Idiopathic pulmonary fibrosis

New approaches to diagnosis and treatment

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Idiopathic pulmonary fibrosis (IPF) is a fibrotic lung disease that, while considered rare, has a prognosis worse than many forms of cancer. It presents with nonspecific symptoms including cough, breathlessness and fatigue. This review provides an overview of the approach to diagnosis and the management options available, including the key role of an interstitial lung disease multidisciplinary team. It also highlights the central co-ordinating role of GPs in IPF patient care.

Idiopathic pulmonary fibrosis (IPF) is a form of interstitial lung disease (ILD) that results in scarring of the lung tissue, progressive lung restriction, breathlessness and, ultimately, death, with a median survival of two to five years.[1] It has traditionally been considered a rare disease; however, the incidence appears to be increasing worldwide. Although IPF can occur in any adult, it is more common in older males; often with a history of smoking.

The diagnosis of IPF can be challenging as symptoms are often vague, and include cough, breathlessness and fatigue. In an elderly population, these symptoms are often attributed to comorbidities such as heart failure and chronic obstructive pulmonary disease. IPF also shares many features with other ILDs. The classification of ILDs is complex. ILDs are often classified according to their associations such as connective tissue diseases, drugs or smoking. Figure 1 shows the current ILD classification, with the classification of IPF highlighted. Early referral to a specialised ILD centre is recommended for accurate diagnosis and treatment.

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The early consideration of an IPF diagnosis is important as treatments that can slow the progression of this disease are now available. Unfortunately, there is still no treatment that can stop or reverse the disease and therefore early initiation of treatment to preserve lung function and quality of life is of great importance.

This article provides an overview of the approach to diagnosis of IPF as well as the management options available. It also discusses two case studies and how to diagnose and manage them:

Key points

- **Idiopathic pulmonary fibrosis (IPF) is an irreversible, progressive lung disease that has significant mortality.**
- **A comprehensive multidisciplinary team meeting is key in establishing a diagnosis of IPF.**
- **New antifibrotic therapies should be considered to slow the progression of IPF in appropriate patients.**
- **Nonpharmacological measures are essential in the treatment of IPF, and include oxygen, pulmonary rehabilitation, treating comorbidities and referral to palliative care.**

- Paul, aged 60 years, presents with a four-month history of breathlessness and dry cough. Chest x-ray shows patchy changes bilaterally with no response to multiple courses of oral antibiotics (Box 1).
- Steven, aged 75 years, presents with a three-year history of worsening breathlessness. GP review finds severe exercise limitation, with hypoxia and bibasilar crackles (Box 2).

Diagnosing IPF

Clinical features

A thorough clinical history is required not only to diagnose idiopathic pulmonary fibrosis (IPF) but also to exclude other causes of ILD (Table 1). It is important to identify any occupational, environmental or medication exposures as these may cause ILD, and cessation of exposure is critical to management. Although most instances of IPF are sporadic, familial IPF does occur and a detailed family history should be taken.

It is also important to ask about specific symptoms of connective tissue disease, a major differential diagnosis for IPF. These symptoms include Raynaud's phenomenon, morning stiffness, joint pain/swelling and muscle pain/weakness. Connective tissue disease-related ILD should be suspected in patients who are female and are younger.

Clinical examination should focus on features of IPF including fine inspiratory crackles, usually at the base of the lungs, as well as clubbing of fingernails (Figure 2). Hypoxia should be assessed for, with oxygen saturations and the presence of peripheral or central cyanosis. Cardiovascular and rheumatological examinations should also be done.

Investigations

Serology

Serological testing is recommended for all patients to assess for underlying connective tissue disease. Connective tissue diseases that are commonly associated with ILD include rheumatoid arthritis, Sjögren's syndrome, scleroderma and polymyositis-dermatomyositis. Serology to look for these diseases is recommended including, at a

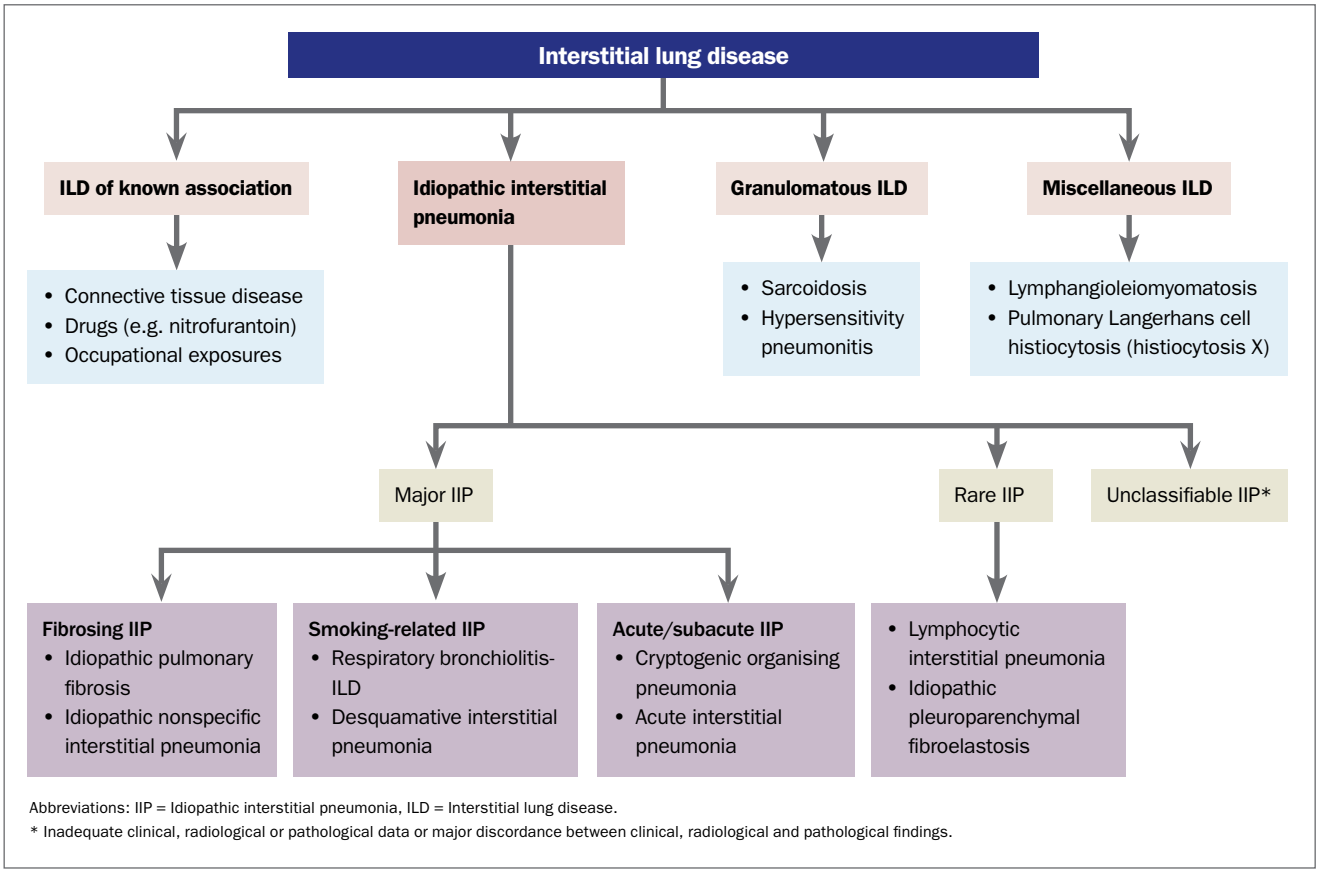


Figure 1. Current classification of interstitial lung disease.

minimum, rheumatoid factor, anticyclic citrullinated peptide and antinuclear antibody titre and pattern.

Lung function testing

Lung function tests of patients with IPF will most commonly show a restrictive pattern. Spirometry will show a normal to high forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio, and a reduced FVC. These patients will also have a reduced total lung capacity (TLC) and diffusing capacity of the lungs the lungs for carbon monoxide (D_LCO). Lung function has important implications in predicting a patient's prognosis, with patients who present with more severe impairment usually having worse outcomes.

High-resolution CT

High-resolution CT (HRCT) plays a central role in the diagnosis of IPF. The presence of a definite usual interstitial pneumonia (UIP) pattern on HRCT is adequate to diagnose IPF in the correct clinical context, without the need for tissue biopsy. A definite radiological UIP pattern shows honeycombing with or without traction bronchiectasis and reticular abnormality in a subpleural, basal distribution (Figure 3).

Lung biopsy

Lung biopsy is sometimes required when the above testing is insufficient for a diagnosis. This decision requires discussion at an ILD multidisciplinary team (MDT) meeting. Lung biopsies, however, are invasive procedures that can be associated with significant morbidity including pain, bleeding, exacerbation of ILD and, in rare cases, death.

Management

The comprehensive management of IPF involves disease-specific therapies and management of comorbidities, disease-related symptoms, pulmonary rehabilitation as well as palliative care and/or lung transplantation (Flowchart 1). Management requires a variety of health professionals, with the local general practitioner vital in co-ordinating care.

Interstitial lung disease multidisciplinary team meeting

Early referral is critical for both the diagnosis and management of IPF. Multiple studies have shown that using an ILD MDT improves accuracy and confidence of IPF diagnosis compared with doctors working individually.[4] In order to confirm a diagnosis of IPF and access medical treatment via PBS, all IPF patients need to be discussed

1. Case study: Paul, aged 60 years, presents with a four-month history of breathlessness

Paul, aged 60 years, presented with four months of progressive shortness of breath and a dry cough, despite antibiotics for presumed recurrent lower respiratory tract infections. Further history-taking showed that Paul was becoming increasingly breathless over the previous 1.5 years. His other medical problems include high blood pressure, high cholesterol and type 2 diabetes. Examination revealed inspiratory crackles to the mid-zones. There was clubbing of the fingernails with mild osteoarthritis of the wrists. He had seen a cardiologist and no cardiac cause for his breathlessness was identified.

Further investigations were done:

- lung function tests showed mild restriction with an FEV_1 of 2.30 L (88% predicted), FVC of 4.49 L (80% predicted), TLC 6.27 L (76% predicted) and D_LCO 74% predicted
- bloods did not show the presence of any autoantibodies
- HRCT showed subpleural reticulation and traction bronchiectasis without honeycombing, consistent with a probable UIP pattern.

Paul was referred to a respiratory physician and presented at the ILD MDT meeting. Given the probable UIP pattern on HRCT with no alternative diagnosis, Paul was given a diagnosis of probable IPF. The decision to perform a lung biopsy was discussed at the meeting, and then with Paul, and was decided against. Paul was started on antifibrotic therapy to slow disease progression, with monthly liver function tests, and was referred for pulmonary rehabilitation. He has remained stable during the subsequent year of follow up and tolerated rehabilitation well.

Abbreviations: D_LCO = diffusing capacity of the lungs for carbon monoxide; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; HCRT = high-resolution CT; ILD MDT = interstitial lung disease multidisciplinary team; IPF = idiopathic pulmonary fibrosis; TLC = total lung capacity; UIP = usual interstitial pneumonia.

2. Case study: Steven, aged 75 years, presents with a three-year history of breathlessness

Steven, aged 75 years, presented with a three-year history of breathlessness after no contact with medical services for 20 years. He had a background of cardiac stent insertion 30 years ago, heavy smoking and heavy alcohol intake. He ceased alcohol and smoking six months ago after becoming housebound due to breathlessness. When he saw his GP, he was referred for a stress test, and he had was found to have a severely impaired exercise tolerance of 10 m. Examination revealed hypoxia with saturations of 85% on room air, fine inspiratory crackles at both lung bases up to the mid-zones and digital clubbing. There were no signs of heart failure.

After further investigations:

- lung function test revealed severe restriction with an FEV_1 of 2.10 L (50% predicted), FVC of 0.95 L (35% predicted), FEV_1/FVC of 85%, TLC of 1.80 L (34% predicted) and D_LCO of 28% predicted
- bloods did not show the presence of any autoantibodies
- HRCT showed a definite UIP pattern.

Steven was referred to a respiratory specialist and was discussed at an ILD MDT meeting. Given the definite UIP pattern with no alternative diagnosis, he was given a definite diagnosis of IPF. It was determined that Steven was not appropriate for antifibrotic treatment given the severity of his disease and his heavy alcohol history. He was referred to the palliative care team for symptomatic management of his breathlessness with low-dose morphine, and oxygen therapy was initiated for his hypoxia. He was offered pulmonary rehabilitation; however, he declined this service.

Abbreviations: D_LCO = diffusing capacity of the lungs for carbon monoxide; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; HCRT = high-resolution CT; ILD MDT = interstitial lung disease multidisciplinary team; IPF = idiopathic pulmonary fibrosis; TLC = total lung capacity; UIP = usual interstitial pneumonia.

Table 1. Clinical features that suggest IPF and those that do not

Feature	Features suggesting IPF	Features not suggesting IPF
Risk factors	• Older age • Male • Smoking history	• Younger age • Female • Environmental exposures/medications known to cause ILD
History	• Exertional breathlessness • Dry cough	• Symptoms of connective tissue disease: morning stiffness, joint pain, Raynaud's syndrome
Examination	• Fine inspiratory crackles at lung bases • Finger clubbing • +/− signs of pulmonary hypertension	• Signs of connective tissue disease: joint swelling/deformity, muscle weakness, skin thickening, ulcers
Investigations	• Lung restriction and reduced diffusion capacity on lung function tests • Presence of UIP pattern on high-resolution CT	• Positive serology: anticyclic citrullinated peptide, antinuclear antibody, extractable nuclear antigen, antineutrophil cytoplasmic antibodies, dsDNA, creatine kinase, myositis panel • Presence of ground-glass change, nodules on high-resolution CT

Abbreviations: ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.

at an ILD MDT meeting. These meetings are typically attended by respiratory physicians, radiologists, pathologists +/- rheumatologists, ILD-specific nurses and allied health staff. In order to co-ordinate referral to an ILD MDT, a GP can either directly refer to the ILD outpatient service or, if not available, can refer to their closest respiratory physician (Flowchart 2).

During the ILD MDT meeting, key elements of the patient's case are discussed including the clinical history and examination, as above, pulmonary function tests and HRCT scans. A consensus diagnosis is reached and suggestions for management are made (Box 3).

Antifibrotic treatments

Until recently, there were no effective treatments available for IPF. In 2014, two landmark trials of the antifibrotic therapies nintedanib and pirfenidone, respectively, were published. These studies resulted in both medications becoming available in Australia through the PBS in 2017.[2,3]

PBS criteria in Australia for use of antifibrotics include MDT diagnosis of IPF, HRCT consistent with UIP pattern within 12 months, FVC greater than 50%, FEV_1/FVC more than 0.7, D_LCO more than 30% and ILD not a result of another known cause.

There is little evidence to support the use of antifibrotics in patients with severe disease outside the PBS criteria (FVC less than 50%, D_LCO less than 30%). Due to absence of trial data at this stage, there is no evidence to support the use of antifibrotic therapy in other ILDs.

Gastrointestinal side effects are commonly associated with both nintedanib and pirfenidone (Table 2). In most cases, side effects with both medications are mild and rarely require cessation of treatment. Both antifibrotic medications can cause liver function abnormalities and thus liver function tests should be done regularly, usually monthly for the first six months, then quarterly while undergoing treatment. For patients experiencing diarrhoea, antidiarrhoeal medications including loperamide can be used. If diarrhoea is significant (more than six stools daily/affecting activities of daily living/requiring intravenous fluids), interruption of treatment may be required.

Figure 2. Clubbing of fingernails.

Treating comorbidities

Smoking cessation is of critical importance and all smokers should be offered nicotine replacement therapy, specialist support and psychological support as required. Gastro-oesophageal reflux is common in patients with IPF and may contribute to chronic cough. Growing evidence suggests that antacid therapy may not be beneficial in patients with IPF and reflux-directed therapy should be considered on an individual basis.[4]

All patients with IPF should be offered the yearly influenza vaccine and the pneumococcal vaccine. These infections are poorly tolerated in patients with IPF and can result in significant morbidity and/or mortality.

In patients with suspected disordered breathing during sleep, referral to a sleep physician and sleep studies should be considered. Disordered breathing during sleep can cause pulmonary hypertension because of nocturnal hypoxia. Pulmonary hypertension in ILD is a strong predictor of poor survival.

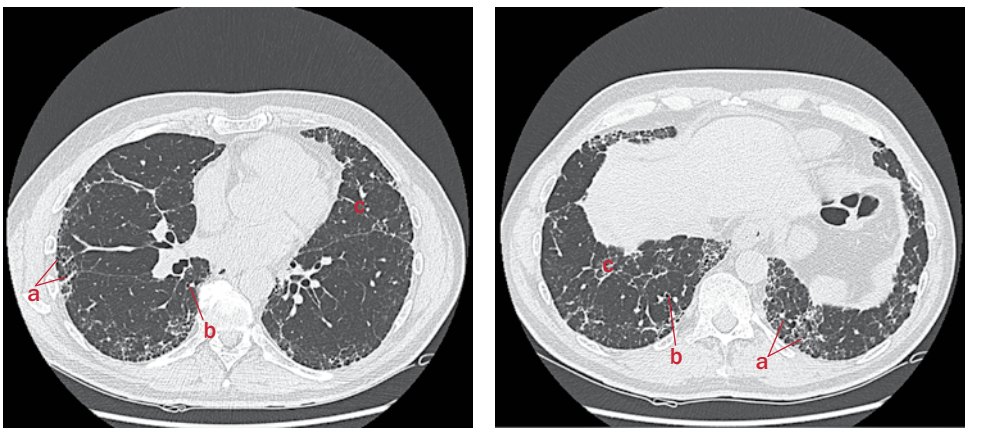
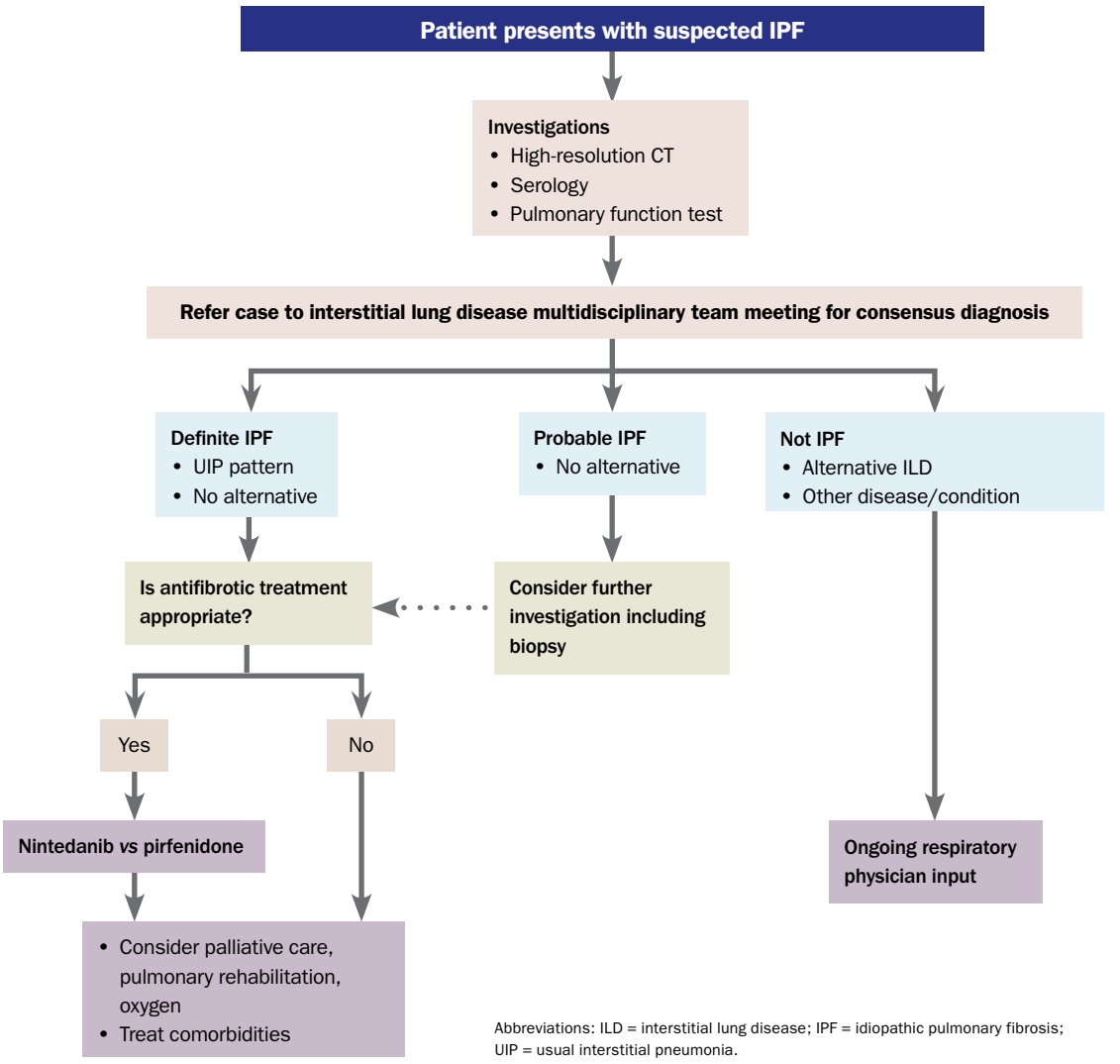


Figure 3. Definite usual interstitial pneumonia (UIP) on high resolution CT showing evidence of
(a) honeycombing,
(b) traction bronchiectasis,
(c) reticulations with a subpleural and basal predominance.
No features of ground glass are evident.

1. Management of idiopathic pulmonary fibrosis



Abbreviations: ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.

Oxygen

Recommendations for supplemental oxygen in IPF are currently the same as those for chronic obstructive pulmonary disease. Oxygen is suggested for patients with resting hypoxaemia (PaO2 less than 55 mmHg, or less than 60 mmHg in the presence of end-organ damage). Nocturnal oxygen can be considered in patients who desaturate below 88% for at least one-third of total sleep time.

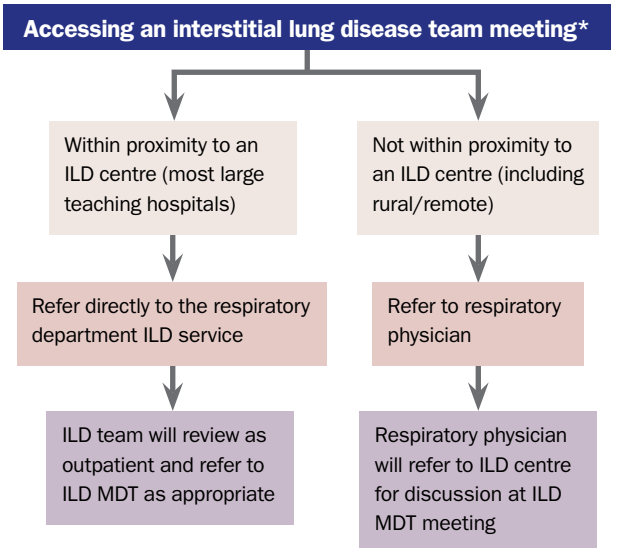
Pulmonary rehabilitation

There is growing evidence that pulmonary rehabilitation has important effects on symptoms, functional capacity and wellbeing in patients with IPF. Studies show that an eight- to 12-week pulmonary rehabilitation program leads to improvements in breathlessness and health-related quality of life. Patients with milder disease appear to have a prolonged benefit and thus early referral should be considered. Maintenance programs after six to 12 months should also be considered to continue the benefit of pulmonary rehabilitation.

Lung transplant

Lung transplant remains the only definitive cure for IPF. Age is no longer a contraindication in Australia but instead disease severity (with evidence of end-organ damage) and the patient's overall health are the main criteria used. As a general rule, patients are considered for transplant when they develop respiratory failure despite optimal medical/surgical management and/or a poor quality of life with intractable symptoms or repeat hospital

2. The interstitial lung disease multidisciplinary team meeting



Abbreviation: ILD = interstitial lung disease; MDT = multidisciplinary team
* Based on New South Wales model of care.

admissions. Exclusion criteria include active malignancy, irreversible dysfunction of other organs (though combined transplants may be considered), noncurable chronic infection, documented non-adherence, or substance addiction within the previous six months.[5] It should be noted that patient appropriateness for lung transplantation is a complex decision and requires extensive input from a specialist lung transplant team.

Table 2. Gastrointestinal side effects of antifibrotics

Side effect	Nintedanib	Pirfenidone
Diarrhoea	Yes (60% of patients)	Yes
Nausea	Yes	Yes
Vomiting	Yes	Yes
Liver function derangement	Yes	Yes
Heartburn	No	Yes
Sun sensitivity	No	Yes
Reduced appetite	Yes	Yes

Palliative care

Palliative care is a key part of IPF management and should be addressed at all stages of the disease. Palliative care focuses on symptom management, advance care directives and end-of-life planning. It aims to improve the quality of life of patients and their families. Nonpharmacological therapies that can be considered for dyspnoea in patients with advanced lung diseases include pursed lip breathing, facial cooling with fans, relaxation therapy and noninvasive positive pressure ventilation. Opioid medications have proven efficacy in the management of breathlessness and should be considered for patients with refractory breathlessness. The medications should be dosed and titrated for each patient based on multiple factors including patient renal and hepatic function, lung function and current/previous use of opioids.[6]

3. Interstitial lung disease multidisciplinary team meeting: diagnosis and management

Attendees

Essential (all with experience in IPF)
- Expert respiratory physicians (minimum 2)
- Radiologists
- Pathologists

Ideal
- Rheumatologist
- Immunologist
- ILD specialist nurse

Abbreviations:
6MWT = six-minute walk test
BMI = body mass index
ILD = interstitial lung disease
IPF = idiopathic pulmonary fibrosis
PFT = pulmonary function test
Sats = oxygen saturation
TTE = transthoracic echocardiogram
UIP = usual interstitial pneumonia

Clinical information presented
- Clinical history: demographics, symptom, family and past medical history
- Clinical examination: sats, BMI, respiratory, cardiovascular and rheumatology examinations
- PFTs (serial, if available)
- Serology: autoimmune, myositis screen
- +/- TTE, sleep studies, 6MWT
- At conclusion, clinician provides clinical suspicion

Discussion
- Images reviewed – radiologist-led discussion of findings, differential diagnoses and confidence (UIP *vs* other)
- If available, pathologist-led discussion of pathology
- Pathology-based diagnosis provided

Consensus and outputs
- If possible, consensus diagnosis reached
- If not, most probable diagnosis of patient referred for further investigation with plan to re-present
- Management options discussed (based on patient's clinical condition, comorbidity and wishes)
- Output forms with suggestions and discussion provided for GP and referring respiratory physician

Patient support

A diagnosis of IPF creates a significant physical and mental burden on patients and their carers. There are several resources available in Australia to provide further information and support. These include the Lung Foundation Australia website or its information and support centre (https://lungfoundation.com.au/patients-carers/living-with-a-lung-disease/ipf/overview/), and other websites (also accessible via the Lung Foundation).

Conclusion

IPF is a progressive disease that requires extensive investigation, with an MDT the key to successful diagnosis and management. The GP has an essential role in the early diagnosis, co-ordination of care and ongoing management of symptoms and medication side effects resulting from this disease. **RMT**

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Further reading

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