

# Management of the idiopathic interstitial pneumonias

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**SUMMARY**

The idiopathic interstitial pneumonias are characterised by varying degrees of lung inflammation and fibrosis. They include primary fibrotic disorders, such as idiopathic pulmonary fibrosis, and primary inflammatory disorders, which may or may not be associated with lung fibrosis.

Distinguishing between idiopathic pulmonary fibrosis and the inflammatory idiopathic interstitial pneumonias is crucial. Early investigation and specialist referral is recommended.

There is no therapy proven to influence the progression or survival of idiopathic pulmonary fibrosis. Patients need supportive and palliative care, and if appropriate, early referral for lung transplantation.

The inflammatory idiopathic interstitial pneumonias are managed with anti-inflammatory drugs with the aim of short-term response followed by longer-term stability. Early treatment is important, as once the disease is severe, it has a similar outcome to idiopathic pulmonary fibrosis.

**Introduction**

Interstitial lung disease refers to a diverse group of parenchymal lung diseases (Fig. 1). They all result in damage to the lung interstitium, with varying patterns of inflammation and fibrosis. Interstitial lung disease may be idiopathic (the so-called idiopathic interstitial pneumonias), or associated with exposure to drugs or environmental triggers, or underlying connective tissue disease.

Over the past decade, there has been reclassification of the idiopathic interstitial pneumonias to include:

- idiopathic pulmonary fibrosis (previously called cryptogenic fibrosing alveolitis)
- non-specific interstitial pneumonia
- cryptogenic organising pneumonia (previously called bronchiolitis obliterans with organising pneumonia or BOOP)
- acute interstitial pneumonia

- respiratory bronchiolitis-interstitial lung disease
- desquamative interstitial pneumonia
- lymphocytic interstitial pneumonia.<sup>1</sup>

Idiopathic pulmonary fibrosis is the most common of the idiopathic interstitial pneumonias. It is a primary fibrotic condition. There is progressive pulmonary fibrosis and the median survival is 3-5 years.<sup>2-5</sup> Although there are several placebo-controlled clinical trials in progress, current treatment options are limited. The emphasis is on supportive care.

In contrast to idiopathic pulmonary fibrosis, the other idiopathic interstitial pneumonias are thought to be primary inflammatory conditions (Table 1). They have a much better prognosis.<sup>2</sup> However, if left untreated, fibrosis becomes more established, and the outlook is similar to that of idiopathic pulmonary fibrosis. In these diseases, treatment with anti-inflammatory drugs is the key, aiming to maximise and preserve functional status.<sup>6</sup>

**Investigation**

A patient with complaints of shortness of breath, exercise intolerance and persistent dry cough may be suspected of having interstitial lung disease. Fine inspiratory crepitations, fingernail clubbing and signs of respiratory compromise increase suspicion. Distinguishing an idiopathic interstitial pneumonia from other interstitial lung diseases requires careful history taking with regard to exposures, family history

**Table 1 Classification of the idiopathic interstitial pneumonias**<sup>6</sup>

| Pathological process             | Idiopathic interstitial pneumonia subtype             |
|----------------------------------|---|
| Primary fibrosis                 | Idiopathic pulmonary fibrosis                         |
| Inflammation leading to fibrosis | Fibrotic non-specific interstitial pulmonary fibrosis |
| Primary inflammation             | Cellular non-specific interstitial pneumonia          |
|                                  | Cryptogenic organising pneumonia                      |
|                                  | Acute interstitial pneumonia                          |
|                                  | Lymphocytic interstitial pneumonia                    |
|                                  | Respiratory bronchiolitis-interstitial lung disease   |

and systemic features. Serological tests may also help to confirm or exclude connective tissue disease. Other investigations help to establish both the diagnosis and the severity of the interstitial lung disease (see Box).

A multidisciplinary approach, combining clinical, radiological and, if available, histological evidence is considered the gold standard for diagnosing idiopathic interstitial pneumonias.<sup>7</sup> Even using this approach, the ultimate diagnosis may remain elusive, particularly in more advanced disease.

With such differing prognoses and treatment approaches, distinguishing idiopathic pulmonary fibrosis from other idiopathic interstitial pneumonias is important early in the illness. Idiopathic pulmonary fibrosis may be diagnosed if there is a typical clinical picture supported by characteristic changes on high resolution computed tomography (for example bilateral sub-pleural honeycomb changes, most marked at the bases). In such cases, histological confirmation is unnecessary, but if there are atypical clinical or radiological features, surgical lung biopsy may be required. Endobronchial or transbronchial biopsies are not considered adequate to make a diagnosis of idiopathic interstitial pneumonia. The 'usual interstitial pneumonia' histological pattern seen at biopsy is consistent with the diagnosis of idiopathic pulmonary fibrosis.<sup>8</sup>

**Referral**

All patients with idiopathic interstitial pneumonia require early review at a specialist referral centre, with

expert radiology and pathology services. This ensures that those with a potentially treatable disease have timely access to appropriate therapies.

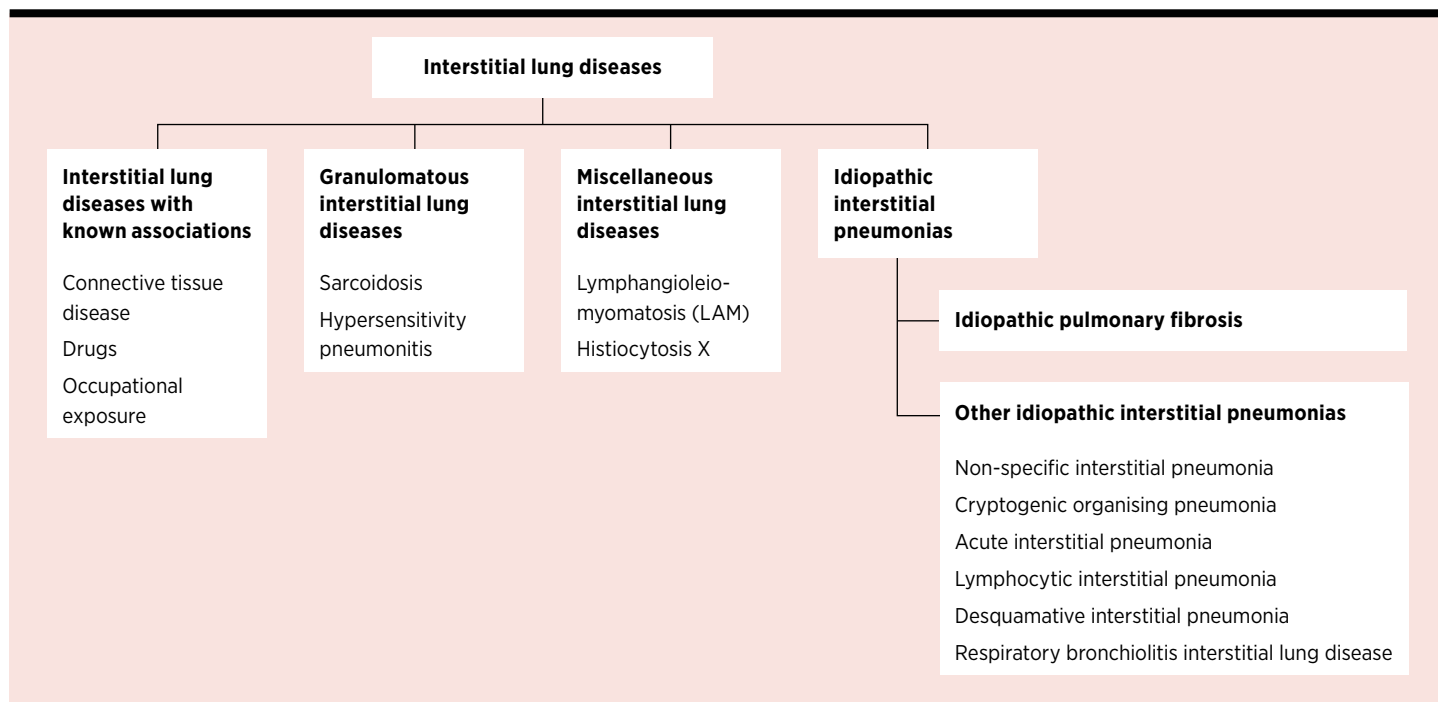
**General management of idiopathic interstitial pneumonia**

Any patients who smoke must be encouraged to stop. Supportive therapy, including access to palliative care and supplemental oxygen therapy, is important to optimise quality of life. Recent studies in interstitial lung disease have shown short-term improvements in dyspnoea, exercise capacity and quality of life

**Box Baseline investigations in idiopathic interstitial pneumonia**

|                                     |
|-------------------------------------|
| <b>Always</b>                       |
| Chest X-ray                         |
| High resolution computed tomography |
| Pulmonary function testing          |
| Arterial blood gas analysis         |
| Serology for autoimmune disease     |
| <b>Sometimes</b>                    |
| Echocardiogram                      |
| Right heart catheterisation         |
| Six minute walk test                |
| Cardiopulmonary exercise test       |
| Bronchoscopy/bronchoalveolar lavage |
| Surgical lung biopsy                |
| Overnight sleep study               |

Fig. 1 Classification of the interstitial lung diseases<sup>1</sup>



following pulmonary rehabilitation,<sup>9-11</sup> although this benefit appears to dissipate at six months.

**Oxygen therapy**

Current recommendations for supplemental oxygen are extrapolated from studies of chronic obstructive pulmonary disease.<sup>8,12</sup> Australian guidelines recommend oxygen therapy for patients with resting hypoxaemia (PaO<sub>2</sub> <55 mmHg, or <60 mmHg in the presence of pulmonary hypertension).<sup>13</sup> Nocturnal and exercise-induced hypoxaemia are markers of a poor prognosis in patients with idiopathic interstitial pneumonia,<sup>14-16</sup> but the benefit of using supplemental oxygen overnight, or during exercise, is not clear and the subject of ongoing research.

**Comorbidities and complications**

All patients with idiopathic interstitial pneumonias should be offered influenza and pneumococcal vaccines routinely. Prompt treatment with appropriate antibiotics for intercurrent infections is important. Patients have an increased prevalence of gastro-oesophageal reflux disease, obstructive sleep apnoea and pulmonary hypertension.<sup>8,17-20</sup> Treatment of these conditions may be beneficial, but this is currently being assessed in clinical trials. Hospitalised patients with idiopathic interstitial pneumonia have an

increased risk of venous thromboembolic disease so prophylactic anticoagulation is needed.

**Palliative care**

General practitioners will often be involved in the palliative care of patients with advanced disease. Aside from oxygen, these patients may benefit from opioids to alleviate dyspnoea and cough. Support from community palliative care services and professionals with mental health training will also be important for many patients and their families.

**Lung transplantation**

In a subgroup of patients with idiopathic interstitial pneumonia, referral for lung transplantation is an appropriate and important strategy. Patients with idiopathic pulmonary fibrosis have the highest overall mortality amongst those awaiting lung transplantation.<sup>17,21</sup> Referral is considered when the diffusing capacity of the lung for carbon monoxide (DLCO) falls below 40%, or there is significant progression over six months (as determined by a 10% or greater drop in forced vital capacity (FVC) and/or 15% or greater fall in DLCO).<sup>8</sup>

**Specific therapy for idiopathic pulmonary fibrosis**

In a disease with such limited prognosis, the goals of therapy are to slow the decline in pulmonary function and to maximise quality of life. Multiple therapies have been tested in randomised placebo-controlled trials, with disappointing results (Table 2). Without any proven effective treatment, expert consensus and international guidelines recommend referral to specialist centres for participation in clinical trials of antifibrotic drugs.<sup>8</sup>

**Antioxidant therapy (N-acetylcysteine)**

Acetylcysteine is the precursor of the antioxidant glutathione. It replenishes glutathione stores in the lung correcting the oxidant-antioxidant imbalance, which is thought to be important in the pathogenesis of idiopathic pulmonary fibrosis.

In one study, the addition of high-dose N-acetylcysteine (600 mg orally three times daily) to low-dose prednisolone and azathioprine was associated with a significant reduction in the fall in lung function (FVC and DLCO) at 12 months.<sup>34</sup> A subsequent placebo-controlled trial aimed to compare this 'triple therapy' with N-acetylcysteine alone. However, the triple therapy arm was recently stopped because of increased mortality (11% versus 1% in the placebo arm). The N-acetylcysteine and placebo arms continue, with results expected in the coming year.<sup>35</sup>

Table 2 Drug trials in idiopathic pulmonary fibrosis

| Drug                          | Action/class                   | Number of patients | Result  |
|-------------------------------|--------------------------------|--------------------|---|
| Pirfenidone <sup>22,23</sup>  | Antifibrotic agent             | 107                | Reduced decline in lung function in 2 of 3 Phase III studies  |
|                               |                                | 779                | Further study in progress (ASCEND)  |
| BIBF1120 <sup>24</sup>        | Antifibrotic agent             | 432                | Reduction in decline in lung function, fewer acute exacerbations per year in Phase II study<br>Phase III study in progress        |
| Colchicine <sup>25</sup>      | Antifibrotic agent             | 487                | No benefit over placebo   |
| Interferon-γ-1b <sup>26</sup> | Antifibrotic agent             | 330                | No benefit over placebo   |
| Etanercept <sup>27</sup>      | TNF-α receptor antagonist      | 88                 | No benefit over placebo   |
| Bosentan <sup>28,29</sup>     | Endothelin receptor antagonist | 158, 616           | No benefit over placebo   |
|                               |                                |                    | May benefit patients with pulmonary hypertension<br>Similar results with ambrisentan <sup>30</sup>                                |
| Sildenafil <sup>31-33</sup>   | Phosphodiesterase 5 inhibitor  | 180, 14, 15        | No improvement in 6 minute walking distance<br>May benefit patients with idiopathic pulmonary fibrosis and pulmonary hypertension |

### Anti-inflammatory therapy

Historically, treatment of idiopathic pulmonary fibrosis was based on the suppression of inflammation. However, it now seems likely that patients who appeared to respond to anti-inflammatory therapy in early studies did not have true idiopathic pulmonary fibrosis. It is now clear that high-dose corticosteroids do not improve quality of life or survival, but have considerable adverse effects. Expert consensus therefore does not support the use of corticosteroid monotherapy in idiopathic pulmonary fibrosis.<sup>8</sup> There is no evidence for the use of other immunosuppressants including cyclophosphamide.<sup>36,37</sup>

### Acute exacerbations

Aside from treating intercurrent infections, and other reversible components, management of acute exacerbations of idiopathic pulmonary fibrosis can be difficult. Most patients will require hospitalisation and specialist care. While many clinicians will give corticosteroids, there are no controlled trials to support this practice.<sup>8</sup>

### Treatment of other idiopathic interstitial pneumonias

Inflammation, with or without progression to fibrosis, plays an important role in the pathogenesis of other idiopathic interstitial pneumonias. In contrast to idiopathic pulmonary fibrosis, the goal of therapy is to first achieve and subsequently maintain the patient's best clinical and functional status.

Initial treatment with high-dose corticosteroids is often warranted, with review of steroid-responsiveness at 4–6 weeks. The steroids are usually tapered to the lowest possible maintenance dose, while monitoring clinical and functional parameters.

If the response to high-dose corticosteroid therapy is suboptimal, addition of other immunosuppressive drugs may be necessary. Immunosuppressive drugs may also be needed as steroid-sparing drugs when corticosteroids cannot be reduced to acceptable doses (generally considered to be a daily dose of prednisone 10 mg or less). The drugs commonly used in maintenance therapy include azathioprine, mycophenolate mofetil and oral or intravenous cyclophosphamide. They are usually used in combination with low-dose prednisone.<sup>6,7</sup>

### Specific treatment strategies

In patients with primary inflammatory processes and fibrosis, as in fibrotic non-specific interstitial pneumonia, close observation is vital. Immunosuppressive therapy should be started in progressive or moderately severe disease so as not to miss an important window of treatment

responsiveness. Once fibrotic non-specific interstitial pneumonia becomes advanced the patients have similar outcomes to those with idiopathic pulmonary fibrosis.

Desquamative interstitial pneumonia and respiratory bronchiolitis interstitial lung disease are both related to tobacco consumption. Smoking cessation must be stressed and is sometimes the only intervention necessary. Corticosteroids and other anti-inflammatory drugs may be considered for cases of refractory desquamative interstitial pneumonia.

Cryptogenic organising pneumonia is usually steroid-responsive, although there is a high incidence of relapse. Some patients may go on to a progressive fibrosing organising pneumonia which may be refractory to steroids, but may respond to more aggressive anti-inflammatory therapies.

Lymphocytic interstitial pneumonia may be associated with autoimmune or lymphoproliferative disease, as well as HIV infection. Corticosteroids can be of benefit, and treating the underlying disorder may also help. Acute interstitial pneumonia and acute exacerbations of the other idiopathic interstitial pneumonias are usually treated in hospital, with attention to reversible factors and implementation of high-dose immunosuppression. Pulsed intravenous methylprednisolone followed by second-line immunotherapy is a reasonable strategy although there is little controlled evidence to support this approach.

### Conclusion

It is important to distinguish between idiopathic pulmonary fibrosis and other idiopathic interstitial pneumonias with a primary inflammatory pathogenesis, as there are major prognostic and therapeutic implications. There are no effective treatments for idiopathic pulmonary fibrosis although there are some potentially promising new antifibrotic drugs in clinical trials. The focus of treatment is on supportive care, including palliation, and management of comorbidities.

In contrast to idiopathic pulmonary fibrosis, the other idiopathic interstitial pneumonias are primary inflammatory conditions and have a better prognosis. Treatment is with anti-inflammatory drugs, aiming to maximise and preserve the patient's clinical and functional status. ◀

*Dr Troy and Dr Corte are involved with the Royal Prince Alfred Hospital Interstitial Lung Disease Clinic which has received an unrestricted educational grant from Actelion.*

## Any patients who smoke must be encouraged to stop



### SELF-TEST QUESTIONS

*True or false?*

7. Patients with idiopathic interstitial pneumonia should not be given pneumococcal vaccine.

8. High-dose corticosteroids improve the survival of patients with idiopathic pulmonary fibrosis.

*Answers on page 211*

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