** 259–68.
20 Raimundo K, Solomon JJ, Olson AL, et al. Rheumatoid arthritis-interstitial lung disease in the United States: prevalence, incidence, and healthcare costs and mortality. *J Rheumatol* 2019; **46:** 360–69.
21 Li Q, Wallace L, Patnaik P, et al. Disease frequency, patient characteristics, comorbidity outcomes and immunosuppressive therapy in systemic sclerosis and systemic sclerosis-associated interstitial lung disease: a US cohort study. *Rheumatology (Oxford)* 2021; **60:** 1915–25.
22 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:** 460–69.
23 Olson AL, Patnaik P, Hartmann N, Bohn RL, Garry EM, Wallace L. Prevalence and incidence of chronic fibrosing interstitial lung diseases with a progressive phenotype in the United States estimated in a large claims database analysis. *Adv Ther* 2021; **38:** 4100–14.
24 Buch MH, Eyre S, McGonagle D. Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis. *Nat Rev Rheumatol* 2021; **17:** 17–33.
25 Zaiss MM, Joyce Wu HJ, Mauro D, Schett G, Ciccia F. The gut-joint axis in rheumatoid arthritis. *Nat Rev Rheumatol* 2021; **17:** 224–37.
26 Kadura S, Raghu G. Rheumatoid arthritis-interstitial lung disease: manifestations and current concepts in pathogenesis and management. *Eur Respir Rev* 2021; **30:** 210011.

27 Lundberg IE, Tjärnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Arthritis Rheumatol* 2017; **69:** 2271–82.

28 Lega JC, Reynaud Q, Belot A, Fabien N, Durieu I, Cottin V. Idiopathic inflammatory myopathies and the lung. *Eur Respir Rev* 2015; **24:** 216–38.

29 Caso F, Galozzi P, Costa L, Sfriso P, Cantarini L, Punzi L. Autoinflammatory granulomatous diseases: from Blau syndrome and early-onset sarcoidosis to NOD2-mediated disease and Crohn's disease. *RMD Open* 2015; **1:** e000097.

30 Grunewald J, Grutters JC, Arkema EV, Saketkoo LA, Moller DR, Müller-Quernheim J. Sarcoidosis. *Nat Rev Dis Primers* 2019; **5:** 45.

31 Lee S, Birnie D, Dwivedi G. Current perspectives on the immunopathogenesis of sarcoidosis. *Respir Med* 2020; **173:** 106161.

32 Vasakova M, Selman M, Morell F, Sterclova M, Molina-Molina M, Raghu G. Hypersensitivity pneumonitis: current concepts of pathogenesis and potential targets for treatment. *Am J Respir Crit Care Med* 2019; **200:** 301–08.

33 Daccord C, Maher TM. Recent advances in understanding idiopathic pulmonary fibrosis. *F1000 Res* 2016; **5:** 5.

34 DePianto DJ, Heiden JAV, Morshead KB, et al. Molecular mapping of interstitial lung disease reveals a phenotypically distinct senescent basal epithelial cell population. *JCI Insight* 2021; **6:** 143626.

35 Yao C, Guan X, Carraro G, et al. Senescence of alveolar type 2 cells drives progressive pulmonary fibrosis. *Am J Respir Crit Care Med* 2021; **203:** 707–17.

36 Adams TS, Schupp JC, Poli S, et al. Single-cell RNA-seq reveals ectopic and aberrant lung-resident cell populations in idiopathic pulmonary fibrosis. *Sci Adv* 2020; **6:** eaba1983.

37 Habermann AC, Gutierrez AJ, Bui LT, et al. Single-cell RNA sequencing reveals profibrotic roles of distinct epithelial and mesenchymal lineages in pulmonary fibrosis. *Sci Adv* 2020; **6:** eaba1972.

38 Philp CJ, Siebeke I, Clements D, et al. Extracellular matrix cross-linking enhances fibroblast growth and protects against matrix proteolysis in lung fibrosis. *Am J Respir Cell Mol Biol* 2018; **58:** 594–603.

39 Parker MW, Rossi D, Peterson M, et al. Fibrotic extracellular matrix activates a profibrotic positive feedback loop. *J Clin Invest* 2014; **124:** 1622–35.

40 Michalski JE, Schwartz DA. Genetic risk factors for idiopathic pulmonary fibrosis: insights into immunopathogenesis. *J Inflamm Res* 2021; **13:** 1305–18.

41 Borie R, Kannengiesser C, Dupin C, Debray MP, Cazes A, Crestani B. Impact of genetic factors on fibrosing interstitial lung diseases. Incidence and clinical presentation in adults. *Presse Med* 2020; **49:** 104024.

42 Adegunsoye A, Vij R, Noth I. Integrating genomics into management of fibrotic interstitial lung disease. *Chest* 2019; **155:** 1026–40.

43 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:** 564–74.

44 Rivera NV, Patasova K, Kullberg S, et al. A gene-environment interaction between smoking and gene polymorphisms provides a high risk of two subgroups of sarcoidosis. *Sci Rep* 2019; **9:** 18633.

45 Juge PA, Lee JS, Ebstein E, et al. MUC5B promoter variant and rheumatoid arthritis with interstitial lung disease. *N Engl J Med* 2018; **379:** 2209–19.

46 Ley B, Newton CA, Arnould I, et al. The MUC5B promoter polymorphism and telomere length in patients with chronic hypersensitivity pneumonitis: an observational cohort-control study. *Lancet Respir Med* 2017; **5:** 639–47.

47 Trapnell BC, Inoue Y, Bonella F, et al. Inhaled molgramostim therapy in autoimmune pulmonary alveolar proteinosis. *N Engl J Med* 2020; **383:** 1635–44.

48 Liu H, Osterburg AR, Flury J, et al. MAPK mutations and cigarette smoke promote the pathogenesis of pulmonary Langerhans cell histiocytosis. *JCI Insight* 2020; **5:** 132048.

49 Behr J, Kreuter M, Hoeper MM, et al. Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. *Eur Respir J* 2015; **46:** 186–96.

50 Guenther A, Krauss E, Tello S, et al. The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. *Respir Res* 2018; **19:** 141.

51 Singh S, Collins BF, Sharma BB, et al. Interstitial lung disease in India. Results of a prospective registry. *Am J Respir Crit Care Med* 2017; **195:** 801–13.

52 Hewson T, McKeever TM, Gibson JE, Navaratnam V, Hubbard RB, Hutchinson JP. Timing of onset of symptoms in people with idiopathic pulmonary fibrosis. *Thorax* 2018; **73:** 683–85.

53 Spagnolo P, Ryerson CJ, Putman R, et al. Early diagnosis of fibrotic interstitial lung disease: challenges and opportunities. *Lancet Respir Med* 2021; **9:** 1065–76.

54 Fischer A, Antoniou KM, Brown KK, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. *Eur Respir J* 2015; **46:** 976–87.

55 Distler O, Assassi S, Cottin V, et al. Predictors of progression in systemic sclerosis patients with interstitial lung disease. *Eur Respir J* 2020; **55:** 1902026.

56 Sverzellati N, Guerci L, Randi G, et al. Interstitial lung diseases in a lung cancer screening trial. *Eur Respir J* 2011; **38:** 392–400.

57 Fernández Pérez ER, Swigris JJ, Forssén AV, et al. Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. *Chest* 2013; **144:** 1644–51.

58 Suzuki A, Kondoh Y, Fischer A. Recent advances in connective tissue disease related interstitial lung disease. *Expert Rev Respir Med* 2017; **11:** 591–603.

59 Meyer KC, Raghu G, Baughman RP, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med* 2012; **185:** 1004–14.

60 Durheim MT, Kim S, Gulack BC, et al. Mortality and respiratory failure after thoracoscopic lung biopsy for interstitial lung disease. *Ann Thorac Surg* 2017; **104:** 465–70.

61 Hutchinson JP, McKeever TM, Fogarty AW, Navaratnam V, Hubbard RB. Surgical lung biopsy for the diagnosis of interstitial lung disease in England: 1997–2008. *Eur Respir J* 2016; **48:** 1453–61.

62 Troy LK, Grainge C, Corte TJ, et al. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med* 2020; **8:** 171–81.

63 Tomassetti S, Ravaglia C, Wells AU, et al. Prognostic value of transbronchial lung cryobiopsy for the multidisciplinary diagnosis of idiopathic pulmonary fibrosis: a retrospective validation study. *Lancet Respir Med* 2020; **8:** 786–94.

64 Maldonado F, Danoff SK, Wells AU, et al. Transbronchial cryobiopsy for the diagnosis of interstitial lung diseases: CHEST guideline and expert panel report. *Chest* 2020; **157:** 1030–42.

65 Jo HE, Glaspole IN, Levin KC, et al. Clinical impact of the interstitial lung disease multidisciplinary service. *Respirology* 2016; **21:** 1438–44.

66 Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. *Eur Respir J* 2015; **46:** 1113–30.

67 Suzuki A, Kondoh Y. The clinical impact of major comorbidities on idiopathic pulmonary fibrosis. *Respir Investig* 2017; **55:** 94–103.

68 Hoffmann-Vold AM, Maher TM, Philpot EE, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. *Lancet Rheumatol* 2020; **2:** e71–83.

69 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:** 1240–48.

70 Newton CA, Oldham JM, Ley B, et al. Telomere length and genetic variant associations with interstitial lung disease progression and survival. *Eur Respir J* 2019; **53:** 1801641.

71 Cadranel J, Canellas A, Matton L, et al. Pulmonary complications of immune checkpoint inhibitors in patients with nonsmall cell lung cancer. *Eur Respir Rev* 2019; **28:** 190058.

72 Skeoch S, Weatherley N, Swift AJ, et al. Drug-induced interstitial lung disease: a systematic review. *J Clin Med* 2018; **7:** E356.

73 Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. *Semin Arthritis Rheum* 2014; **43:** 613–26.

74 Cottin V, Wollin L, Fischer A, Quaresma M, Stowasser S, Harari S. Fibrosing interstitial lung diseases: knowns and unknowns. *Eur Respir Rev* 2019; **28:** 180100.

75 Gimenez A, Storrer K, Kuranishi L, Soares MR, Ferreira RG, Pereira CAC. Change in FVC and survival in chronic fibrotic hypersensitivity pneumonitis. *Thorax* 2018; **73:** 391–92.

76 George PM, Spagnolo P, Kreuter M, et al. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. *Lancet Respir Med* 2020; **8:** 925–34.

77 Wijsenbeek M, Kreuter M, Olson A, et al. Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. *Curr Med Res Opin* 2019; **35:** 2015–24.

78 Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Progressive decline of lung function in rheumatoid arthritis-associated interstitial lung disease. *Arthritis Rheumatol* 2017; **69:** 542–49.

79 Hoffmann-Vold AM, Allanore Y, Alves M, et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. *Ann Rheum Dis* 2021; **80:** 219–27.

80 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:** 147–57.

81 Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; **381:** 1718–27.

82 Behr J, Prasse A, Kreuter M, et al. 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:** 476–86.

83 Olson A, Hartmann N, Patnaik P, et al. Estimation of the prevalence of progressive fibrosing interstitial lung diseases: systematic literature review and data from a physician survey. *Adv Ther* 2021; **38:** 854–67.

84 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:** e18–47.

85 Salisbury ML, Gu T, Murray S, et al. Hypersensitivity pneumonitis: radiologic phenotypes are associated with distinct survival time and pulmonary function trajectory. *Chest* 2019; **155:** 699–711.

86 Brown KK, Martinez FJ, Walsh SLF, et al. The natural history of progressive fibrosing interstitial lung diseases. *Eur Respir J* 2020; **55:** 2000085.

87 Ryerson CJ, Vittinghoff E, Ley B, et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. *Chest* 2014; **145:** 723–28.

88 Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 2008; **177:** 1248–54.

89 Jacob J, Hirani N, van Moorsel CHM, et al. Predicting outcomes in rheumatoid arthritis related interstitial lung disease. *Eur Respir J* 2019; **53:** 1800869.

90 Kreuter M, Lee JS, Tzouvelekis A, et al. Monocyte count as a prognostic biomarker in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2021; **204:** 74–81.

91 Inoue Y, Kaner RJ, Guiot J, et al. Diagnostic and prognostic biomarkers for chronic fibrosing interstitial lung diseases with a progressive phenotype. *Chest* 2020; **158:** 646–59.

92 Kreuter M, Polke M, Walsh SLF, et al. Acute exacerbation of idiopathic pulmonary fibrosis: international survey and call for harmonisation. *Eur Respir J* 2020; **55:** 1901760.

93 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:** 265–75.

94 Suzuki A, Kondoh Y, Brown KK, et al. Acute exacerbations of fibrotic interstitial lung diseases. *Respirology* 2020; **25:** 525–34.

95 Wong AW, Lee TY, Johannson KA, et al. A cluster-based analysis evaluating the impact of comorbidities in fibrotic interstitial lung disease. *Respir Res* 2020; **21:** 322.

96 Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. *Nat Rev Dis Primers* 2020; **6:** 71.

97 Gono T, Masui K, Nishina N, et al. Risk prediction modeling based on a combination of initial serum biomarker levels in polymyositis/dermatomyositis-associated interstitial lung disease. *Arthritis Rheumatol* 2021; **73:** 677–86.

98 Wijsenbeek MS, Holland AE, Swigris JJ, Renzoni EA. Comprehensive supportive care for patients with fibrosing interstitial lung disease. *Am J Respir Crit Care Med* 2019; **200:** 152–59.

99 Kreuter M, Bendstrup E, Russell AM, et al. Palliative care in interstitial lung disease: living well. *Lancet Respir Med* 2017; **5:** 968–80.

100 Glaspole IN, Chapman SA, Cooper WA, et al. Health-related quality of life in idiopathic pulmonary fibrosis: data from the Australian IPF Registry. *Respirology* 2017; **22:** 950–56.

101 van Manen MJG, Wijsenbeek MS. Cough, an unresolved problem in interstitial lung diseases. *Curr Opin Support Palliat Care* 2019; **13:** 143–51.

102 Cox IA, Borchers Arriagada N, de Graaff B, et al. Health-related quality of life of patients with idiopathic pulmonary fibrosis: a systematic review and meta-analysis. *Eur Respir Rev* 2020; **29:** 1–22.

103 King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014; **370:** 2083–92.

104 Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; **370:** 2071–82.

105 Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012; **366:** 1968–77.

106 Farrand E, Vittinghoff E, Ley B, Butte AJ, Collard HR. Corticosteroid use is not associated with improved outcomes in acute exacerbation of IPF. *Respirology* 2020; **25:** 629–35.

107 Gupta N, Finlay GA, Kotloff RM, et al. Lymphangioleiomyomatosis diagnosis and management: high-resolution chest computed tomography, transbronchial lung biopsy, and pleural disease management. An official American Thoracic Society/Japanese Respiratory Society clinical practice guideline. *Am J Respir Crit Care Med* 2017; **196:** 1337–48.

108 McCormack FX, Gupta N, Finlay GR, et al. Official American Thoracic Society/Japanese Respiratory Society Clinical Practice guidelines: lymphangioleiomyomatosis diagnosis and management. *Am J Respir Crit Care Med* 2016; **194:** 748–61.

109 Thillai M, Atkins CP, Crawshaw A, et al. BTS clinical statement on pulmonary sarcoidosis. *Thorax* 2021; **76:** 4–20.

110 Hoffmann-Vold AM, Maher TM, Philpot EE, Ashrafzadeh A, Distler O. Assessment of recent evidence for the management of patients with systemic sclerosis-associated interstitial lung disease: a systematic review. *ERJ Open Res* 2021; **7:** 00235-2020.

111 Baughman RP, Valeyre D, Korsten P, et al. ERS clinical practice guidelines on treatment of sarcoidosis. *Eur Respir J* 2021; **58:** 2004079.

112 Miedema JR, Bonella F, Grunewald J, Spagnolo P. Looking into the future of sarcoidosis: what is next for treatment? *Curr Opin Pulm Med* 2020; **26:** 598–607.

113 Tashkin DP, Roth MD, Clements PJ, et al. 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:** 708–19.

114 Trang G, Steele R, Baron M, Hudson M. Corticosteroids and the risk of scleroderma renal crisis: a systematic review. *Rheumatol Int* 2012; **32:** 645–53.

115 Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2020; **8:** 963–74.

116 van Laar JM, Farge D, Sont JK, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA* 2014; **311:** 2490–98.

117 Sullivan KM, Goldmuntz EA, Keyes-Elstein L, et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. *N Engl J Med* 2018; **378:** 35–47.

118 Spagnolo P, Lee JS, Sverzellati N, Rossi G, Cottin V. The lung in rheumatoid arthritis: focus on interstitial lung disease. *Arthritis Rheumatol* 2018; **70:** 1544–54.

119 Juge PA, Lee JS, Lau J, et al. Methotrexate and rheumatoid arthritis associated interstitial lung disease. *Eur Respir J* 2021; **57:** 2000337.

120 Morisset J, Johnson C, Rich E, Collard HR, Lee JS. Management of myositis-related interstitial lung disease. *Chest* 2016; **150:** 1118–28.

121 Mariampillai K, Granger B, Amelin D, et al. Development of a new classification system for idiopathic inflammatory myopathies based on clinical manifestations and myositis-specific autoantibodies. *JAMA Neurol* 2018; **75:** 1528–37.

122 Yanagihara T, Inoue Y. Insights into pathogenesis and clinical implications in myositis-associated interstitial lung diseases. *Curr Opin Pulm Med* 2020; **26:** 507–17.

123 Tsuji H, Nakashima R, Hosono Y, et al. Multicenter prospective study of the efficacy and safety of combined immunosuppressive therapy with high-dose glucocorticoid, tacrolimus, and cyclophosphamide in interstitial lung diseases accompanied by anti-melanoma differentiation-associated gene 5-positive dermatomyositis. *Arthritis Rheumatol* 2020; **72:** 488–98.

124 Jee AS, Sheehy R, Hopkins P, et al. Diagnosis and management of connective tissue disease-associated interstitial lung disease in Australia and New Zealand: a position statement from the Thoracic Society of Australia and New Zealand. *Respirology* 2021; **26:** 23–51.

125 Morisset J, Johannson KA, Vittinghoff E, et al. Use of mycophenolate mofetil or azathioprine for the management of chronic hypersensitivity pneumonitis. *Chest* 2017; **151:** 619–25.

126 De Sadeleer LJ, Hermans F, De Dycker E, et al. Effects of corticosteroid treatment and antigen avoidance in a large hypersensitivity pneumonitis cohort: a single-centre cohort study. *J Clin Med* 2018; **8:** E14.

127 Adegunsoye A, Oldham JM, Fernández Pérez ER, et al. Outcomes of immunosuppressive therapy in chronic hypersensitivity pneumonitis. *ERJ Open Res* 2017; **3:** 00016-2017.

128 Ferreira M, Borie R, Crestani B, et al. Efficacy and safety of rituximab in patients with chronic hypersensitivity pneumonitis (cHP): a retrospective, multicentric, observational study. *Respir Med* 2020; **172:** 106146.

129 Kubo K, Azuma A, Kanazawa M, et al. Consensus statement for the diagnosis and treatment of drug-induced lung injuries. *Respir Investig* 2013; **51:** 260–77.

130 Sears CR, Peikert T, Possick JD, et al. Knowledge gaps and research priorities in immune checkpoint inhibitor-related pneumonitis. An official American Thoracic Society research statement. *Am J Respir Crit Care Med* 2019; **200:** e31–43.

131 Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; **28** (suppl 4)**:** iv119–42.

132 Papiris SA, Kagouridis K, Kolilekas L, et al. Survival in idiopathic pulmonary fibrosis acute exacerbations: the non-steroid approach. *BMC Pulm Med* 2015; **15:** 162.

133 Naccache JM, Jouneau S, Didier M, et al. Cyclophosphamide added to glucocorticoids in acute exacerbation of idiopathic pulmonary fibrosis (EXAFIP): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2022; **10:** 26–34.

134 Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med* 2015; **192:** e3–19.

135 Dempsey TM, Sangaralingham LR, Yao X, Sanghavi D, Shah ND, Limper AH. Clinical effectiveness of antifibrotic medications for idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2019; **200:** 168–74.

136 Petnak T, Lertjitbanjong P, Thongprayoon C, Moua T. Impact of antifibrotic therapy on mortality and acute exacerbation in idiopathic pulmonary fibrosis: a systematic review and meta-analysis. *Chest* 2021; **160:** 1751–63.

137 Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019; **380:** 2518–28.

138 Wells AU, Flaherty KR, Brown KK, et al. 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:** 453–60.

139 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:** 1349–79.

140 Invernizzi R, Molyneaux PL. The contribution of infection and the respiratory microbiome in acute exacerbations of idiopathic pulmonary fibrosis. *Eur Respir Rev* 2019; **28:** 190045.

141 Invernizzi R, Barnett J, Rawal B, et al. Bacterial burden in the lower airways predicts disease progression in idiopathic pulmonary fibrosis and is independent of radiological disease extent. *Eur Respir J* 2020; **55:** 1901519.

142 Wilson AM, Clark AB, Cahn T, et al. 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:** 2282–91.

143 Martinez FJ, Yow E, Flaherty KR, et al. Effect of antimicrobial therapy on respiratory hospitalization or death in adults with idiopathic pulmonary fibrosis: the CleanUP-IPF randomized clinical trial. *JAMA* 2021; **325:** 1841–51.

144 Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med* 2021; **384:** 325–34.

145 Lee JYT, Tikellis G, Corte TJ, et al. The supportive care needs of people living with pulmonary fibrosis and their caregivers: a systematic review. *Eur Respir Rev* 2020; **29:** 190125.

146 Kolb M, Bondue B, Pesci A, et al. Acute exacerbations of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev* 2018; **27:** 180071.

147 Dowman LM, McDonald CF, Hill CJ, et al. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. *Thorax* 2017; **72:** 610–19.

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

149 Liem SIE, Vliet Vlieland TPM, Schoones JW, de Vries-Bouwstra JK. The effect and safety of exercise therapy in patients with systemic sclerosis: a systematic review. *Rheumatol Adv Pract* 2019; **3:** rkz044.

150 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:** 759–70.

151 Lim RK, Humphreys C, Morisset J, Holland AE, Johannson KA. Oxygen in patients with fibrotic interstitial lung disease: an international Delphi survey. *Eur Respir J* 2019; **54:** 1900421.

152 Jacobs SS, Krishnan JA, Lederer DJ, et al. Home oxygen therapy for adults with chronic lung disease. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2020; **202:** e121–41.

153 Aronson KI, Danoff SK, Russell AM, et al. Patient-centered outcomes research in interstitial lung disease: an official American Thoracic Society research statement. *Am J Respir Crit Care Med* 2021; **204:** e3–23.

154 Johannson KA, Chaudhuri N, Adegunsoye A, Wolters PJ. Treatment of fibrotic interstitial lung disease: current approaches and future directions. *Lancet* 2021; **398:** 1450–60.

155 Richeldi L, Scholand MB, Lynch DA, et al. Utility of a molecular classifier as a complement to high-resolution computed tomography to identify usual interstitial pneumonia. *Am J Respir Crit Care Med* 2021; **203:** 211–20.

156 Moor CC, Oppenheimer JC, Nakshbandi G, et al. Exhaled breath analysis by use of eNose technology: a novel diagnostic tool for interstitial lung disease. *Eur Respir J* 2020; **57:** 2002042.

157 Walsh SLF, Humphries SM, Wells AU, Brown KK. Imaging research in fibrotic lung disease; applying deep learning to unsolved problems. *Lancet Respir Med* 2020; **8:** 1144–53.

158 Salisbury ML, Hewlett JC, Ding G, et al. Development and progression of radiologic abnormalities in individuals at risk for familial interstitial lung disease. *Am J Respir Crit Care Med* 2020; **201:** 1230–39.

159 Hobbs BD, Putman RK, Araki T, et al. Overlap of genetic risk between interstitial lung abnormalities and idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2019; **200:** 1402–13.

160 Newton CA, Zhang D, Oldham JM, et al. Telomere length and use of immunosuppressive medications in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2019; **200:** 336–47.

161 Adegunsoye A, Morisset J, Newton CA, et al. Leukocyte telomere length and mycophenolate therapy in chronic hypersensitivity pneumonitis. *Eur Respir J* 2021; **57:** 2002872.

162 Maher TM, Oballa E, Simpson JK, et al. An epithelial biomarker signature for idiopathic pulmonary fibrosis: an analysis from the multicentre PROFILE cohort study. *Lancet Respir Med* 2017; **5:** 946–55.

163 Maher TM, Stowasser S, Nishioka Y, et al. Biomarkers of extracellular matrix turnover in patients with idiopathic pulmonary fibrosis given nintedanib (INMARK study): a randomised, placebo-controlled study. *Lancet Respir Med* 2019; **7:** 771–79.

164 Bowman WS, Newton CA, Linderholm AL, et al. Proteomic biomarkers of progressive fibrosing interstitial lung disease: a multicentre cohort analysis. *Lancet Respir Med* 2022; **10:** 593–602.

165 Aronson KI, Suzuki A. Health related quality of life in interstitial lung disease: can we use the same concepts around the world? *Front Med (Lausanne)* 2021; **8:** 745908.

166 Marcoux V, Wang M, Burgoyne SJ, et al. Mobile health monitoring in patients with idiopathic pulmonary fibrosis. *Ann Am Thorac Soc* 2019; **16:** 1327–29.

167 Moor CC, Mostard RLM, Grutters JC, et al. Home monitoring in patients with idiopathic pulmonary fibrosis. a randomized controlled trial. *Am J Respir Crit Care Med* 2020; **202:** 393–401.

168 Nakshbandi G, Moor CC, Wijsenbeek MS. Home monitoring for patients with ILD and the COVID-19 pandemic. *Lancet Respir Med* 2020; **8:** 1172–74.