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# The diagnosis and management of interstitial lung diseases

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The interstitial lung diseases comprise a complex group of pulmonary disorders principally affecting the pulmonary interstitium. The group includes idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, sarcoidosis, and connective tissue disease associated interstitial lung disease.

The aim of this review is to highlight the salient features in the history and examination that can suggest a specific interstitial lung disease, and suggest an approach to diagnosis and management for the non-specialist.

### How common are they?

Idiopathic pulmonary fibrosis is the commonest interstitial lung disease, with an estimated incidence in the United Kingdom of around 7.44 per 100 000 population<sup>1</sup> and an estimated prevalence varying from as many as 23.4 cases per 100 000 in Europe to as many as 63 per 100 000 in the United States.<sup>2</sup> Idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, sarcoidosis, and connective tissue disease associated interstitial lung disease constitute the majority of cases encountered in everyday clinical practice. Other interstitial lung diseases such as alveolar proteinosis are rare (estimated incidence around one per two million population).<sup>3</sup>

### How are they classified?

The interstitial lung diseases are a heterogeneous group of conditions with varying prognoses and clinical behaviours. Their classification is complex (box 1).

The range of causal factors attributed to interstitial lung disease include underlying connective tissue disease and occupational or environmental exposures such as to asbestos, toxic drugs, and radiation. Idiopathic pulmonary fibrosis is the most common of the group

### SOURCES AND SELECTION CRITERIA

We carried out an electronic search of Medline and Embase for relevant original papers and systematic reviews using the search terms “pulmonary fibrosis”, “interstitial lung disease”, and “diffuse parenchymal lung disease”, prioritising those published from 2010. Relevant articles from the Cochrane databases and personal references were also included.

of idiopathic interstitial pneumonias (see box 1).<sup>6</sup> The term cryptogenic fibrosing alveolitis is no longer used to describe idiopathic pulmonary fibrosis.

Some cases of interstitial lung disease remain unclassifiable despite a multidisciplinary approach. In a cohort study, 10% of interstitial lung disease remained unclassified.<sup>7</sup>

### How are they assessed?

Although dyspnoea is typical, a high index of clinical suspicion is necessary to facilitate early diagnosis as patients often present with non-specific signs and symptoms. In some cases interstitial lung disease may only be suspected after an incidental finding on a chest radiograph. A lack of response to treatments for infection or pulmonary oedema should prompt consideration of a diagnosis of interstitial lung disease.

### Symptoms

As well as suggesting a diagnosis of interstitial lung disease, a detailed history can in some cases provide sufficient information to indicate a specific form or cause of the disease. Box 2 lists the key points to cover in the history.

The time course over which symptoms develop can help to differentiate the types of disease. Some interstitial lung diseases, such as organising pneumonia or acute interstitial pneumonia, can present rapidly, whereas the more usual time course for many forms such as idiopathic pulmonary fibrosis is insidious, with breathlessness often present for more than a year. Age is also important. Some interstitial lung diseases, including hypersensitivity pneumonitis and connective tissue disease associated interstitial lung disease, more typically present in patients aged less than 50 years. Most patients with sarcoidosis present at ages 25-40 years, but the disease is not uncommon in older people, and a Japanese study found a bimodal distribution, with 30% of cases occurring after the age of 50 years.<sup>8</sup> Idiopathic pulmonary fibrosis typically presents in patients in their 60s or 70s.

Cough is commonly encountered and is often dry and exacerbated by reflux (itself implicated as a causative factor in interstitial lung disease). Patients may feel general malaise and constitutional upset, particularly those with underlying connective tissue disease, vasculitis, and some cases of sarcoidosis. Haemoptysis is unusual

### THE BOTTOM LINE

- The interstitial lung diseases are a complex group of disorders, but idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, connective tissue disease associated interstitial lung disease, and sarcoidosis make up the majority seen in clinical practice
- Patients present with non-specific signs and symptoms and so a high index of suspicion is required
- Typical findings of bi-basal crepitations can be mistaken for pulmonary oedema, but patients usually lack other features of this; a lack of response to treatment for oedema or infection should raise suspicion
- Early referral to specialist services enables prompt diagnosis and management to optimise outcome, and this process can be facilitated by investigations in the community, including chest radiography and some serology
- Symptom control, occupational therapy, and palliative care are also important aspects of managing patients with interstitial lung disease, requiring input from multiple agencies and specialists

**Box 1 | Simplified classification of interstitial lung disease**

**Interstitial pneumonias (often idiopathic)**

Chronic fibrosing—idiopathic pulmonary fibrosis, idiopathic non-specific interstitial pneumonia

Acute or subacute—organising pneumonia, acute interstitial pneumonia

Smoking related—respiratory bronchiolitis associated interstitial lung disease, desquamative interstitial pneumonia

**Unclassifiable**

**Connective tissue disease associated**

Rheumatoid arthritis, scleroderma, dermatomyositis, polymyositis

**Drug associated**

Methotrexate, bleomycin

**Inhalational exposures**

Asbestosis, hypersensitivity pneumonitis, pneumoconioses

**Granulomatous**

Sarcoidosis, hypersensitivity pneumonitis

**Familial and other inherited syndromes**

**Others and rare conditions**

Lymphangiomyomatosis, Langerhans cell histiocytosis

**Box 2 | Key points in the history of suspected interstitial lung disease**

- Symptoms of interstitial lung disease: dyspnoea, cough (often dry)
- Non-specific symptoms: fever, fatigue, weight loss
- Symptoms of reflux disease
- Dysphagia (connective tissue disease associated interstitial lung disease)
- Joint pains, morning stiffness, dry eyes or mouth, skin changes, Raynaud’s phenomenon, photosensitivity (connective tissue disease associated interstitial lung disease)
- Neurological, rashes (sarcoidosis, connective tissue disease associated interstitial lung disease)
- Ocular symptoms (connective tissue disease associated interstitial lung disease, sarcoidosis)
- Family history
- Medical history—for example, autoimmune disorders, inflammatory bowel disease, and renal disorders such as granulomatous polyangitis
- Exposures, including drugs (for example, nitrofurantoin, bleomycin, methotrexate), occupation (for example, metal, wood, or asbestos workers), and environmental (for example, birds)
- Personal characteristics of patients, including age, sex, and smoking status

**Box 4 | Drugs known to cause pulmonary toxicity**

- Antirheumatoid agents—methotrexate (can occur after dose or formulation change even in long term users), gold, leflunamide, sulphasalazine, penicillamine
- Chemotherapeutic agents—bleomycin, chlorambucil, tyrosine kinase inhibitors (for example, imatinib), cyclophosphamide
- Biological agents—antitumour necrosis factor (etanercept, infliximab)
- Selective serotonin reuptake inhibitors—citalopram, fluoxetine
- Antibiotics—nitrofurantoin, cephalosporins
- Cardiac agents—amiodarone, angiotensin converting enzyme inhibitors, statins
- Others—talc, illicit drugs (including cocaine and talc used to cut many drugs), azothioprine, interferons
- Any drug can potentially cause pulmonary toxicity. If in doubt see [www.pneumotox.com](http://www.pneumotox.com)

and may suggest a complication such as infection, pulmonary embolism, malignancy, or a pulmonary vasculitis. Patients with known connective tissue disease and increasing respiratory symptoms should be referred to a respiratory specialist.

Retrospective trials suggest that gastro-oesophageal reflux disease contributes to the pathogenesis of fibrosis.<sup>9</sup> Patients should be specifically questioned about symptoms relating to gastro-oesophageal reflux disease.

**Drugs and exposures**

There are several important occupational and environmental factors implicated in hypersensitivity pneumonitis (box 3, see [thebmj.com](http://thebmj.com)).

Pulmonary toxicity has been attributed to a wide variety of prescription and over the counter medicines as well as illicit drugs (box 4). Patients starting new implicated drugs or established on them should be warned about and assessed for the development of respiratory symptoms.

**Family history**

Familial interstitial pneumonia is defined as two or more family members with an idiopathic interstitial pneumonia. In over 40% of these families there is more than one type of fibrosis in affected members, suggesting a shared genetic susceptibility. A familial component is seen in at least 20% of cases of idiopathic pulmonary fibrosis.<sup>10</sup>

**Examination**

Bilateral fine end inspiratory crepitations are classic on pulmonary examination, but other auscultatory findings are also associated with interstitial lung diseases (box 5). A pleural rub may be present in patients with rheumatoid arthritis or systemic lupus erythematosus. Despite severe disease, patients with sarcoidosis often have a relative paucity of chest findings.

A multitude of extrapulmonary findings exist. Finger clubbing occurs in over half of patients with idiopathic pulmonary fibrosis but can be seen in other interstitial lung diseases, including desquamative interstitial pneumonitis. Clubbing typically suggests progressive severe pulmonary fibrosis in patients with sarcoidosis. A meta-analysis of white patients with connective tissue disease associated interstitial lung disease found a high prevalence of pulmonary hypertension.<sup>11</sup> Patients may have peripheral oedema. Some of the interstitial lung diseases are associated with a greater risk of cardiac involvement, including sarcoidosis (cardiomyopathy and conduction disorders) and connective tissue disease associated interstitial lung disease (myocarditis, pericarditis, pericardial effusion).

**How are they investigated?**

**Initial investigations**

Patients with suspected interstitial lung disease should be referred promptly to specialist services. Several investigations can be requested in the community to facilitate a more rapid diagnosis and to assess for complications before referral. Guidance from the British Thoracic Society suggests a full blood count, urea and electrolytes, liver function tests, calcium, erythrocyte sedimentation rate, and C reactive protein as initial tests. Other tests depend on the clinical context and will typically be arranged by the interstitial lung disease clinic.<sup>12</sup>

Urinalysis is helpful in suspected vasculitis. Community spirometry may demonstrate a restrictive lung defect. However, many patients with emphysema also develop fibrosis, and because of the contrasting physiologies, spirometry may be normal or obstructive and so this alone should not detract from a suspected diagnosis.

**Box 5 | Key features in the clinical examination of interstitial lung disease**

- Bi-basal end inspiratory crepitations (fibrosis)
- Inspiratory squeaks (hypersensitivity pneumonitis)
- Finger clubbing
- Pleural effusion (connective tissue diseases, lymphangioleiomyomatosis, sarcoidosis)
- Pulmonary hypertension (particularly connective diseases)—a and v waves, murmurs of tricuspid regurgitation or pulmonic regurgitation, peripheral oedema
- Arthritis (connective tissue disease or sarcoidosis)
- Skin—erythema nodosum (sarcoidosis), Raynaud's phenomenon/sclerodactyly/telangiectasia (systemic sclerosis), heliotropic rash (dermatomyositis)
- Lymphadenopathy and hepatosplenomegaly (sarcoidosis)
- Neurological findings (sarcoidosis, vasculitis, and connective tissue diseases)
- Ocular signs (sarcoidosis, connective tissue diseases)

**Radiological investigation**

**Chest radiography**—Although neither sensitive nor specific,<sup>14</sup> radiography should not be overlooked. Reviewing serial radiographs can help determine whether changes are acute or chronic. Patterns of disease such as upper or lower lung predominance can suggest particular conditions, and underlying causal factors may be found such as asbestos pleural plaques. Chest radiography may help exclude oedema or infection and can screen for complications, including malignancy. Typical findings in idiopathic pulmonary fibrosis include reticulations and reduced lung volumes.

**High resolution computed tomography**—This is now a standard investigation in patients with suspected interstitial lung disease. In some cases where history is compatible it may be diagnostic, precluding the need for bronchoscopy or surgical biopsy.<sup>15</sup> Idiopathic pulmonary fibrosis causes a “usual interstitial pneumonia” pattern of fibrosis associated with honeycombing (cystic dilation of distal bronchioles secondary to fibrotic destruction of adjacent airspaces<sup>16</sup>).

Figure 2 gives a representation of the typical appearance on high resolution computed tomography of the most commonly encountered interstitial lung diseases.

**Other specialist investigations**

Patients should undergo full pulmonary function tests including gas transfer measurement. Serial results are useful in assessing response to treatment or deterioration. The typical pattern of pulmonary function tests in interstitial lung disease is a restrictive one, but several smokers may have coexistent airways disease and in these patients restrictive patterns are uncommon. Patients with sarcoidosis may have an obstructive pattern owing to endobronchial involvement. A low gas transfer measurement at baseline indicates those with worst prognosis.<sup>17</sup>

The six minute walk test gives a useful baseline for pulmonary rehabilitation<sup>18</sup> and correlates with disease severity and long term outcome in idiopathic pulmonary fibrosis.<sup>19</sup> Other investigations are tailored to the suspected diagnosis. Serological testing can determine allergen responses in hypersensitivity pneumonitis or underlying or emergent connective tissue disease.

**How is the diagnosis confirmed?**

A multidisciplinary team, composed of respiratory physicians, thoracic radiologists, pathologists, and specialist

nurses, is the current standard in the diagnosis of interstitial lung disease.<sup>20</sup> The typical diagnostic strategy is to confirm the presence of interstitial lung disease, establish a diagnosis where possible (with emphasis on excluding underlying causes), stage the disease, and discuss treatment objectives.

Some patients' conditions are more complex, and the multidisciplinary team cannot always reach a confident diagnosis. In this case the risks and benefits of further sampling with bronchoscopy or surgical lung biopsy will be considered. It may be necessary for the team to come up with a working diagnosis to facilitate treatment strategies. Not all cases require histological confirmation; particularly where clinical and radiological opinion is in agreement.<sup>20</sup>

**How are they treated?**

Treatment objectives vary depending on the clinical behaviour of the interstitial lung disease.<sup>15</sup> In many interstitial lung diseases such as idiopathic pulmonary fibrosis the aim will be to slow or stabilise disease progression. Other interstitial lung diseases, such as respiratory bronchiolitis associated interstitial lung disease, are self limiting and potentially reversible. In patients with unclassifiable disease, representing around 10% of the interstitial lung disease cohort<sup>7</sup> the multidisciplinary team will have to reach a working diagnosis and use this to determine a pragmatic approach to treatment and monitoring. Treatment plans should also include supportive therapies, including pulmonary rehabilitation, symptomatic relief (for example, cough, anxiety), and supplementary oxygen.

**Therapeutics****Idiopathic pulmonary fibrosis**

Idiopathic pulmonary fibrosis constitutes over half of the cases of interstitial lung disease encountered in clinical practice<sup>24</sup> and carries a prognosis worse than many malignancies.

Previous treatment strategies including steroids, cyclophosphamide, triple treatment (prednisolone, azathioprine and N-acetyl cysteine), or N-acetyl cysteine alone have been shown to be ineffective or harmful.<sup>25 26</sup> These are no longer recommended options. However, N-acetyl cysteine and other mucolytics are sometimes used as expectorant adjuncts.

Pirfenidone is the only licensed treatment currently approved by the National Institute for Health and Care Excellence for idiopathic pulmonary fibrosis in the UK. NICE recommends its use in patients with a forced vital capacity of 50-80% predicted.<sup>27</sup> It is expensive, requires monitoring of lung function tests, and side effects include nausea, dyspepsia, fatigue, and photosensitivity. Randomised controlled trials have shown that it does not reverse established fibrosis but slows the rate of decline in pulmonary function tests and modestly reduces all cause mortality.<sup>28 29</sup>

Nintedanib, an intracellular tyrosine kinase inhibitor with antifibrotic and anti-inflammatory properties, is newly licensed but not yet approved by NICE and in clinical trials also slows the rate of decline of pulmonary function tests similar to pirfenidone.<sup>30</sup>

**Idiopathic pulmonary fibrosis constitutes over half of the cases of interstitial lung disease encountered in clinical practice and carries a prognosis worse than many malignancies**

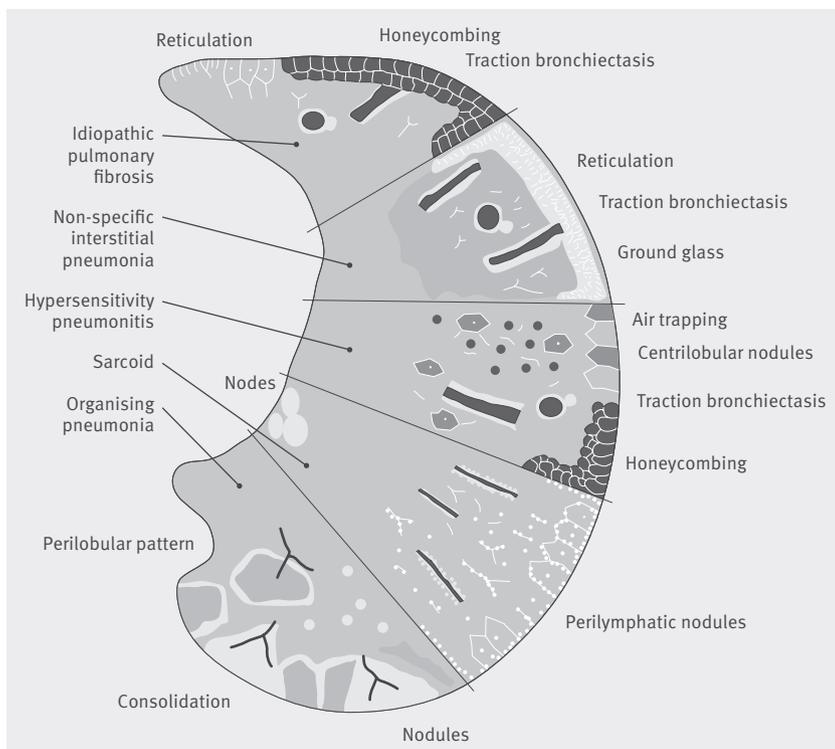


Fig 2 | Simplified diagram of typical high resolution computed tomography appearance of the most commonly encountered interstitial lung diseases

**Twenty three per cent of lung transplants worldwide are performed on patients with idiopathic pulmonary fibrosis**

*Connective tissue disorder associated interstitial lung disease*  
Lung involvement in connective tissue diseases ranges from fibrosis to pulmonary vascular disease, vasculitis, and pleural complications.

The only randomised controlled trials relate to the use of cyclophosphamide in scleroderma. One showed a significant modest effect on lung function and health related quality of life.<sup>31</sup> Although in the second there was no significant improvement, there was a trend towards improvement in forced vital capacity, and treatment was well tolerated.<sup>32</sup> Immunosuppressants are the treatment agents of choice. The evidence base for their use is minimal with little data to guide optimal initiation and duration of treatment. Corticosteroids and steroid sparing agents, including azathioprine and mycophenolate, are generally used in mild disease, with cyclophosphamide for more severe or refractory cases.

*Sarcoidosis*

In a large American cohort the chest was affected in over 90% of cases of sarcoidosis.<sup>33</sup> Patients can progress from stage 1 disease (bihilar lymphadenopathy only) to stage 2 or more (parenchymal lung involvement) without being aware. As many as 10% may progress to fibrosis.

British Thoracic Society guidelines suggest that treatment is not required for asymptomatic stage 1 sarcoidosis, nor asymptomatic stage 2 and 3 disease with only mild pulmonary function test abnormalities. Steroids have been used since the 1950s as first line treatment for progression or symptoms in sarcoidosis.<sup>34</sup> Inability to minimise the dose, side effects, or failure to respond may require alternative immunosuppressive agents, but evidence is lacking. Methotrexate is the most commonly used steroid sparing agent,<sup>35</sup>

with response rates of up to 60%.<sup>36</sup> Inhaled corticosteroids may help control troubling cough or associated airways disease and avoid some side effects associated with higher dose oral steroids. A systematic review of their use showed that effects are small and results generally inconclusive.<sup>40</sup>

*Hypersensitivity pneumonitis*

Hypersensitivity pneumonitis (extrinsic allergic alveolitis) can occur at any age. It can present in acute, subacute, and chronic forms—as many as 20% of interstitial lung disease is due to chronic hypersensitivity pneumonitis.<sup>41</sup>

Management involves identifying and removing the sensitising agent. Steroids are often used to abate symptoms. There are no controlled trials of the management of chronic hypersensitivity pneumonitis. Intravenous cyclophosphamide may be successful and there are case reports of success using biologicals in refractory cases.<sup>42</sup>

**Pulmonary rehabilitation**

There is good evidence that pulmonary rehabilitation helps breathless patients. A meta-analysis confirmed the benefit of pulmonary rehabilitation in patients with interstitial lung disease.<sup>43</sup> Patients in randomised controlled trials showed meaningful improvements in distances achieved in six minute walk tests.<sup>44 45</sup> Unfortunately pulmonary rehabilitation is not universally available and in many regions is restricted.

**Lung transplantation**

Lung transplantation offers survival benefits in carefully selected patients. The prognosis without transplant should be less than 50% survival at five years. Twenty three per cent of lung transplants worldwide are performed on patients with idiopathic pulmonary fibrosis.<sup>46</sup> Patient selection is important, and guidelines<sup>47</sup> suggest referring patients with idiopathic pulmonary fibrosis for consideration of transplant when they demonstrate a 10% or greater reduction in forced vital capacity over six months and a decrease in oxygen saturations to below 89% or the need for oxygen at rest. In patients without idiopathic pulmonary fibrosis, transplant should be considered in those with forced vital capacities less than 50% or hypoxaemia (partial pressure of oxygen <55 mm Hg).<sup>49</sup> The International Society of Heart and Lung Transplantation suggests an upper age limit of 65 years, although an American registry report of results from 1988 to 2011 shows improving graft and patient survival in those over this age limit.<sup>50</sup> One in six patients on the waiting list dies before a suitable donor organ is identified.

**What are the considerations for end of life care?**

Managing patients with interstitial lung disease (particularly idiopathic pulmonary fibrosis) very much encompasses end of life care. Some patients present too late for antifibrotic treatment, and supportive care with symptom based management is all that is available. Managing patient expectations from the outset is important, even in those in whom specific treatment is indicated, as effects of treatments remain modest in most.

Early involvement of teams such as occupational therapists, community nursing teams, and palliative care specialists is vital.