

An update on interstitial lung disease

Abstract

Interstitial lung diseases are a complex group of conditions that cause inflammation and scarring of the lung interstitium. This article discusses the diagnosis and management of common interstitial lung diseases including idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, connective tissue disease associated-interstitial lung disease, sarcoidosis and drug-induced interstitial lung disease. A multidisciplinary approach to diagnosis of interstitial lung disease is the gold standard; key history and examination features, blood panel, pulmonary function tests, high resolution computed tomography imaging, and when required bronchoalveolar lavage and lung biopsy results are discussed to reach a multidisciplinary consensus diagnosis. Advances, including the development of the disease-modifying anti-fibrotic medications nintedanib and pirfenidone, continue to shape the future management of interstitial lung disease. A holistic approach to the care of patients with interstitial lung disease is paramount, as they often have a high symptom burden and considerable palliative care needs.

Key words: Connective tissue disease; Drug-induced interstitial lung disease; Hypersensitivity pneumonitis; Idiopathic pulmonary fibrosis; Interstitial lung disease; Sarcoidosis

Submitted: 14 September 2020; accepted following double-blind peer review: 15 September 2020

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Introduction

The term interstitial lung disease is synonymous with diffuse parenchymal lung diseases and is the umbrella term for a heterogeneous group of conditions that lead to inflammation and scarring of the lung interstitium. Interstitial lung disease is a significant cause of morbidity and mortality worldwide, and its diverse and often multisystem presentation means that it can be seen by clinicians in many different specialities. This review outlines the diagnosis and management of interstitial lung disease.

Interstitial lung diseases can be divided into those with known aetiologies including autoimmune drivers in connective tissue diseases, or those related to environmental exposures such as birds in hypersensitivity pneumonitis. Most interstitial lung diseases have no defined cause and are termed idiopathic interstitial pneumonias (Figure 1). This article focuses on the more common interstitial lung diseases including idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, connective tissue disease-associated interstitial lung disease, sarcoidosis, and drug-induced interstitial lung disease. Further types are beyond the scope of this review.

Accurate diagnosis is essential in ensuring correct treatment and prognosis. Comprehensive clinical history and examination should ensure that vital aetiologies and drivers of inflammation and fibrosis are explored (Table 1). Key investigations include chest radiograph, blood panel (Table 2), pulmonary function tests and high-resolution computed tomography. In specific cases bronchoalveolar lavage is beneficial, and in a minority, balancing risks of biopsy vs benefit, transbronchial lung cryobiopsy or surgical lung biopsy may be required (Raghu et al, 2018).

A multidisciplinary team approach to the diagnosis and management of interstitial lung disease is the gold standard, as defined by international clinical guidelines (Raghu et al, 2018). The multidisciplinary team typically consists of a respiratory physician(s), thoracic radiologist, histopathologist and interstitial lung disease specialist nurse, and in certain scenarios benefits from the presence of a rheumatologist. The multidisciplinary team discusses the clinical history coupled with results from key investigations to reach a consensus diagnosis (Richeldi et al, 2019). Walsh et al (2016) found inter-multidisciplinary team agreement to be moderate-to-good for idiopathic pulmonary fibrosis ($k=0.60$) and connective tissue disease associated-interstitial lung disease ($k=0.64$), but less favourable for hypersensitivity pneumonitis ($k=0.24$).

How to cite this article:

Mudawi D, Heyes K, Hastings R, Rivera-Ortega P, Chaudhuri N. An update on interstitial lung disease. *Br J Hosp Med*. 2021. <https://doi.org/10.12968/hmed.2020.0556>

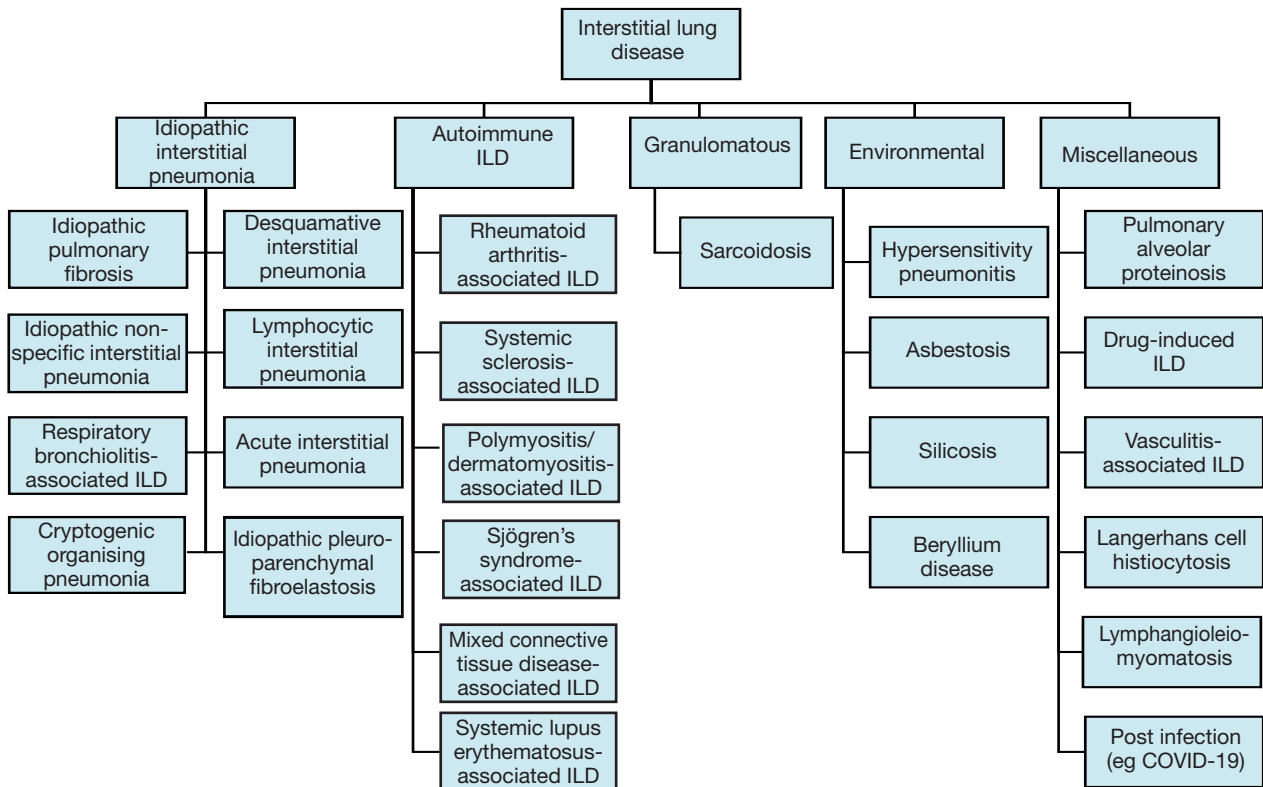


Figure 1. Classification of interstitial lung disease (ILD) (adapted from Cottin et al, 2018).

Table 1. Key clinical history, examination findings and drug exposures		
History	Respiratory symptoms and history of infections	<ul style="list-style-type: none"> ■ Dyspnoea ■ Cough ■ Reduced exercise tolerance ■ Recurrent infections
	Occupational exposures	<ul style="list-style-type: none"> ■ Asbestos ■ Coal dust ■ Silica ■ Beryllium
	Environmental exposures	<ul style="list-style-type: none"> ■ Cigarette smoking and use of electronic cigarettes ■ Birds ■ Feather duvets or pillows ■ Mould ■ (for extensive list see Table 4)
	Systemic symptoms or autoimmune disease features	<ul style="list-style-type: none"> ■ Arthralgia ■ Sicca symptoms ■ Rashes ■ Raynaud phenomenon ■ Dysphagia ■ Constitutional symptoms ■ Proximal muscle weakness ■ Fatigue ■ Weight loss

The management of interstitial lung disease is tailored towards patient- and disease-specific aspects. A holistic approach to the care of these patients is paramount given the frequently high symptom burden and existing comorbidities (Garibaldi and Danoff, 2016).

Table 1. Key clinical history, examination findings and drug exposures (continued)

Examination	Respiratory examination	<ul style="list-style-type: none"> ■ Hypoxia ■ Tachypnoea ■ Digital clubbing ■ Cyanosis ■ Crepitations ■ Reduced chest expansion ■ Pedal oedema ■ Raised jugular venous pressure ■ Parasternal heave ■ Loud P2
	Systemic examination	<ul style="list-style-type: none"> ■ Synovitis ■ Dry eyes or mouth ■ Rashes ■ Features of Raynaud's ■ Proximal myopathy ■ Telangiectasia ■ Sclerodactyly ■ Mechanic's hands ■ Calcinosis ■ Gottron papules ■ Digital ulcers ■ Oral ulcers
Drug exposures (not exhaustive)	Chemotherapeutic agents	<ul style="list-style-type: none"> ■ Bleomycin ■ Gemcitabine ■ Epidermal growth factor receptor-directed therapies ■ Mechanistic target of rapamycin protein inhibitors ■ Immune checkpoint inhibitors
	Rheumatological therapy	Biological disease-modifying anti-rheumatic drugs, eg methotrexate, leflunomide, sulfasalazine
	Antibiotics	<ul style="list-style-type: none"> ■ Nitrofurantoin ■ Daptomycin
	Other agents	<ul style="list-style-type: none"> ■ Antiarrhythmic (amiodarone) ■ Non-steroidal anti-inflammatory drugs

Van Manen et al (2017) suggest an ABCDE approach to management. Assessment should be Backed up with patient and carer education about their illness, referral to patient support groups and pulmonary rehabilitation. Comorbidities and Comfort care should be considered with management of cough and breathlessness. When appropriate, offer Disease-modifying drug therapies or lung transplantation, and consider End of life care and palliative needs.

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis is characterised by progressive dyspnoea and irreversible loss of lung function. With an incidence of 4.6–7.4 per 100 000 (Navaratnam et al, 2011), it is defined by the histopathological and/or radiological pattern of usual interstitial pneumonia. Healthy lung tissue is replaced by altered extracellular matrix leading to loss of alveolar architecture, reduction in lung compliance and gas exchange, and consequently respiratory failure. The typical presentation is of gradual onset, exertional breathlessness and cough. Examination typically reveals bi-basal inspiratory crepitations with clubbing in over 40% (Cai et al, 2014).

High-resolution computed tomography features of definite, probable and indeterminate patterns of usual interstitial pneumonia are shown in [Table 3](#), and typical high-resolution

Table 2. Interstitial lung disease blood panel

Autoimmune screen	<ul style="list-style-type: none"> ■ Antinuclear antibody ■ Anti-double stranded DNA ■ Anti-ribonucleoprotein antibody ■ Anti-Smith antibody ■ Anti-SCI70 ■ Anti Ro (SSA) and Anti La (SSB) ■ Rheumatoid factor ■ Anticyclic citrullinated peptide ■ Anti-Jo-1 antibody ■ Creatinine kinase ■ Erythrocyte sedimentation rate
Vasculitis screen	<ul style="list-style-type: none"> ■ Anti-neutrophil cytoplasmic antibody ■ Anti-glomerular basement membrane antibody
Specific tests	<ul style="list-style-type: none"> ■ Avian precipitins ■ Fungal precipitins ■ Farmer's lung precipitins ■ Serum angiotensin-converting enzyme

Table 3. High-resolution computed tomography scanning patterns for usual interstitial pneumonia

Definite usual interstitial pneumonia	<ul style="list-style-type: none"> ■ Subpleural and basal predominant ■ Heterogenous distribution ■ Honeycombing ■ +/- traction bronchiectasis or bronchiolectasis
Probable usual interstitial pneumonia	<ul style="list-style-type: none"> ■ Subpleural and basal predominant ■ Heterogenous distribution ■ Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis ■ May have mild ground-glass opacification
Indeterminate for usual interstitial pneumonia	<ul style="list-style-type: none"> ■ Subpleural and basal predominant ■ Subtle reticulation; may have mild ground-glass opacification or distortion ■ Computed tomography features and/or distribution of lung fibrosis that do not suggest any specific aetiology

From Raghu et al (2018)

computed tomography imaging of idiopathic pulmonary fibrosis in [Figure 2](#). With a definite usual interstitial pneumonia pattern, bronchoalveolar lavage and biopsy are not required, but international guidelines conditionally recommend bronchoalveolar lavage and biopsy in those with probable or indeterminate usual interstitial pneumonia or alternative patterns, after carefully considering contraindications and risks (Raghu et al, 2018).

The histology of idiopathic pulmonary fibrosis typically shows a fibrosing usual interstitial pneumonia pattern characterised by temporal and spatial heterogeneity, architectural distortion, honeycombing and fibroblastic foci.

Prognosis in idiopathic pulmonary fibrosis is historically poor with a median survival of 3 years (Ley et al, 2011). In the last decade, its management has been transformed by the approval of two disease-modifying anti-fibrotic medications, pirfenidone and nintedanib.

Pirfenidone has anti-inflammatory and anti-fibrotic properties through its action on transforming growth factor-β1 (Oku et al, 2008). Pirfenidone has been evaluated in three multicentre phase III trials: CAPACITY 004 and 006 (Noble et al, 2011) and ASCEND (King et al, 2014). Pooled analysis of these trials found that treatment with pirfenidone 2403 mg/

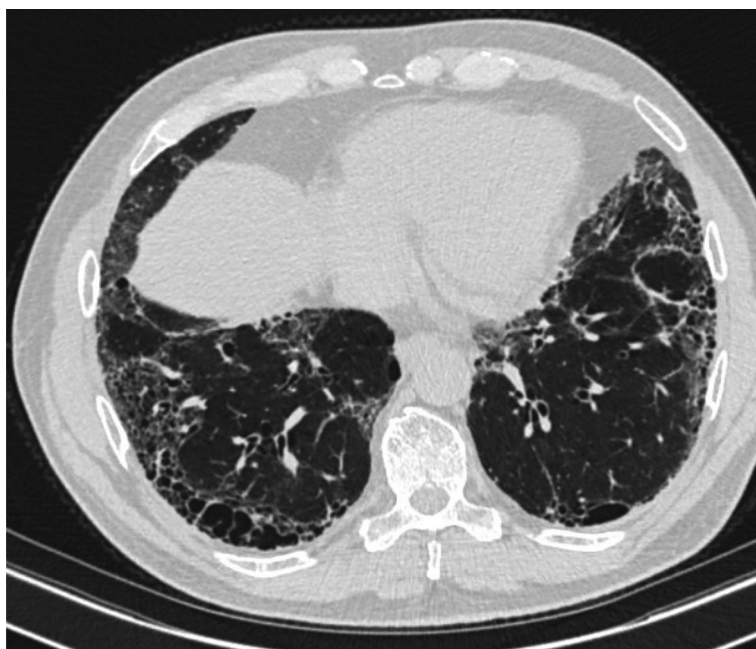


Figure 2. High-resolution computed tomography showing characteristic usual interstitial pneumonia pattern of idiopathic pulmonary fibrosis: fibrosis with basal predominant reticulation with architectural distortion, traction bronchiectasis and honeycombing.

day reduced the proportion of patients experiencing a forced vital capacity decline of $\geq 10\%$ or death by 43.8% (Noble et al, 2016). Gastrointestinal and skin-related adverse events were more common in the pirfenidone group but rarely led to treatment discontinuation. Based on cost-effectiveness analysis, pirfenidone can be offered in the UK to patients with forced vital capacity 50–80% (National Institute for Health and Care Excellence, 2018).

Nintedanib is an intracellular inhibitor that targets multiple tyrosine kinases. The INPULSIS trials demonstrated a significant reduction in the rate of forced vital capacity decline over a 52-week period in patients with idiopathic pulmonary fibrosis receiving nintedanib compared to placebo (Richeldi et al, 2014). The mean difference in forced vital capacity decline was 109.9 ml/year and significantly fewer patients suffered a ≥ 5 or $\geq 10\%$ decline. Nintedanib was frequently associated with diarrhoea, which led to discontinuation of the study medication in $<5\%$ of patients. Nintedanib can be offered to patients in the UK with a forced vital capacity 50–80% (National Institute for Health and Care Excellence, 2016).

Meta-analyses indicate that both anti-fibrotics have similar efficacy (Canestaro et al, 2016), so treatment decisions are guided by comorbidities, relative contraindications and potential side-effect profiles (Table 4).

The National Institute for Health and Care Excellence (2015) quality standards advise that patients with idiopathic pulmonary fibrosis should have access to an interstitial lung disease specialist nurse, oxygen assessment, pulmonary rehabilitation and palliative care services if needed. Appropriate patients can be referred for lung transplant assessment if eligible.

Table 4. Antifibrotic therapy

	Target dose	Common side effects	Contraindications and cautions
Pirfenidone	801 mg three times daily	Nausea, dyspepsia, vomiting, anorexia, photosensitive rash, deranged liver function tests	<ul style="list-style-type: none"> ■ Contraindication: estimated glomerular filtration rate <30 ml/min/1.73m² ■ Cautions: hepatic impairment; avoid exposure to direct sunlight and use high factor sunscreen
Nintedanib	150 mg twice daily	Diarrhoea, deranged liver function tests, nausea, abdominal pain and weight loss	<ul style="list-style-type: none"> ■ Contraindication: peanut or soya hypersensitivity ■ Cautions: anticoagulation, prolonged QTc, high risk cardiovascular disease, previous abdominal surgery, hepatic impairment, severe renal impairment

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis results from exposure and sensitisation to inhaled antigens (Riario Sforza and Marinou, 2017). Many causative agents have been identified, some of which are summarised in Table 5. Pathogenicity results from a combination of both immune complex-mediated (type III) and delayed type (type IV) hypersensitivity reactions. Chemokines and proinflammatory cytokines mediate a sustained CD8 cytotoxic T-cell response, macrophage activation, granuloma formation and fibrosis (Miller et al, 2018). Incidence of hypersensitivity pneumonitis is approximately 1.16 per 100 000 (Rittig et al, 2019).

Hypersensitivity pneumonitis can be classified as acute or inflammatory or as chronic or fibrotic. In acute hypersensitivity pneumonitis, symptom duration is less than 6 months and patients typically develop fever, dyspnoea, cough and malaise. There is rapid resolution of symptoms providing the offending agent is removed. The presence of fibrotic changes on high-resolution computed tomography or histology defines chronic hypersensitivity pneumonitis, and reflects prolonged exposure (Vasakova et al, 2017). Physical examination may reveal inspiratory crackles or squeaks.

Characteristic findings on high-resolution computed tomography include mosaic attenuation and ground-glass opacification in the mid to upper zones (Figure 3), as well as centrilobular nodularity and honeycombing (Silva et al, 2008). Bronchoalveolar lavage lymphocytosis of >50% supports the diagnosis of hypersensitivity pneumonitis (Meyer et al, 2012).

Diagnosing hypersensitivity pneumonitis is challenging because of the lack of defined international diagnostic criteria, up to 60% antigen indeterminacy (Miyazaki et al, 2016), low levels of inter-multidisciplinary team diagnostic agreement (Walsh et al, 2016), and the similar radiological appearances of chronic hypersensitivity pneumonitis and idiopathic pulmonary fibrosis (Silva et al, 2008). Lung biopsy should be considered if diagnostic uncertainty remains despite initial investigation. Characteristic histology findings are bronchiolocentric inflammation, poorly formed non-necrotising granulomas and peribronchiolar giant cells. Fibrosis with honeycombing is seen in severe chronic hypersensitivity pneumonitis (Morisset et al, 2018).

Table 5. Antigen causes of hypersensitivity pneumonitis (not exhaustive)

Antigen	Sources	Diseases
<i>Aspergillus clavatus</i>	Mouldy barley	Malt worker's lung
Avian proteins	Bloom on bird feathers and droppings	Bird fancier's lung
<i>Aspergillus</i> spp, <i>Thermoactinomyces vulgaris</i>	Compost	Compost lung
<i>Botrytis cinerea</i>	Grape mould	Wine grower's lung
<i>Mycobacterium avium</i> complex	Hot tub mist, ceiling mould	Hot tub lung
<i>Penicillium casei</i>	Cheese mould	Cheese worker's lung
Rat proteins	Rat droppings	Rat lung
Shell proteins	Oyster or mollusc shell	Shell lung
Thermophilic actinomycetes	Mouldy hay	Farmer's lung
	Mushroom	Mushroom lung
	Sugar cane	Bagassosis
Thermophilic actinomycetes, (<i>Thermoactinomyces candidus</i> , <i>Thermoactinomyces vulgaris</i>), <i>Penicillium</i> spp, <i>Cephalosporium</i> spp, amoebae	Humidifier and conditioner	Humidifier lung
Toluene diisocyanate	Paints	Isocyanate hypersensitivity pneumonitis
<i>Trichosporon cutaneum</i>	House dust	Summer-house hypersensitivity pneumonitis (Japan)

A full list of causes is available at <https://www.hplung.com/>

The modified Delphi survey involving an international group of experts attached highest importance to the following criteria for diagnosis of chronic hypersensitivity pneumonitis: time relation between exposure and disease, identification of a causative antigen, mosaic attenuation on imaging, and poorly formed non-necrotising granulomas on histology (Morisset et al, 2018).

Removal of the responsible antigen (if known) should be the first step managing patients with hypersensitivity pneumonitis. Oral corticosteroids are the first-line treatment, despite the paucity of randomised controlled trial data demonstrating efficacy (Vasakova et al, 2017). A reasonable empirical treatment regimen consists of prednisone 0.5–1 mg/kg daily for 1–2 weeks in acute hypersensitivity pneumonitis, or for 4–8 weeks in chronic hypersensitivity pneumonitis, followed by a gradual taper (Spagnolo et al, 2015).

Evidence for second-line immunosuppression in hypersensitivity pneumonitis is again limited. Morisset et al (2017) evaluated 71 patients treated with mycophenolate mofetil or azathioprine and found no improvement in forced vital capacity after 1-year treatment but a statistically significant improvement in diffusion capacity of 4.2%.

A proportion of patients with hypersensitivity pneumonitis will progress to end-stage lung fibrosis and lung transplantation may be considered in this group (Kern et al, 2015).

Connective tissue disease-associated interstitial lung disease

Connective tissue diseases include a spectrum of systemic autoimmune diseases in which circulating autoantibodies lead to inflammation and ultimately end organ damage. Those associated with fibrosing interstitial lung disease include rheumatoid arthritis, systemic sclerosis or scleroderma, idiopathic inflammatory myopathies (polymyositis, dermatomyositis and anti-synthetase syndrome), Sjögren's syndrome, systemic lupus erythematosus and mixed connective tissue diseases.

It is difficult to provide accurate data on the prevalence of interstitial lung disease in connective tissue disease but evidence of interstitial lung disease has been shown on chest radiograph and lung function in up to 20% of patients with rheumatoid arthritis (Jurik et al, 1982) and 10% of patients with systemic lupus erythematosus (Eisenberg et al, 1973), and pulmonary fibrosis is found at autopsy in up to 75% of patients with systemic sclerosis (D'Angelo et al, 1969). Analysis of 3656 patients with systemic sclerosis revealed that

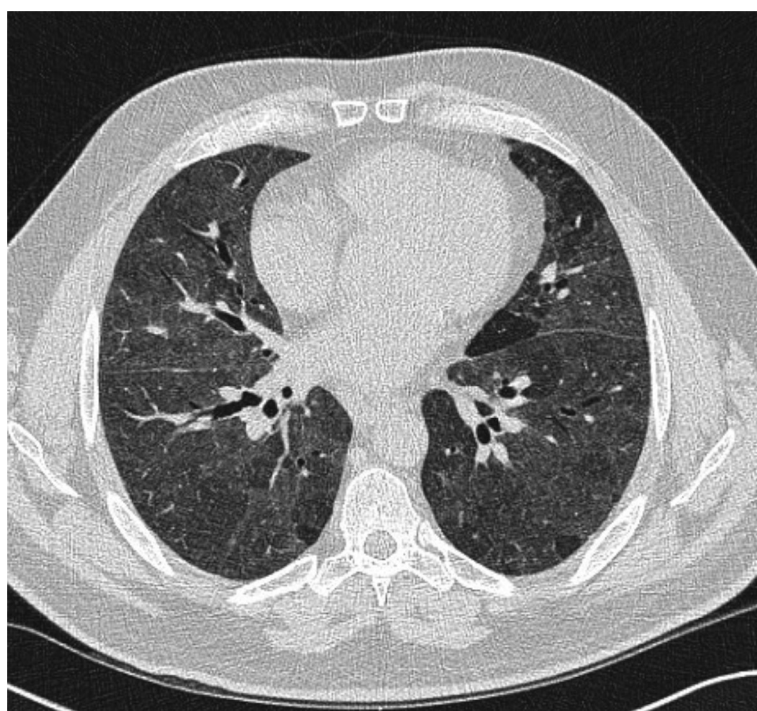


Figure 3. High-resolution computed tomography showing features of hypersensitivity pneumonitis: diffuse ground-glass opacification and mosaic attenuation.

interstitial lung disease is present in 53% of cases with diffuse cutaneous systemic sclerosis and in 35% of cases with limited cutaneous systemic sclerosis (Walker et al, 2007). The risk of connective tissue disease-interstitial lung disease appears to be higher in women and in those less than 50 years of age (Cottin, 2016).

Connective tissue disease-associated interstitial lung disease is characterised predominantly by non-specific interstitial pneumonia and organising pneumonia patterns of fibrosis (Cottin, 2016), with the exception of rheumatoid arthritis-interstitial lung disease, which typically has a usual interstitial pneumonia pattern. Connective tissue disease related-interstitial lung disease may behave in a progressive fibrosing fashion.

Systemic sclerosis-associated interstitial lung disease

The pathogenesis of systemic sclerosis-associated interstitial lung disease is believed to involve repetitive epithelial injury, activation of innate and adaptive immune mechanisms, and fibroblast activation (Castillo-Tandazo et al, 2013). Approximately 25% of patients with systemic sclerosis develop significant pulmonary involvement within 3 years of diagnosis and it accounts for approximately one-third of deaths (Tyndall et al, 2010). The majority of patients test positive for antinuclear antibodies, and systemic sclerosis-specific antibodies (eg anti-topoisomerase I/anti scl-70, anti-centromere) are commonly found (Cappelli et al, 2015). Exertional dyspnoea, cough and fatigue are common symptoms.

High-resolution computed tomography and histology reveals a non-specific interstitial pneumonia pattern, although a usual interstitial pneumonia pattern may also be seen (Desai et al, 2004). Characteristic features of fibrotic non-specific interstitial pneumonia pattern are demonstrated in **Figure 4**, with a high proportion of ground-glass opacities and a lower proportion of coarse reticulations.

The mainstay of treatment in all patients with connective tissue disease-associated interstitial lung disease is immunomodulation. The Scleroderma Lung Study I reported that treatment with oral cyclophosphamide for 1 year had a beneficial effect on lung function, dyspnoea, thickening of skin, and quality of life (Tashkin et al, 2006). The Scleroderma Lung Study II compared the effects of mycophenolate mofetil to cyclophosphamide and found that the adjusted % predicted forced vital capacity improved by 2.19 and 2.88 in the two groups respectively. Given its better tolerability and non-inferiority to cyclophosphamide (Tashkin et al, 2016), mycophenolate mofetil is recommended as first-line treatment.

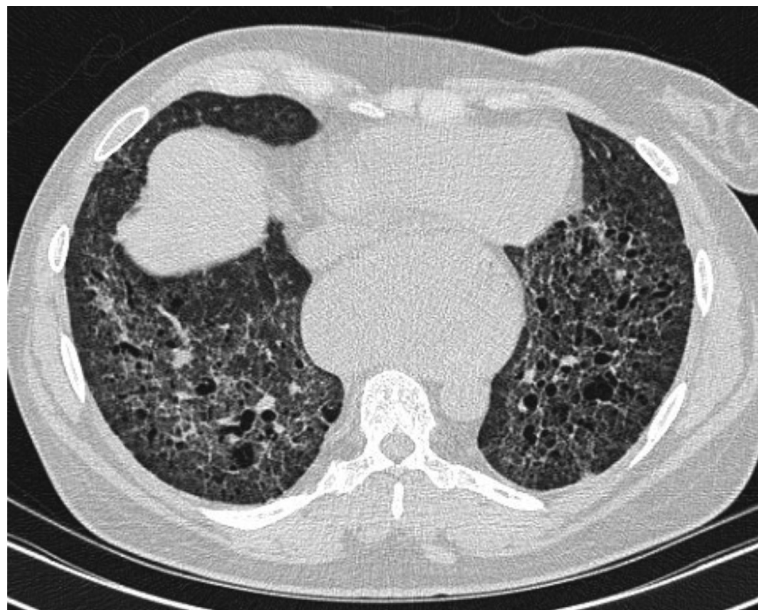


Figure 4. Characteristic high-resolution computed tomography of non-specific interstitial pneumonia pattern associated with systemic sclerosis. Coarse reticulation with marked traction bronchial dilation and diffuse ground-glass opacities are seen, with relative sparing of the immediate subpleural lung consistent with a non-specific interstitial pneumonia pattern.

The SENSICIS trial (Distler et al, 2019) compared nintedanib with placebo in patients with systemic sclerosis-associated interstitial lung disease and found a relative 44% reduction in the annual rate of forced vital capacity decline with nintedanib. This prompted the European Medicines Agency to recommend expanding the indication for nintedanib to include systemic sclerosis-associated interstitial lung disease.

Rheumatoid arthritis-related interstitial lung disease

Interstitial lung disease can be the presenting feature of rheumatoid arthritis and is thought to be caused by chronic immune activation and inflammation, which stimulates fibroproliferation in the lung parenchyma. There are strong associations between rheumatoid arthritis-interstitial lung disease and older age, male sex, cigarette smoking, high rheumatoid factor titres and increased anti-citrullinated protein antibody levels (Cottin, 2016).

The most common pattern seen on high-resolution computed tomography or lung biopsy in these patients is usual interstitial pneumonia (Lee et al, 2005), which is associated with a poorer survival than a non-specific interstitial pneumonia pattern (Kim et al, 2010).

The evidence base for treatment of rheumatoid arthritis-interstitial lung disease is limited because of the lack of prospective randomised controlled trials (Shaw et al, 2015), so the rationale for treatment is extrapolated from the treatment of rheumatoid arthritis. Anti-inflammatory and/or immunosuppressive agents are recommended regardless of the pattern of fibrosis, although non-specific interstitial pneumonia and organising pneumonia patterns are felt to be more responsive (O'Dwyer et al, 2013).

Corticosteroids are the mainstay of therapy, but cyclophosphamide and azathioprine have been used with varying success along with mycophenolate mofetil and rituximab. A meta-analysis showed that use of methotrexate is not associated with an increased risk of rheumatoid arthritis-interstitial lung disease (Juge et al, 2021). Further studies are required to assess the safety and efficacy of rituximab, tumour necrosis factor inhibitors and other biologics.

The INBUILD trial has shown that nintedanib reduced lung function decline by 57% over 52 weeks in patients with progressive fibrosing interstitial lung disease, a proportion of whom had rheumatoid arthritis-interstitial lung disease (Flaherty et al, 2019). It is yet to be decided how this will be translated into clinical practice.

Sarcoidosis

Sarcoidosis is a multi-system disorder of unknown aetiology, likely resulting from a combination of environmental and genetic factors. With an incidence of 1.0–35.5 per 100 000, the highest rates are reported in northern European or Scandinavian and African-American individuals (Valeyre et al, 2014). The characteristic features are of non-caseating granulomata and CD4+ Th1-biased T-cell response in the affected organs. Extrapulmonary manifestations include cardiac sarcoidosis, neurosarcoidosis, arthritis, parotitis, uveitis or cutaneous lesions. Löfgren's syndrome consists of bilateral hilar lymphadenopathy, erythema nodosum and arthritis.

Patients with node-limited disease may be asymptomatic or display constitutional symptoms. Parenchymal sarcoidosis can present with dyspnoea and cough (Mana et al, 2017).

Routine investigations include chest radiograph, on which the Scadding staging classification is based (Table 6), full blood count, serum calcium, renal and liver function tests, and electrocardiogram. Ophthalmic review is appropriate in any patient with ocular symptoms. Serum angiotensin-converting enzyme has a sensitivity of only 57% (Sharma, 1986), so its value as a screening or monitoring tool is limited.

High-resolution computed tomography findings include symmetrical hilar and mediastinal lymphadenopathy, perilymphatic nodularity and a mid-upper zone predominance (Figure 5).

The diagnosis is established when clinical and radiological findings are supported by histological evidence of non-caseating granulomatous inflammation. In cases such as patients with Löfgren's syndrome, presumptive diagnosis may be made based on clinical and radiological findings alone. Otherwise, biopsy confirmation should be sought from the most accessible site to exclude differential diagnoses including tuberculosis, lymphoma or malignancy, or fungal disease.

Table 6. Scadding radiological classification of thoracic sarcoidosis

Stage 0	Normal
Stage I	Hilar lymphadenopathy
Stage II	Hilar lymphadenopathy and parenchymal infiltrate
Stage III	Parenchymal infiltrate
Stage IV	Fibrosis

From Scadding (1961)

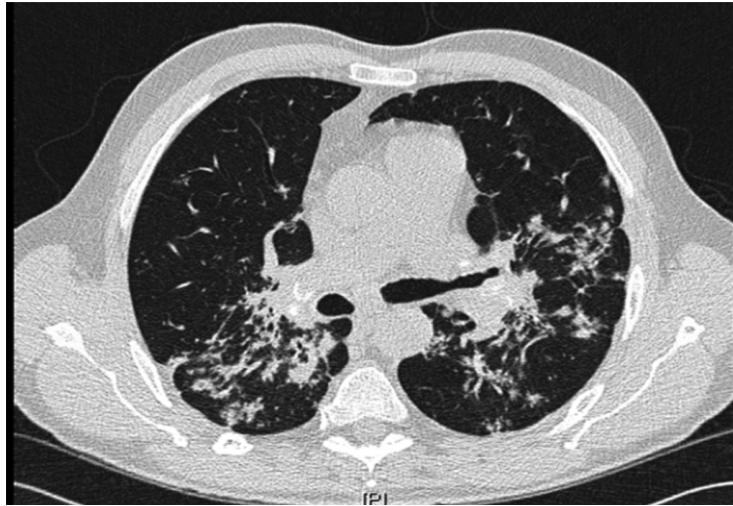


Figure 5. High-resolution computed tomography showing characteristic features of pulmonary sarcoidosis: bilateral hilar lymphadenopathy and peribronchovascular nodules in a mid-upper zone predominant pattern.

Endobronchial ultrasound-guided transbronchial needle aspiration is an appropriate primary diagnostic approach for stage I and II sarcoidosis (Mehta and Almeida, 2014), while transbronchial biopsy should be considered in predominantly parenchymal disease. Cardiac magnetic resonance imaging is the tool of choice for diagnosing cardiac sarcoidosis (Kouranos et al, 2017) and pulmonary artery catheterisation for confirming pulmonary hypertension, a major predictor of mortality in sarcoidosis (Kirkil et al, 2018).

Treatment of sarcoidosis is usually limited to the symptomatic patient, or those with evidence of end-organ damage (Baughman and Wells, 2019). Usual practice is to start prednisolone at 20–40 mg/day for 4–6 weeks, followed by slow tapering to a maintenance dose, usually 5–10 mg/day. Approximately 40% of patients will spontaneously remit within 6 months while others may progress to chronic disease (Gibson et al, 1996).

Indications for second-line agents include progressive disease, unacceptable symptom burden despite steroids, intolerable steroid side effects or inability to taper prednisolone below 10–15 mg/day. Options for escalation include methotrexate, mycophenolate mofetil, leflunomide and azathioprine. All these agents carry a significant risk of toxicity, particularly myelosuppression, hepatotoxicity and opportunistic infection. Tumour necrosis factor inhibitors are third-line therapeutic agents (Crouser et al, 2010).

In those with advanced pulmonary fibrosis and/or associated pulmonary hypertension, lung transplantation may be considered.

Drug-induced interstitial lung disease

Drug-induced interstitial lung disease occurs when exposure to an agent causes inflammation and ultimately fibrosis of the lung interstitium. Mechanisms of injury include pneumotoxic agents causing direct injury to the lung parenchyma or drugs acting as antigens inducing an immune cascade leading to immune-mediated lung toxicity (Schwaiblmair et al, 2012).

Drug-induced interstitial lung disease is a diagnosis of exclusion and should be based on clinical and radiological findings consistent with interstitial lung disease, a temporal relationship between the onset of symptoms and drug exposure, and the absence of a more likely cause.

Over 350 drugs may cause drug-induced interstitial lung disease and this accounts for 3–5% of cases of prevalent interstitial lung disease (Skeoch et al, 2018). A systematic review by Skeoch et al (2018) found that cancer drugs were the leading cause in most studies (23–51%), followed by disease-modifying anti-rheumatic drugs (6–72%) and antibiotics (6–26%), with nitrofurantoin the most common antibiotic cause.

Bleomycin causes injury via immune-mediated and direct toxic effects and has a reported incidence of 6.8–21% (Skeoch et al, 2018). Gemcitabine has a reported incidence rate of 1–20% and is highest when used in combination with other agents. Amiodarone has been shown to cause drug-induced interstitial lung disease at an incidence of 1.2–8.8% in registry studies. Mechanistic target of rapamycin (mTOR) inhibitors have been associated with radiographic features of drug-induced interstitial lung disease in clinical trials. Immunotherapy is an expanding area in cancer therapy and immune checkpoint inhibitors such as PD-1 and PD-L1 have a 3.6% and 1.1% rate of drug-induced interstitial lung disease in clinical trials respectively.

Methotrexate exposure has historically been implicated as a common cause of drug-induced interstitial lung disease. However, evidence suggests an overestimation of risk; a 2015 meta-analysis found no increased risk in patients who did not have rheumatoid arthritis but were treated with methotrexate (Conway et al, 2015) and methotrexate treatment was not associated with an increased risk of rheumatoid arthritis-interstitial lung disease (Kiely et al, 2019).

The most common radiological pattern in patients with drug-induced interstitial lung disease is ground-glass opacification with or without consolidation, in a basal, peripheral and bilateral distribution. Radiological appearance can resemble organising pneumonia or non-specific interstitial pneumonia. Qualitative computed tomography changes are not specific to drug-induced interstitial lung disease and are highly variable for the same drug (Schwaiblmair et al, 2012). On bronchoalveolar lavage a lymphocytic (>15% lymphocytes) or eosinophilic cellular pattern (>1% eosinophils) is most suggestive of drug-induced interstitial lung disease (Meyer et al, 2012), but these are not specific and so bronchoalveolar lavage is mainly used to help exclude other causes.

Treatment of drug-induced interstitial lung disease begins with withdrawal of the causative medication(s). Corticosteroids are advised if the disease progresses despite withdrawal of the medication. Once drug-induced interstitial lung disease has progressed to a fibrotic stage, corticosteroids have a limited role.

Registration of drug-related lung diseases has been coordinated by the Pneumotox group in Dijon, France (www.pneumotox.com) and this is an excellent resource for clinicians.

Conclusions

Interstitial lung diseases are a complex and diverse group of conditions that require a multidisciplinary approach to diagnosis and management. Advances in diagnostic techniques such as transbronchial lung biopsy, and the development of novel drug therapies including anti-fibrotic medications, continue to shape the future management of interstitial lung disease. Reaching an accurate diagnosis is paramount in optimising management and outcomes, and the value of this should not be discounted amid the emerging phenomenon of progressive fibrotic interstitial lung disease. Despite optimal management, many interstitial lung diseases carry a poor prognosis, thus a holistic approach to care and close working relationship with palliative care networks are essential.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Key points

- Patients with idiopathic pulmonary fibrosis and forced vital capacity of 50–80% predicted should be offered anti-fibrotic therapy with pirfenidone or nintedanib. There is country-by-country variation in approval.
- Diagnosis of hypersensitivity pneumonitis requires a high index of suspicion by the clinician, thorough history taking including environmental and occupational exposures, coupled with characteristic high-resolution computed tomography findings.
- Connective tissue disease-associated interstitial lung disease should be suspected in patients with clinical features of connective tissue disease and positive autoantibodies, and is supported by specialist rheumatological review.
- Sarcoidosis is a multisystem disorder and treatment with steroids is governed by the risk of end organ damage and is not always warranted.
- Drug-induced interstitial lung disease is a diagnosis of exclusion.

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