



On behalf of Lung Foundation Australia and the Thoracic Society of Australia and New Zealand

TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS IN AUSTRALIA AND NEW ZEALAND

FROM THE THORACIC SOCIETY OF AUSTRALIA AND NEW
ZEALAND AND THE LUNG FOUNDATION AUSTRALIA*

POSITION STATEMENT

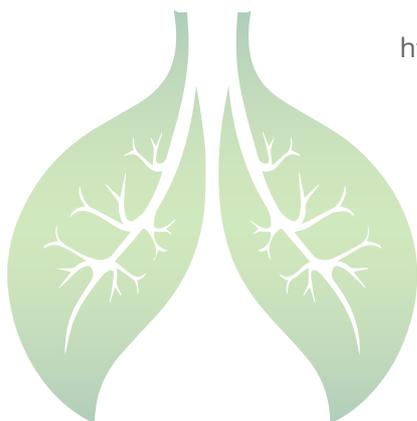
AUGUST 2017

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: *This document has been peer reviewed by independent experts and subsequently endorsed by the Thoracic Society of Australia and New Zealand (TSANZ) Board on 7 August 2017

<http://onlinelibrary.wiley.com/doi/10.1111/resp.13146/full>



ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a fibrosing interstitial lung disease (ILD) of unknown aetiology with a median survival of only 2-5 years. It is characterized by progressive dyspnoea and worsening lung function, ultimately resulting in death.

Until recently, there were no effective therapies for IPF, however with the publication of two landmark clinical trials in 2014, the anti-fibrotic therapies, nintedanib and pirfenidone, have gained widespread approval.

This position paper aims to highlight the current evidence for the treatment of IPF, with particular application to the Australian and New Zealand population. We also consider areas in which evidence is currently lacking, especially with regard to the broader IPF severity spectrum and treatment of co-morbid conditions. The utility of non-pharmacological therapies including pulmonary rehabilitation, oxygen as well as symptom management thought to be important in the holistic care of IPF patients are also discussed.



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1. INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a fibrosing interstitial lung disease (ILD) of unknown aetiology. IPF is characterized by progressive dyspnoea and worsening of lung function, ultimately resulting in death, with a median survival of only 2-5 years.¹ While the pathogenesis remains unclear, it is likely multifactorial, with both a genetic predisposition, as well as environmental factors including smoking and industrial dust exposures thought to contribute. While the exact incidence of IPF in Australia is unknown, recent studies indicate that the prevalence of IPF is increasing globally and is estimated to be between 1.25 to 63 cases per 100 000.²

The hallmark of IPF is the presence of a usual interstitial pneumonia (UIP) pattern on imaging and/or histopathology.¹ The diagnosis of IPF can be difficult as clinical and radiological features often overlap with other ILDs including chronic hypersensitivity pneumonitis (CHP), connective tissue disease related ILD (CTD-ILD) and fibrotic non-specific interstitial pneumonia (fNSIP). There is also significant phenotypic heterogeneity within IPF, with some patients having rapidly progressive disease, and others having a more stable disease course.³ This complexity is acknowledged within the most recent 2011 ATS/ERS/JRS/ALAT guidelines which call for a multidisciplinary discussion to exclude other known causes of ILD and to assess for a usual interstitial pneumonia (UIP) pattern on radiology and/or histology. According to these guidelines, IPF diagnosis can be categorized as 'definite', 'probable', 'possible' or 'inconsistent with' IPF, according to the presence of UIP features. The diagnosis of IPF by multidisciplinary evaluation is further discussed in detail in an accompanying position paper in this edition of the *Journal*.

This position paper aims to highlight the current evidence for the treatment of IPF, adopted from the international guidelines on IPF treatment published in 2015,⁴ with particular application to the Australian and New Zealand population. We also consider areas in which evidence is currently lacking, especially with regard to the broader IPF severity spectrum, as well as non-pharmacological therapies thought to be important in the holistic care of IPF patients. A suggested treatment algorithm based upon current evidence and expert opinion is also presented.

2. METHODS

This position paper highlights important aspects of the treatment of IPF as it pertains to Australia and New Zealand, and do not represent treatment guidelines *per se*. T.J.C was appointed to chair a panel of 18 members, who were selected for their expertise in various aspects of IPF diagnosis and management. The expert panel was comprised of 15 respiratory physicians, 1 physiotherapist, 1 respiratory nurse as well as a patient representative (D.B) who had opportunity to contribute to all stages of the writing process. There was widespread representation from both Australia and New Zealand. After an initial discussion with all authors, authors were assigned specific sections for completion. Comprehensive literature review was performed and articles for inclusion were determined by each writing group for their assigned sections and were not systematically evaluated. Where evidence was lacking, expert opinion was provided on how to address these areas. All sections, including referenced articles, were then reviewed and discussed at subsequent meetings where all authors had the opportunity to contribute to all sections.

After the completion of specific sections by assigned authors, three authors compiled and edited the complete manuscript (H.E.J, P.H, T.J.C). All authors reviewed and approved the final manuscript. The committee did not receive any commercial sponsorship and all panel members worked on an honorary basis. This position paper is endorsed by the Thoracic Society of Australia and New Zealand and will be disseminated by publication in *Respirology*, and via the TSANZ and Lung Foundation Australia in a collaborative pre-specified translation plan. The clinical relevance of the document will be reviewed after a maximum of 5 years.



3. GENERAL MEASURES

It is important to discuss general health measures with all patients with IPF, as well as their families, to ensure active engagement. The management of IPF patients involves many health professionals including the respiratory physician, IPF nurses, pharmacists, physiotherapists and other allied health professionals, as well as palliative care and transplant teams. As such, the patient's local general practitioner plays a vital role in the coordination of care of these patients and should be involved at all stages.

The comprehensive management of patients with IPF not only involves the consideration of IPF specific pharmacological therapies for disease management but also the management of other co-morbidities, disease related symptoms, overall general health as well as patient education. While specific evidence for the management of general health measures is lacking in IPF, these global health factors can have implications beyond IPF disease. For example, it is important for patients to maintain good nutrition and a healthy body weight as this is often a consideration for transplant eligibility. Smoking cessation is also important in that regard and also has implications regarding the use of long-term oxygen therapy. Smoking has also been shown to decrease systemic exposure to both nintedanib and pirfenidone and smoking cessation should be strongly advised when initiating either of these medications.⁵

Depression and anxiety are other common but often overlooked co-morbidities in IPF patients, associated with a poorer quality of life and poorer outcomes.⁶ Underlying depression and anxiety are often correlated with the presence of debilitating symptoms such as dyspnoea, a symptom affecting up to 90% of patients at diagnosis.⁷ Depression and anxiety may also be exacerbated by medication side effects, acute exacerbations and deterioration requiring hospital admission, as well as fear associated with the overall poor prognosis in IPF. There are no controlled studies addressing the management of depression and/or anxiety in IPF patients.

4. PHARMACOLOGICAL THERAPY

4.1 Anti-fibrotic therapy

Until recently, no effective therapies were available for idiopathic pulmonary fibrosis (IPF). However, following a number of landmark clinical trials (Table 1), nintedanib and pirfenidone are now recommended for the treatment of IPF in the updated multinational clinical practice guidelines,¹ and are licensed for the treatment of IPF in an increasing number of countries. Figure 1 suggests an algorithm for the management of patients with IPF.

4.1.1 Pirfenidone

Pirfenidone is a novel anti-fibrotic agent, and while its precise molecular target remains unknown, it exhibits pleiotropic anti-fibrotic actions via several pathways. The first human clinical trial of pirfenidone in IPF was reported in 1999,⁸ and since that time, it has been evaluated in four phase 3 randomised controlled trials. Taniguchi et al. initially reported reduced decline in vital capacity and improved progression free survival in 275 Japanese patients,⁹ and this was followed by two concurrent multinational studies (CAPACITY 004 and 006) involving 779 patients in the United States, Europe and Australia.¹⁰ In the positive 004 study, high dose pirfenidone (2403 mg/day) was associated with a significantly reduced mean decline in percentage predicted forced vital capacity (FVC) compared with placebo at week 72 (-8.0% [\pm 16.5] and -12.4% [\pm 18.5] respectively) ($p=0.001$). While the 006 study was negative (with a decline in mean FVC of -9.0% [\pm 19.6] and -9.6% [\pm 19.0] in the pirfenidone and placebo arms respectively) ($p=0.5$), the pre-specified pooling of the study data demonstrated a significant effect of pirfenidone (2403 mg/day) in reducing the rate of decline in FVC.



While the European Medicines Agency approved pirfenidone for use in IPF in 2011, regulatory authorities in the US requested additional trial data. The ASCEND study¹¹ confirmed the positive effect of pirfenidone, with a relative reduction of 47.9% in the proportion of patients who had an absolute decline of $\geq 10\%$ FVC % predicted, or who died, at week 52. A pre-specified survival analysis (including data from the CAPACITY and ASCEND studies), demonstrated a reduction in all cause, and IPF related mortality (hazard ratio 0.35; $p=0.03$). Subgroup analysis (using pooled data from both CAPACITY and ASCEND studies)¹² demonstrated the treatment effect of pirfenidone to be generally consistent across all demographic variables and baseline measures of IPF disease severity. An analysis of safety outcomes for the CAPACITY and ASCEND studies, including 1299 patients with a median duration of pirfenidone exposure of 1.7 years (range 1 week to 9.9 years), reported nausea (37.6%), diarrhoea (28.1%), dyspepsia (18.4%), vomiting (15.9%) and photo sensitive rash (25%) as the most common adverse events; although these were generally mild and without significant clinical consequences.¹³ Nausea and rash were the adverse events most commonly associated with treatment discontinuation, in 1.7% and 1.5% of patients respectively. Particularly relevant to the Australian and New Zealand climate is the risk of photosensitivity, and patients should be counseled regarding the avoidance of direct sunlight exposure.

4.1.2 Nintedanib

Nintedanib (formally known as BIBF 1120), an intracellular inhibitor of tyrosine kinases, attenuates fibrosis via several mechanisms, including reduction in fibroblast proliferation and differentiation of fibroblasts to myofibroblasts.^{14, 15} In a randomised, double-blind, placebo controlled phase 2 dose finding study (TOMORROW),¹⁶ 431 patients were assigned to various nintedanib doses (50 mg daily, 100 mg daily, 150 mg daily and 150 mg twice daily) or placebo for 52 weeks. Compared with placebo, nintedanib 150 mg twice daily was associated with reduced decline in FVC, a reduction in investigator-reported acute exacerbations of IPF (AE-IPF), and preservation of health related quality of life.

Subsequently, in two replicate randomised, double-blind, placebo controlled phase 3 studies (INPULSIS-1 and INPULSIS-2),¹⁷ 1066 patients were assigned in a 3:2 ratio to receive nintedanib (150 mg twice daily) or placebo. Compared with placebo, nintedanib was associated with a reduced annual rate of FVC decline in both trials (with a difference of 125.3 ml/year; 95% confidence interval [CI], 77.7-172.8; $p<0.001$ in INPULSIS-1 and 93.7 ml/year 95% CI 44.8-142.7; $p<0.001$ in INPULSIS-2).¹⁷ In a key secondary end point, there was a reduction favouring nintedanib in time to first investigator-reported AE-IPF in INPULSIS-1 but not INPULSIS-2, but when AE-IPFs were centrally adjudicated, there was a significant reduction favouring nintedanib in the pooled dataset. In a pre-specified analysis, the effect of nintedanib on annual rate of decline in FVC was similar across a range of subgroups, irrespective of age, gender, baseline FVC severity or smoking status.¹⁸ Furthermore, in patients with a 'possible' pattern of UIP with traction bronchiectasis on HRCT (but without a surgical lung biopsy), the treatment effect of nintedanib was similar to patients with honeycombing on HRCT and/or confirmation of UIP on surgical lung biopsy.¹⁹

The most frequent adverse event in the nintedanib groups was diarrhoea (with rates of approximately 60%), which resulted in cessation of the drug in less than 5%. Other common adverse events included nausea, vomiting and decreased appetite, occurring in 8-25% of patients.

4.1.3 Clinical experience with anti-fibrotic medications

There is increasing data for the use of both pirfenidone and nintedanib emerging from single centres and larger IPF registries, with findings broadly consistent with clinical trial data. PASSPORT, a prospective, observational long term registry, was established in 2011 following the approval of pirfenidone by the European Medicines Agency. Following interim analysis of the first 530 patients (who had received at least one dose of pirfenidone), the PASSPORT investigators have concluded that the longer term safety profile of pirfenidone is consistent with that seen in clinical trials, and no new or unexpected safety signals have emerged.²⁰

INPULSIS-ON is a single arm extension study in which patients participating in the INPULSIS studies then



received open label treatment with nintedanib.²¹ Interim analysis demonstrated the beneficial effect of nintedanib in slowing disease progression was maintained over 2 years, and long-term treatment with nintedanib had a manageable safety and tolerability profile similar to that seen in the initial INPULSIS studies.

Numerous single centre experiences²²⁻²⁵ have reported similar findings with regard to treatment efficacy and safety profile, including successful management of side-effects and acceptable but higher discontinuation rates in 'real world' populations who were older with more severe lung function impairment and co-morbidities compared to clinical trial populations.²⁵

4.1.4 Combination therapy

There is little data on the combination of pirfenidone and nintedanib to date. Since they have different mechanisms of action, it has been postulated that combination may induce a greater reduction in FVC decline. In a small group of 50 patients, Ogura *et al.*²⁶ conducted a randomised, double-blind, phase II, dose escalation trial to assess the safety, tolerability and pharmacokinetics of nintedanib, alone and in combination with pirfenidone. Overall, while the patients on combination therapy reported slightly higher rates of nausea and vomiting, adverse events were mostly mild to moderate with the authors concluding that combination therapy had an acceptable safety and tolerability. There are 2 ongoing studies currently assessing combination treatment in IPF.²⁷

4.1.5 Practical Questions with regard to Anti-fibrotic therapy

While clinical trials (with clearly defined inclusion and exclusion criteria) provide broad guidelines as to who may benefit from anti-fibrotic therapy, in real world clinical practice, deciding which drug to use, when, and in whom is not often as straightforward. Both pirfenidone and nintedanib appear to have similar efficacy in slowing FVC decline, and while a mortality benefit has been demonstrated with pirfenidone, nintedanib has been shown to reduce adjudicated acute exacerbations of IPF. The substantially different side-effect profile for each drug, compliance with tablet medications, medication interactions and patient preference are likely to be key factors in deciding which agent to use.

Evidence supporting early initiation of treatment has recently been published, with both nintedanib and pirfenidone demonstrating similar treatment efficacy irrespective of baseline lung function severity, suggesting a beneficial effect of anti-fibrotic therapy even in patients with well-preserved physiology.^{28, 29} There is also evidence from small studies to suggest that patients with a more rapid decline in the months prior to therapy with pirfenidone may have better attenuation of FVC decline.³⁰⁻³²

While IPF disease heterogeneity is increasingly recognized, tools for predicting disease behaviour in individual patients (in particular, identifying those at risk of progressive disease) remain frustratingly imprecise. A focus on 'personalised medicine' and predictive biomarkers in IPF may provide vital information in identifying patients at risk for progressive disease in the future, although such information is not currently routinely available.^{28, 29}

Despite therapeutic intervention with anti-fibrotic agents, it is likely that patients with IPF will continue to experience disease progression. Pooled data from the CAPACITY and ASCEND studies suggest that in patients who progress on pirfenidone (defined as a decline in FVC of $\geq 10\%$ during a six month period), continued treatment with pirfenidone resulted in a lower risk of subsequent FVC decline or death.³³ Similar data are available for nintedanib.³⁴ With the availability of two proven therapies, some patients and clinicians will opt for switching treatment in the event of disease progression, although little evidence exists to support or refute this approach.

Summary:

- ***In the 2015 multinational IPF treatment guidelines,³⁵ both nintedanib and pirfenidone received positive treatment recommendations for IPF. Consistent with these recommendations, in patients with a multi-disciplinary confirmed diagnosis of IPF of***



mild to moderate severity, monotherapy with either pirfenidone or nintedanib should be considered as first line therapy.

- *The choice of anti-fibrotic agent should be individualized to the patient according to their co-morbidities and likely tolerability of either medication.*

4.1.6 Treatment of IPF patients with varying disease severity

There is no universal consensus on how to define disease severity of IPF patients, with several different methods including baseline FVC, DL_{CO} , GAP (gender, age and physiology) index,³⁶ composite physiological index (CPI)³⁷ and Japanese disease severity classification (JSC)³⁸ described. Whilst there is some difficulty using a single measure of FVC to judge severity of impairment in the clinical setting where a pre-morbid value is often unknown, it has been widely accepted as a measure of disease progression and despite its failings, has been repeatedly used as a primary outcome measure for clinical trials.³⁹

Very mild asymptomatic disease

It is currently unclear whether patients with very mild, asymptomatic disease would benefit from anti-fibrotic treatment as there are no specific randomized controlled trials in this group. In a post-hoc analysis of the pooled INPULSIS data, patients with FVC >90% predicted were found to have the same rate of FVC decline as those with FVC ≤ 90%,²⁹ as did the patients stratified by FVC >80% or GAP stage I disease in the pooled ASCEND/CAPACITY cohorts.²⁸ Treatment with anti-fibrotic medications appeared to attenuate progression of IPF to the same degree in these mild cohorts as they did in the more severe groups. While this data appears to support the use of anti-fibrotic medications in this cohort, these are post-hoc analyses and it is yet to be determined whether these results translate into meaningful clinical benefit, especially in patients who have preserved and stable lung function. In this cohort with mild, asymptomatic disease, the decision to treat should be individualized, taking into consideration the patient's age, co-morbidities and potential side effects of treatment.

Mild to Moderate disease

In this population with mild to moderate IPF, there is currently the most data for treatment with anti-fibrotic medications. All major anti-fibrotic clinical trials have required an FVC ≥ 50% for inclusion, with the ASCEND trial alone stipulating an upper limit of ≤ 90%. The mean FVC was higher in the nintedanib (78.1 – 80.5%) than the pirfenidone trials (ASCEND mean FVC 67.8%, CAPACITY mean 74.4 – 76%). In the recent international consensus guidelines, treatment of this group with anti-fibrotic medications was given a conditional positive recommendation.³⁵ This mild to moderate IPF cohort is also the group that funding bodies in some countries have chosen for government funded anti-fibrotic therapy.

Severe disease

There is very little evidence to guide clinicians with regard to treatment of patients with severe IPF, as this cohort of patients was systematically excluded from all large controlled trials. There have been a number of small 'real world' cohort studies suggesting that those with more severe disease may actually have greater benefit from pirfenidone with a similar rate of adverse events.^{30-32, 40} A controlled study using nintedanib in severe IPF is currently recruiting patients globally (NCT02802345). Further data is required before any suggested management recommendations can be made with regard to anti-fibrotic agents in severe IPF. Local prescribing restrictions have prohibited the use of anti-fibrotic agents in severe disease in many countries until more data is available.

4.1.7 Definite versus Probable and Possible IPF

In clinical practice, there are often patients in whom a definite IPF diagnosis cannot be secured, usually due to atypical imaging and lack of a surgical lung biopsy. Surgical lung biopsy is not without risk and many patients with IPF have co-morbidities precluding a biopsy, or elect not to consent to the procedure.⁴¹ In such patients, a definite diagnosis of IPF cannot be confirmed and are given a pragmatic diagnosis of probable or



possible IPF, without lung biopsy. There has been growing support for this pragmatic approach with several studies showing that a UIP pattern on histopathology is often confirmed at surgical lung biopsy in patients with possible IPF.⁴²⁻⁴⁵

It is likely those with possible IPF have the potential to benefit from treatment with anti-fibrotic therapy, 31.9% of the patients enrolled in the INPULSIS trials had possible UIP with traction bronchiectasis on HRCT, without a surgical lung biopsy. A post-hoc analysis of data from these studies demonstrated that these patients have disease progression and treatment response no different from those with definite UIP.¹⁹ Small retrospective cohort studies of pirfenidone also suggest treatment equivalence.^{32, 46}

4.1.8 Usual interstitial pneumonia pattern in non-IPF disease and unclassifiable ILD

While IPF frequently presents with a UIP pattern on HRCT, a UIP pattern does not exclusively represent a diagnosis of IPF. Other fibrosing ILDs including CTD-ILD, chronic hypersensitivity pneumonitis and asbestosis can also present with a UIP pattern on HRCT and/or histopathology and thus may incorrectly be diagnosed as IPF. Given that treatment of these conditions differs considerably from IPF, it is crucial that any patient with a fibrosing ILD undergo a thorough assessment including a detailed history of environmental exposures as well as specific questioning for subtle symptoms and signs of a CTD.⁴⁷ Evaluation of autoantibodies as well as serum precipitins should also be considered in a compatible clinical context.⁴⁸ The use of bronchoscopy and bronchoalveolar lavage is debated and should be considered on an individual basis.¹ All patients should undergo an ILD multidisciplinary meeting (MDM) with physicians, radiologists and histopathologists specialized in ILD present, as subtle features that may help differentiate these conditions may be present. Despite the biological plausibility for the use of anti-fibrotic agents in patients with non-IPF UIP, there are no current data to support this practice.

Despite thorough investigation and discussion at an ILD MDM however, a significant minority of patients with ILD remain unclassifiable.^{49, 50} This is often due to the absence of, or inadequate histopathology, as well as conflicting clinical, radiological and histopathological data. While there is no consensus definition of 'unclassifiable ILD', this group is likely to be heterogeneous, reflected by their overall prognosis which lies between IPF and non-IPF ILDs.⁴⁹ While there may be biologic plausibility for efficacy of anti-fibrotic therapy in these 'unclassifiable' fibrosing ILDs, there is no current evidence to support their use. There are ongoing clinical studies with both pirfenidone and nintedanib recruiting unclassifiable ILD, and progressive fibrosing ILD patients respectively.

Summary:

- ***Anti-fibrotic therapy appears to have similar efficacy in slowing disease progression in patients with both mild and moderate disease severity.***
- ***The overall treatment benefit in very mild, asymptomatic disease is unknown and treatment should be considered on an individual basis.***
- ***Despite biologic plausibility, there is no controlled evidence to support the use of anti-fibrotic therapy for IPF patients with severe disease, or those with non-IPF UIP or unclassifiable ILD. Such patients should be encouraged to enrol in clinical trials.***

4.2 Therapies proven not to have effect in IPF

IPF clinical trials have historically suffered from two major problems: firstly, older studies included patients who would now not be considered to have true IPF; and secondly, small initial investigations reported positive outcomes, but these findings were not replicated in larger, appropriately powered studies. The randomised controlled trials that have been performed, as well as their overall outcomes, are summarized in Table 1. As demonstrated by this table, there have been a number of trials, particularly with the use of immunomodulation, pulmonary vasodilators and N-acetylcysteine (NAC) which have had disappointing results.



The use of combination prednisolone, azathioprine and NAC in IPF, as well as anticoagulation, offer useful lessons regarding interpretation of data on which clinical 'best practice' is based. Although the small initial trials of these therapies were promising, larger, appropriately powered trials demonstrated not only lack of efficacy, but also increased harm.

4.2.1 Combination Prednisolone, Azathioprine and N-acetylcysteine.

For many years, the standard of care for IPF was immunosuppression with a variety of agents, with or without the addition of the oral antioxidant, N-acetylcysteine (NAC). In the late 2000s most respiratory physicians used either prednisolone (PRED) plus azathioprine (AZA) with or without NAC for their patients,⁵¹ in keeping with consensus guidelines at the time.⁵² The data supporting triple therapy (PRED/AZA/NAC) was obtained from a study examining PRED/AZA vs PRED/AZA/NAC, suggesting the addition of NAC improved outcomes.⁵³ The use of PRED/AZA in IPF was based on a single study in the early 1990s using small numbers (27 patients) with no statistically significant outcomes,⁵⁴ and whilst there had been observational studies regarding prednisolone in pulmonary fibrosis in the early 1980s⁵⁵ there had never been a randomised trial examining the use of prednisolone alone.

In order to address these knowledge gaps, the PANTHER IPF trial was established examining the effect of NAC alone (plus matched placebos for AZA and PRED), PRED/AZA/NAC triple therapy and triple placebo⁵⁶. The study was stopped early, as the death rate in the triple therapy arm was 10% vs 1% in the triple placebo group, with a concomitant increased rate of hospitalisation and acute exacerbations. As such, triple therapy of IPF halted worldwide. The question of whether NAC alone was beneficial in IPF was addressed by a later publication that showed no benefit of NAC vs placebo in any outcome measure.⁵⁷

In Europe, oral NAC has been used in combination with Pirfenidone, despite an absence of data. This approach has now been assessed in a randomised clinical trial, which has demonstrated that the addition of NAC therapy increases the risk of photosensitivity, and an exploratory analysis of change in FVC suggests that NAC plus pirfenidone may worsen lung function decline.⁵⁸ As such, use of Pirfenidone with oral NAC cannot be recommended.

Summary:

- **Consistent with the international guidelines, the combination of prednisolone, azathioprine and N-acetylcysteine should not be used in the treatment of IPF.**
- **The current evidence does not support the use of NAC alone or in combination with pirfenidone for the treatment of IPF.**

4.2.2 Anticoagulation: warfarin

In IPF, a systemic pro-coagulant state is present, with an increase in both circulating factor VIII and platelet activation. An initial small and poorly controlled clinical trial of warfarin in IPF demonstrated a survival benefit⁵⁹ however, a larger, definitive study (ACE-IPF) was stopped early due to an increased risk of death in the warfarin group.⁶⁰ The increased mortality was not due to excess bleeding, but rather from disease progression, suggesting that warfarin worsens the fibrotic process.

Following this study, primary treatment of IPF using warfarin was abandoned, but the question remained, what should be done in patients who need anticoagulation for other clinical indications? This has been controversial, but there is growing evidence, though often retrospective and uncontrolled, that patients with confirmed IPF who are anticoagulated with warfarin for appropriate indications have an increased mortality.⁶¹ ⁶² The most recent data,⁶³ using a post-hoc analysis of patients in the placebo arms of IPF trials analysed by warfarin use, has demonstrated a significant increase in mortality, with a hazard ratio of nearly five. At present it is unclear if this risk is related only to warfarin or if it also applies to direct oral anticoagulants.



Summary:

- **Current evidence does not support the use of anticoagulation for the treatment of IPF.**
- **For patients on anticoagulation for other indications, careful consultation with appropriate specialists regarding the indications, risks and benefits of anticoagulation is suggested before any alterations are made.**

4.3 Anti-reflux therapy

Patients with IPF have a high prevalence of gastro-oesophageal reflux disease (GORD), although the reported prevalence varies widely depending at least in part on how GORD is ascertained,⁶⁴⁻⁶⁶ and in half it is asymptomatic. Patients with IPF are also more likely to have a hiatus hernia.⁶⁷ This strong and long-recognised association suggests either that GORD contributes to IPF pathogenesis (for instance through micro-aspiration with subsequent alveolar epithelial injury), and/or that IPF predisposes to GORD (for instance via changes in intrathoracic pressures during respiration), or that the two diseases share a common cause; and has further led to the idea that antacid therapy, or even surgical fundoplication, may be an effective therapeutic strategy for IPF.

Unfortunately there are no randomised-controlled studies to address this hypothesis; however in 2006 two relatively small retrospective studies were published suggesting a possible therapeutic benefit of antacid therapy⁶⁸ and surgery,⁶⁹ leading the ATS/ERS to cautiously recommend treatment of asymptomatic gastro-oesophageal reflux in the 2011 Guidelines¹. A more recent, larger, but again post-hoc analysis of the patients enrolled in the placebo arms of the three IPFnet randomised trials provided further support for this position⁷⁰ leading the ATS/ERS in the 2015 Guideline Update to again cautiously suggest that antacid treatment should be prescribed for patients with IPF,³⁵ although the confidence of this recommendation was low. Most recently, two large post-hoc analyses of the pooled data from the pirfenidone⁷¹ and nintedanib⁷² studies, found no benefit of antacid therapy. Concerningly, in the pirfenidone studies, use of antacid therapy was associated with an increased risk of generalised and respiratory infections in patients with more severe (FVC <70%) IPF.⁷¹ There are no suitably controlled data to define the effect of fundoplication on the natural history of IPF, but an NHLBI sponsored randomised controlled trial of laparoscopic fundoplication in IPF (NCT01982968) is ongoing and is expected to report results in 2017.

Summary:

- **There is conflicting evidence regarding the role of antacid therapy in IPF. Only observational data exist, with some studies suggesting benefit, some suggesting no benefit and one suggesting potential for harm. Since appropriately designed studies assessing the roles of medical or surgical treatment of gastro-oesophageal reflux in IPF are awaited, it remains unclear whether these treatment strategies confer benefit.**

4.4 Current and Future trials

While the discovery of anti-fibrotic therapy has been the recent focus of IPF management, it is important to highlight that there has also been significant progress in the understanding of IPF pathobiology. Pre-clinical trials have resulted in the discovery of several pathways thought to contribute to inflammation and fibrosis in IPF and are now the subject of targeted therapy. Despite recent advances in IPF treatment, anti-fibrotic medications only slow the disease progression by approximately 50% at 12 months, still leaving a large unmet clinical need for further therapies. Table 2 describes a comprehensive list of novel therapies currently undergoing study from clinical trials databases including NIH,⁷³ European Union clinical trials register and "IPF watch". These trials are at various stages of recruitment and completion.

In addition to pharmacological interventions, cell therapy is at an early stage of development. A seminal phase I study establishing the safety of mesenchymal stromal cell infusion in IPF⁷⁴ has been completed. There are

further studies underway and the 'Study of Autologous Mesenchymal Stem Cells to Treat IPF' (NCT01919827) is a phase I, open, multi-centre, non-randomized, study with escalating doses, which will evaluate the safety and efficacy of mesenchymal stem cells in IPF.

4.5 Treatment of acute exacerbations

Acute exacerbation (AE) of IPF has been defined by an international task-force as an acute, clinically significant respiratory deterioration characterised by evidence of new, widespread alveolar abnormality, in a patient with a previous or concurrent diagnosis of IPF, where the deterioration is not fully explained by cardiac failure or fluid overload.⁷⁵ This definition has recently been modified to include exacerbations with a known cause (e.g. infection), as well as those of unknown aetiology. The rationale behind this change is that although the aetiology of AE-IPF remains uncertain, it appears likely that many exacerbations may be triggered by an external insult such as infection or micro-aspiration,⁷⁶ and there are little data to suggest that there is a meaningful distinction between these two. Identification of a cause for an AE of IPF does not appear to alter prognosis, although this is an area of ongoing research interest.

AE-IPF are more common in patients with physiologically advanced lung disease, with low FVC being the most consistent risk factor;⁷⁶⁻⁷⁸ other physiological parameters have also been associated with increased risk, including low DL_{CO} and reduced 6 minute walk distance (6MWD).

The prognosis of AE of IPF is poor. The median survival of patients who have AE-IPF is approximately 3-4 months,^{76, 77} and up to 46% of deaths in IPF are preceded by an AE.⁷⁸ Respiratory failure from AE of IPF is associated with high in-hospital mortality (greater than 50% in most series).^{76, 79}

There remain no proven, effective therapies for AE of IPF. Management includes supportive care including supplemental oxygen to correct hypoxaemia, palliation of symptoms, consideration of broad spectrum antibiotics to cover the possibility of infection, and consideration of mechanical ventilation. The decision to undertake mechanical ventilation in this setting needs to be carefully considered, as the in-hospital mortality is as high as 90% in this population.⁷⁵ In individual situations (e.g. following identification of a specific treatable cause for the exacerbation such as infection or pulmonary embolism; or as a bridge to lung transplant) such a decision may be considered appropriate. The ATS/ERS guidelines recommend against mechanical ventilation, stating that *'the majority of patients with respiratory failure due to IPF should not receive mechanical ventilation, but mechanical ventilation may be a reasonable intervention in a minority'* (weak recommendation, low-quality evidence).¹

Corticosteroids are often used in AE of IPF, although there is no controlled evidence to support this. Although there are only anecdotal reports of benefit, in the absence of other therapies, and in view of the poor prognosis of AE-IPF, corticosteroids are often given in this situation. The ATS/ERS guidelines include a weak recommendation that the majority of patients with acute exacerbation of IPF should be treated with corticosteroids.¹ Other treatments may be considered for AE of IPF. Observational cohort studies of a number of therapies (cyclophosphamide, cyclosporine, rituximab combined with plasma exchange and intravenous immunoglobulin, tacrolimus, intravenous thrombomodulin, polymyxin-B immobilized fiber column hemoperfusion) have suggested benefit, however there are no randomised controlled trials, and the routine use of these agents outside a clinical trial setting is not supported by the current evidence.⁷⁵

In the absence of effective treatment for AE of IPF, prevention of such events becomes important. There are some data to support the use of nintedanib to prevent the development of AE-IPF.^{9, 16, 17} Additionally, a cohort study using subjects from placebo arms of clinical trials showed a reduction in acute exacerbations in those on anti-acid therapy.⁷⁰ Further studies are required before recommendations can be made for prevention of AE-IPF.

Summary:

- **The prognosis of AE-IPF is poor. Available treatment options are limited, and not supported by controlled trial data. Further studies of prevention and treatment strategies for AE-IPF are needed.**



4.6 Treatment of co-morbidities

Optimization of comorbidities in IPF patients can enhance quality of life and, in some cases longevity. Early recognition and treatment of infections, regular vaccinations and routine health screening are also important preventative strategies in this population. Prevalent comorbid diseases in IPF patients include cardiovascular disease, gastro-oesophageal reflux disease (GORD), pulmonary embolism, lung cancer, pulmonary hypertension (PH), emphysema/ airways disease and obstructive sleep apnoea (OSA).⁸⁰⁻⁸³ Whilst there is limited specific evidence for treatment of these conditions in IPF patients, targeted therapy may be considered where benefits are likely to outweigh potential harm.^{4, 84}

4.6.1 Pulmonary hypertension

Pulmonary hypertension (PH) is reported to occur in 3 - 86% of IPF patients, resulting in poorer survival.⁸⁵⁻⁸⁷ Variations in the severity of fibrotic lung disease across study populations, as well as differences in PH diagnostic methodology account for this wide range, and thus the true prevalence is uncertain. Most IPF patients with PH will have only mild or moderate severity pulmonary vascular disease, however a subset of approximately 10% will develop severe PH, with associated right heart failure.⁸⁷

The majority of cases fall within Group 3 of the classification scheme set out by the European Society of Cardiology/ European Respiratory Society (ESC/ERS), that is 'PH associated with lung diseases and/or hypoxia', although some patients may also have elevated pulmonary pressures from concomitant left heart disease (Group 2 PH).⁸⁸ There are currently no specific vasodilator therapies indicated for Group 3 PH. Trials in sildenafil, bosentan, ambrisentan and macitentan have been disappointing, with all failing to demonstrate efficacy in the IPF population (Table 1).⁸⁹⁻⁹³ A recent placebo-controlled trial using riociguat in the idiopathic interstitial pneumonias, including IPF (the RISE-IIP study) was discontinued prematurely due to an increased risk of death and serious adverse events in the treatment arm.

The STEP-IPF trial using sildenafil versus placebo in patients with advanced IPF, (but not necessarily with PH), provides some indirect support for vasodilator therapy in selected cases. Whilst the primary outcome measure of 20% improvement in six-minute walk distance (6MWD) was not met, secondary outcomes of gas transfer, oxygenation, breathlessness and quality of life were significantly improved with the intervention.⁸⁹ Patients with suspected moderate to severe PH may be referred to specialist centres for consideration of right heart catheterization and a trial of sildenafil, with ongoing close surveillance.⁹⁴ Supplemental oxygen and diuretics may also improve symptom burden and haemodynamics in severe cases with associated right heart failure.

Summary:

- **All trials of specific vasodilator therapy for PH in IPF have been negative in terms of their primary endpoint.**

4.6.2 Sleep disordered breathing

Sleep disordered breathing (SDB) is reportedly common in IPF cohorts, with observed frequency ranging between 59 and 90%.^{82, 95-97} Nocturnal hypoxaemia is also prevalent, occurring both with and without associated apnoeas, due to ventilation/ perfusion inequality, alveolar hypoventilation and their position on the steep portion of the oxy-haemoglobin dissociation curve. Two studies have linked increased mortality risk with the number of nocturnal desaturation events and nadir sleep oxygen saturation in ILD patients.^{97, 98} Justifications for investigation and treatment of SDB in this population include the association between OSA and the development of PH, as well as the impact of sleep fragmentation on daytime functional status and quality of life.⁹⁸⁻¹⁰² Standard screening questionnaires for the presence of SDB (such as the Epworth Sleepiness Scale) are poorly sensitive in IPF patients and thus identifying those at risk can be challenging.^{82, 97, 103, 104} In-laboratory polysomnography or home based sleep studies may be considered in IPF patients



for the detection of OSA and/ or significant nocturnal hypoxaemia, however the optimal timing of these investigations is unclear.

A non-randomised study of IPF patients with moderate to severe OSA suggested improved daytime functioning and sleep quality at 12 months along with improved survival at 2-years, in those compliant with continuous positive airway pressure (CPAP) versus those who were non-compliant.¹⁰⁵ Although potentially subject to confounding bias, this study provides supportive evidence for a proactive approach to SDB in this patient group. Thus, when moderate to severe OSA is identified in IPF patients, a trial of CPAP therapy may be appropriate. Specialist sleep clinic input is recommended, given the difficulties that many fibrotic lung disease patients have with tolerating positive pressure ventilation during sleep. Supplemental nocturnal oxygen therapy is recommended for IPF patients with significant nocturnal hypoxia (as described in further detail in *Oxygen Therapy in IPF*). This may also be a reasonable strategy for patients poorly tolerant of CPAP, however there is limited published evidence to support this.

Summary:

- ***Obstructive sleep apnoea and nocturnal hypoxia occur frequently in IPF patients.***
- ***Sleep studies could be considered when sleep apnoea or nocturnal hypoxia is suspected.***

4.6.3 Combined pulmonary fibrosis and emphysema

Combined pulmonary fibrosis and emphysema (CPFE) is a recently defined syndrome describing the coexistence of pulmonary fibrosis and radiological emphysema in individuals with significant tobacco exposure.¹⁰⁶ It is presently unclear whether this entity represents a distinct disease phenotype or is simply the coincidence of two processes with a common aetiology. The majority of patients with CPFE have the UIP pattern of IPF on HRCT, although other ILD patterns can be seen, including desquamative interstitial pneumonia.^{106,107} Patients with CPFE typically have preserved spirometry and lung volumes despite extensive disease. Airflow obstruction is present in some, but not all CPFE patients.¹⁰⁸ Both DL_{CO} and K_{CO} are usually severely reduced. Profound oxygen desaturation is common and the majority will progress to develop resting hypoxaemia.¹⁰⁹ Pulmonary hypertension is present in up to 50% of CPFE cases at diagnosis, with an associated increased mortality risk beyond that of CPFE patients without PH, and of IPF patients without emphysema.^{110,111} The risk of lung cancer is also higher for CPFE than for either IPF or COPD alone.¹¹²

Therapeutic options for CPFE are currently very limited, with a paucity of clinical trials in this disease subset. Patients with emphysema greater than the extent of pulmonary fibrosis were specifically excluded from the trials of pirfenidone and nintedanib.^{11,113} Patients who had emphysema extent less than fibrosis on HRCT with an FEV1/FVC ratio of >80% were however, included in the ASCEND and INPLUSIS studies suggesting that the presence of emphysema may not necessarily preclude response to treatment. A post-hoc analysis from the INPLUSIS studies of patients with emphysema on HRCT compared to those without emphysema demonstrated similar efficacy for nintedanib in patients with CPFE.¹¹⁴

Vasodilator agents have not been trialled in CPFE patients with associated PH. Such therapies should be administered with caution, given the potential for worsening hypoxaemia due to increased ventilation/perfusion mismatch.¹¹⁵ As with IPF-related PH, CPFE-PH requires specialist centre management. Standard bronchodilator therapy may benefit those with airflow limitation. Supplemental oxygen is suggested for patients with PH and developing right heart failure. CPFE patients should be referred to either lung transplantation or palliative care services where appropriate.

Summary:

- ***There is increased risk of both PH and lung malignancy in patients with CPFE.***
- ***Supplemental oxygen and inhaled bronchodilator therapy may help relieve breathlessness in some patients with CPFE.***
- ***In a subset of patients with fibrosis greater than emphysema and FEV1/FVC >80%, there is evidence to suggest a benefit from anti-fibrotic therapy.***



5. NON-PHARMACOLOGICAL THERAPY

5.1 Oxygen

Adverse outcomes are predicted by resting oxygen requirements as well as degree of exercise- and sleep-related hypoxaemia in IPF.^{97, 98, 116-118} At the present time, it is unknown whether prevention of hypoxaemia with supplemental oxygen under these circumstances assuages the increased mortality risk. Surprisingly there are very few studies investigating the use of oxygen in IPF populations.

Oxygen prescribing guidelines: Current recommendations for supplemental oxygen in IPF and other ILD patients are extrapolated from two landmark trials in COPD.^{84, 119, 120} Australian/ New Zealand guidelines advise oxygen therapy for patients with chronic lung disease who have resting hypoxaemia [$\text{PaO}_2 < 55$ mmHg, or < 60 mmHg in the presence of hypoxic organ damage (including polycythaemia, pulmonary hypertension or right heart failure)].^{121, 122} Intermittent ambulatory oxygen may be considered for those with exercise-induced desaturation where an improvement is seen in exercise capacity or dyspnoea, as assessed with a blinded trial of oxygen versus air during 6MWT.¹²² Guidelines also recommend nocturnal oxygen for respiratory patients who desaturate below 88% for at least one third of total sleep time, in the absence of concomitant sleep-disordered breathing. With largely equivocal evidence, an individualized approach for the latter two indications is advised.

Ambulatory oxygen during exercise: In many countries, oxygen is routinely provided during exercise training in ILD patients who are known to desaturate. Two small IPF study cohorts demonstrated improved endurance and maximal work-rate whilst breathing FiO_2 60% (versus 21%) during incremental cardiopulmonary exercise testing.^{123, 124} Ambulatory oxygen during 6MWT was seen to improve walk distance, heart rate, SpO_2 recovery and subjective dyspnoea scores in two retrospective studies of IPF subjects.^{125, 126} The improvement in walk distance remained significant in the subgroup that carried their portable cylinders during the test, reflective of an encumbrance that could potentially limit the benefits of ambulatory oxygen in everyday practice.¹²⁵ In a more recent prospective trial however, IPF patients did not improve their 6MWD using 4L/min of oxygen compared with air.¹²⁷ To date, there have been no published studies examining the longer-term benefits of ambulatory oxygen for those who desaturate with exercise but are not hypoxic at rest. There are also no data on its impact on quality of life, however a large randomised control trial addressing this question is currently underway (AmbOx study, NCT02286063).

Nocturnal oxygen: Guidelines advocate supplemental nocturnal oxygen for chronic lung disease patients with significant sleep desaturation, albeit with minimal supportive data. In the COPD literature, overnight oxygen therapy has not been demonstrated to improve survival in those patients with nocturnal hypoxia but daytime normoxia.^{119, 120, 128} Pulmonary haemodynamics may be improved in COPD patients receiving long-term nocturnal oxygen, however this has not been investigated in IPF populations.¹²⁹ In two single-night studies in ILD subjects, oxygen reduced breathing frequency and heart rate through elimination of sleep-associated desaturation, however, sleep quality and arousal index were not significantly altered.^{130, 131}

Continuous oxygen therapy: The literature is equally sparse in the application of oxygen for IPF patients who are hypoxaemic at rest. A Cochrane review, updated in 2010, included only 1 unpublished reference.¹³² This trial randomised 62 ILD patients to receive either long-term oxygen therapy (LTOT) or no oxygen.¹³³ Mortality at 12, 24 and 36 months was the same in each group. Physiologic and quality of life data were not reported. With ethical considerations of allocating placebo to hypoxaemic subjects, it is unlikely that such a study will be repeated. IPF-specific guidelines make a strong recommendation for LTOT in those with resting hypoxaemia, but acknowledge the lack of evidence specific to this disease group.^{84, 119, 120}

General considerations and summary: There are many practical issues to take into account when prescribing oxygen, particularly in the ambulatory setting. Important factors include the cost of portable concentrators,



the physical challenges of carrying or pulling a delivery device, and the limited duration of cylinder oxygen delivery and need for frequent refills. It is currently not known whether continuous versus pulse flow delivery meet patient needs equally, particularly in advancing disease. Local oxygen funding bodies vary in their equipment provision for those who fulfil criteria, and this will also influence choice of delivery modality.

Summary:

- ***Consistent with international guidelines, clinicians should offer long-term oxygen therapy for IPF patients with resting hypoxaemia, and consider supplemental oxygen for those with significant exercise- and sleep-related oxygen desaturation.***

5.2 Pulmonary Rehabilitation

It is common for people with IPF to experience dyspnoea on exertion, poor health-related quality of life and marked exercise intolerance. These impacts persist in patients using anti-fibrotic therapies^{17, 134} and often worsen as the disease progresses. There is growing evidence that pulmonary rehabilitation has important effects on symptoms, functional capacity and wellbeing in people with IPF. A Cochrane review examining randomised controlled trials of pulmonary rehabilitation in ILD¹³⁵ reported that in the subgroup with IPF, 8-12 weeks of supervised pulmonary rehabilitation produced improvements in 6-minute walk distance that exceed the minimal important difference (mean 36 metres, 95%CI 16 to 55 metres). There were also significant improvements in dyspnoea and health-related quality of life with moderate effect sizes. All pulmonary rehabilitation programs included whole body endurance training (walking or cycling), most included resistance (strength) training and some also included education, nutrition counselling and psychosocial support.

The ATS/ERS guideline for IPF management makes a weak recommendation in favour of pulmonary rehabilitation for IPF, which indicates that pulmonary rehabilitation should be used in the majority of patients.⁸⁴ This recommendation recognises the uncertainty regarding the duration of benefit; the only trials that have examined long term outcomes have reported that gains in exercise capacity diminish in the 6-12 months following pulmonary rehabilitation, although health-related quality of life may be better preserved.^{136, 137} Early referral to pulmonary rehabilitation should be considered as patients with milder disease appear to have more sustained benefit.¹³⁸ The ATS/ERS pulmonary rehabilitation statement¹³⁹ also reports that pulmonary rehabilitation delivers meaningful short-term benefits in people with IPF, whilst acknowledging the challenges in providing rehabilitation for patients who may have progressive disease. Recently the Australian and New Zealand Pulmonary Rehabilitation Guidelines have made a weak recommendation for pulmonary rehabilitation in people with ILD, including those with IPF.¹⁴⁰ The guideline authors found no evidence that exercise prescription should differ from the standard protocols that have been used for many years in patients with chronic obstructive pulmonary disease (COPD), suggesting that patients with IPF can be successfully treated in existing pulmonary rehabilitation services.

In Australia and New Zealand most pulmonary rehabilitation programs will accept referrals for patients with IPF. However those with IPF experience similar barriers to pulmonary rehabilitation attendance as others with chronic lung disease, including fear of exercise and associated breathlessness, the burden of regular travel to attend the program and a lack of perceived benefit. These barriers should be explicitly addressed at the time of referral, preferably by the treating medical team, as encouragement from the doctor is a key facilitator of pulmonary rehabilitation uptake.¹⁴¹ Because people with IPF frequently use supplemental oxygen or experienced marked exercise-induced desaturation, it is preferable for pulmonary rehabilitation to take place in programs that have the capacity to deliver oxygen during training, consistent with exercise training protocols for people with IPF of known effectiveness.¹³⁵ Although the educational curriculum for pulmonary rehabilitation was originally designed for COPD, people with IPF would prefer that disease-specific information was delivered during the program, including management of cough, how to handle IPF medications and their side-effects, and optimal disease management for IPF.¹⁴²

Summary:

- ***Pulmonary rehabilitation confers meaningful benefits in exercise capacity, symptoms and health-related quality of life, especially in patients with milder disease.***



- ***Patients with IPF can be successfully managed in existing pulmonary rehabilitation programs and early referral to pulmonary rehabilitation is encouraged.***

5.3 Lung transplant

Despite the recent advances in IPF therapy, there is still no cure for this relentlessly progressive disease. As a result, lung transplantation remains the only definitive treatment for selected patients with IPF.

The timing of referral for lung transplantation consideration is important and should be early in the course of the disease. Patients can wait a long period of time for suitable lungs, as the small chest cavity can limit the suitability of donor organs and thus prolong wait times. A recent consensus document for the selection of lung transplant candidates¹⁴³ recommends referral of appropriate candidates with a diagnosis of IPF at the time the diagnosis is made, regardless of the severity of their disease at lung function testing. This recommendation reflects the phenotypic heterogeneity of IPF, the difficulty in predicting disease course and overall poor prognosis of IPF patients compared with other indications for lung transplantation.

The heterogeneity of IPF is illustrated by the fact that although the median wait list time to transplant is lower in IPF than in other diagnoses, the mortality on the waiting list is higher.¹⁴⁴ A recent paper from a single centre in Italy also shows a diagnosis of IPF was associated with the highest mortality on their lung transplant waiting list. Factors associated with greater mortality include higher levels of CO₂ and the need for higher flows of O₂.¹⁴⁵

Indications for listing for lung transplantation include: a fall in FVC \geq 10% or DLCO \geq 15% over 6 months, desaturation to \leq 88% on 6 minute walk testing, a fall in 6 minute walk distance during follow up, pulmonary hypertension as well as hospitalisation for respiratory decline, pneumothorax, or acute exacerbation.

The absolute and relative contraindications for lung transplantation are outlined in table 3. Of note, age greater than 65 years is no longer an absolute contraindication to lung transplantation. Rather than chronological age alone, the physiological reserve of the patient as assessed by a variety of frailty measures and the presence of co-morbidities with end organ damage are important contributing factors to the decision for lung transplant listing.¹⁴³

Outcomes after lung transplantation are less than ideal, with a median survival post lung transplantation for IPF of 4.5 years. This is well below that of lung transplantation for cystic fibrosis and chronic obstructive pulmonary disease (7.8 years and 5.4 years respectively).¹⁴⁶ The reasons for this discrepancy are not clear, but include the age of the recipients and the presence of comorbidities. This does not however explain all of the variance. Recent attempts to further define the risks of early mortality post lung transplantation have not however, found IPF to be an independent risk factor.¹⁴⁷

Unlike suppurative lung diseases, IPF patients are eligible for single, as well as double lung transplants. The choice is dependent on a number of factors including:

1. The availability of suitable donor lungs: Two recipients can be transplanted from the same donor. This is particularly relevant for smaller, blood group O potential recipients.
2. The size of the chest cavity: It is possible to transplant a larger single lung as the mediastinum will move over to accommodate the lung. This is particularly important in small potential recipients as the disease inherently further reduces the size of the chest cavity.

Reported outcomes comparing single versus double lung in IPF are conflicting with previous data suggesting no difference¹⁴⁸, with one recent publication reporting better outcomes for double lungs.¹⁴⁹

Summary:

- ***Lung transplantation is a viable option for selected patients with IPF and confers a survival benefit.***



- **Consistent with the international lung transplantation consensus document, early referral to a transplant centre is essential, as it is difficult to accurately predict disease trajectory in IPF.**

5.4 Palliative care

Despite advances in pharmacotherapy, dyspnoea, cough and fatigue remain debilitating symptoms¹⁵⁰ and are often difficult to manage. It is important to recognise that these symptoms can affect patient's quality of life and sense of well-being independent of physiologic measures of disease.¹⁵¹ Palliative care focuses on symptom management, advance directives and end-of-life planning, aiming to improve the quality of life of patients and their families. Palliative care is an integrated and individualised process which should be addressed at all stages of disease and not exclusively at the end of life.¹⁵² It is a dynamic process where goals shift to meet the changing needs of patients.

There is emerging data on palliative treatments and their benefits in IPF¹⁵³ although approaches have often been extrapolated from studies of other chronic lung diseases. Management consists of both non-pharmacologic (e.g. counselling, spiritual care support) and pharmacologic approaches, and are often used in parallel. In addition to treatment for specific symptoms, effective management of psychological stress¹⁵⁴ and pulmonary rehabilitation^{135, 138} is vital, with beneficial effects across multiple domains. The use of oral opioids¹⁵⁵⁻¹⁵⁸ have been reported to reduce dyspnoea, whilst limited evidence exist for the use of benzodiazepine¹⁵⁹ or supplemental oxygen.^{127, 160, 161} A thorough search for reversible causes of cough (including gastroesophageal reflux, post nasal drip, ACE-inhibitor use etc.) is crucial before considering the use of opioids or over the counter cough suppressants, although there is little evidence that these measures are effective in IPF.^{154, 162} Low dose prednisolone may benefit some patients, although a risk/benefit assessment must be considered for each individual patient.¹⁶³ Thalidomide has been reported to significantly reduce cough,^{164, 165} however it is not widely available and is associated with significant side effects.

Although confronting, IPF patients desire information about their prognosis and how IPF manifests in the end stages¹⁶⁶ however, many physicians fail to address this.¹⁶⁷⁻¹⁶⁹ This could be due to a number of reasons, including prognostic uncertainty of IPF, fear of diminishing hope, discomfort with palliative care discussions, and limited understanding of potential benefits of palliative care.^{168, 170-172} The main obstacle is likely to be fear of diminishing hope, although findings from studies of cancer and other terminal illnesses suggest that patients who were referred early to palliative care had a better quality of life, experienced less depressive symptoms and even had a longer survival.¹⁷³ Advance care planning should be offered to patients when they are well and are able to discuss their wishes. Palliative care should be viewed as "supportive care", and should be addressed early as pharmacotherapy in IPF remains largely ineffective for the control of symptoms.

Summary:

- **Dyspnoea, cough and fatigue are prominent and debilitating symptoms, independent of disease severity. To date, no therapeutic options in IPF have been shown to improve these symptoms. Early palliative/ supportive care may be helpful to address this.**
- **Advance care planning, although daunting to patients, families and their doctors, can be offered when patients are relatively well, so that their wishes and those of their families can be heard and respected.**

5.5 Psychosocial support

Living with IPF is challenging for patients and their families. Patients describe struggling to manage dyspnoea, cough and fatigue; a lack of good quality information about their condition and their treatment options; loss of independence and loss of previous life roles; and inadequate emotional support.^{142, 174-177} Because IPF is poorly understood in the community, patients report difficulty in explaining their disease to family and friends.¹⁷⁷ The most common unmet needs reported by patients across the world are for high quality,



honest and reliable disease information that is accessible from the time of diagnosis; emotional support to assist patients and their families to cope with the diagnosis and deal with the ongoing anxiety of living with a progressive disease; and patient-based advocacy groups who could effectively represent the needs of people with IPF in the broader community.^{142, 175-177}

There are a variety of models for patient and family support. A disease management program for IPF was tested in a randomised controlled trial where 21 patient/carer dyads received either six once-weekly group sessions covering important aspects of IPF management (pathophysiology and treatment; management of stress and depression; cognitive behavioural therapy; end of life planning; and symptom management) or usual care.¹⁷⁸ Whilst carers reported a significant reduction in perceived stress at the end of the program, patients reported worse health-related quality of life and a trend to worse anxiety. However, in qualitative interviews patients reported benefits including reduced isolation, putting the disease in perspective and providing comfort. An alternative model is IPF Care, which provides support and education for patients receiving pirfenidone in Europe, funded by the supplier.¹⁷⁹ Participants receive regular telephone calls and/or home visits from nurses, as well as individually tailored information booklets. Although a major function of the program is to support treatment adherence, 30% of topics discussed were not related to pirfenidone and included oxygen therapy, test results, home supports, exercise, transplantation and concerns for the future. Retention in the program was 71% over 18 months and patient-reported satisfaction was high.¹⁷⁹

Many tertiary referral centres for IPF in Australia and New Zealand also provide extensive support to patients and families through their multidisciplinary teams, particularly IPF specialist nurses and clinic coordinators as well as community support organisations. Additionally, local general practitioners continue to provide support and education to patients and their families on a regular basis. In Australia, the Lung Foundation Australia provides patients with IPF and their families with a range of resources for education, psychosocial support and advocacy. These include disease-specific educational materials; a peer support program that connects patients living with IPF via telephone to share experiences, knowledge and support; regular scientific conferences that include a consumer stream to ensure that patients and their families can access the most up-to-date information on IPF care; and public advocacy for evidence-based care and research to improve IPF outcomes. Further information can be found on the Lung Foundation Australia website www.lungfoundation.com.au.¹⁸⁰ Unfortunately, no such resource is currently available for the New Zealand population specifically.

6. PRECISION MEDICINE

The heterogeneity of the natural history of IPF, has led to a world-wide search for a panel of biomarkers enabling physicians to target treatment to the individual IPF patient. Investigators are searching for biomarkers which can aid in IPF diagnosis and in assessing prognosis. Most of this work is being conducted to identify circulating biomarkers in peripheral blood, however biomarker discovery using lung biopsies is also underway. Some of the most promising early candidates are the matrix metalloproteinases (MMPs, especially MMP-7), surfactant protein-D and endothelin-1.^{181, 182}

IPF, including not only its rare familial forms but also its much more common sporadic form, is a disease associated with gene mutations. The genes most commonly mutated are the mucin 5B (MUC5B), surfactant protein and toll-interacting protein (TOLLIP) genes, as well as those associated with maintenance of telomere length. Importantly, not only do mutations in these genes increase the risk of developing IPF, but some of them also provide important prognostic information. For instance, patients with MUC5B mutations appear to have better survival,¹⁸³ whilst those with short telomere length have worse survival.¹⁸⁴ In fact, assessing telomere length and identifying germline mutations in genes which assist in telomere maintenance in patients suspected of having a mutation is emerging as a part of the work-up for patients presenting with fibrotic interstitial lung disease (f-ILD) since these mutations lead to a variety of f-ILDs but appear to universally confer a worse prognosis.¹⁸⁵

Although prospective studies are awaited, it is likely that determination of a patient's genotype and their specific biomarker profile will become an essential part of clinical practice, for example to not only diagnose IPF, but to assist the physician in deciding if and when to recommend commencement of anti-fibrotic therapy,



and when to refer for transplantation. The strength of these associations mean that future large studies in IPF will likely stratify by genotype and/or biomarker profile, meaning that ultimately specific therapies will be found to be appropriate for a subpopulation of patients with IPF – allowing ‘precise’ use of powerful medicines.

This idea that treatments should be personalized to maximize efficacy and safety is of course not new, especially in oncology, but does imply a more in-depth understanding of disease pathogenesis. Examples of this kind of approach are already appearing for IPF – for example in a post-hoc analysis, mutations in the TOLLIP gene predicted response to N-acetylcysteine (NAC) in what was otherwise a negative trial when all patients were pooled.¹⁸⁶ Naturally, prospective studies are required to confirm these potentially exciting observations. Nevertheless, this accumulated experience, and the strength and frequency of the genetic associations so far observed, point to IPF, alongside cancer, being one of the first respiratory diseases to enter the ‘personalised’ or ‘precision’ medicine era.

Summary:

- *While biomarkers show early promise in identifying IPF, assessing prognosis and stratifying management, further studies are required before any clinical recommendations can be made.*

7. SPECIFIC APPLICATION TO AUSTRALIA AND NEW ZEALAND

Regional factors specific to Australia and New Zealand influence the manner in which the above therapies are applied to their respective IPF populations. Within both countries, funding for anti-fibrotic therapy is dependent on the patient displaying features representing an amalgamation of the inclusion criteria of the phase 3 studies of nintedanib and pirfenidone.

In Australia, the PBS has approved funding for both pirfenidone and nintedanib. Specific features of Australia’s prescribing criteria include the need for diagnosis to be confirmed by a multi-disciplinary team, and the presence of a mild to moderate restrictive pattern on lung function testing (Table 4). In New Zealand PHARMAC has approved funding of pirfenidone only, but has restricted prescription to patients with moderate disease, providing there is no disease progression (defined as a decline in percent predicted FVC of 10% or more) within any 12 month period while on therapy (Table 4). The differences in the funding criteria between Australia and New Zealand likely reflect differences in the interpretation of the evidence for these medications.

These restrictions to supply anti-fibrotic medications for subjects for which there is clear evidence of efficacy is understandable in the context of the burden of such therapies on health budgets. Equally important though is the reconsideration of such restrictions as further data are published on the use of anti-fibrotic therapy, given the evolving nature of this relatively new therapeutic field. For example, there is gathering evidence to suggest that mandating the cessation of anti-fibrotics based on crossing thresholds of FVC percentage decline may be questionable. Analysis of the pooled ASCEND and CAPACITY data has demonstrated that, after a decline in FVC by $\geq 10\%$ in the initial six months of therapy, continued therapy reduced the likelihood of further such decline or death over the subsequent six months compared to the placebo group.¹² As the evidence for these medications continues to grow, physicians as well as patients, must advocate for evolution of funding restrictions.

For the non-pharmacological therapies, each country has unique regulations for practice. In Australia, oxygen therapy may be funded by either federal or state governments and differences exist between jurisdictions with regards to funding criteria, particularly for ambulatory therapy, where a relative absence of evidence exists to confirm its utility. While the limited nature of the availability of donor organs leads to a waiting list



for lung transplantation, access is dependent on meeting those criteria outlined in table 3, and no regional differences exist based on other patient features, such as duration of listing. While pulmonary rehabilitation, advanced care planning and palliative care services are readily available in many regional centres, in remote and rural locations providing community services is challenging.

In New Zealand, funding for oxygen and other support services, such as pulmonary rehabilitation, is provided by the district health boards as part of a capitated funding system. Lung transplantation is provided by a single centre and criteria for listing are similar to Australia. Rurality impacts access to services for patients with pulmonary fibrosis in both countries, but telemedicine and shared care allow improved access to MDM discussion and a variety of supports.

Concluding statement

It is an exciting time for IPF management with new therapies shown to slow disease progression now available. Enthusiasm to prescribe these medications however has to be tempered by the lack of evidence in many subgroups, as well as local restrictions for government funding of these therapies. The management of IPF patients is not constrained to anti-fibrotic therapies, and it is important to address comorbidities and manage symptoms using pharmacological and non-pharmacological therapies. Despite new treatments, IPF remains a progressive and fatal disease and thus pulmonary rehabilitation, consideration of lung transplantation, palliative care and end of life planning are essential to the holistic care of IPF patients.



TABLES

Table 1. Randomised Controlled Trials in Idiopathic Pulmonary Fibrosis

Study	Year	intervention	Mode of action	N	Duration (weeks)	Primary outcome	Result
Anti-fibrotic Medications							
Azuma <i>et al</i> ¹⁸⁷	2005	Pirfenidone	anti-fibrotic	107	63	SpO2 change on 6MWT	NEG
Taniguchi <i>et al</i> ⁹	2010	Pirfenidone	anti-fibrotic	275	52	VC change	POS
CAPACITY 004 & 006 ¹⁰	2011	Pirfenidone	anti-fibrotic	779	72	FVC change	POS*
TOMORROW ¹⁶	2011	Nintedanib	anti-fibrotic	432	52	FVC change	POS
INPULSIS 1&2 ¹⁷	2014	Nintedanib	anti-fibrotic	1066	52	FVC change	POS
ASCEND ¹¹	2014	Pirfenidone	anti-fibrotic	555	52	FVC change	POS
Pulmonary vasodilators							
BUILD-1 ⁹¹	2008	Bosentan	Pulmonary vasodilator	158	52	6MWD change	NEG
STEP-IPF ⁸⁹	2010	Sildenafil	Pulmonary vasodilator	180	12	6MWD>20% improvement	NEG
BUILD-3 ¹⁸⁸	2011	Bosentan	Pulmonary vasodilator	616	52	Disease progression	NEG
ARTEMIS-IPF ⁹⁰	2013	Ambrisentan	Pulmonary vasodilator	492	35	Death, hospitalization, disease progression	NEG
MUSIC ⁹²	2013	Macitentan	Pulmonary vasodilator	178	52	FVC change	NEG
Antioxidants							
IFIGENIA ⁵³	2005	NAC (background Prednisone, azathioprine)	antioxidant	182	52	FVC change, DLco change	POS
Homma <i>et al</i> ¹⁸⁹	2012	inhaled NAC	antioxidant	76	48	FVC change	NEG
PANTHER ¹⁹⁰	2014	NAC	antioxidant	264	60	FVC change	NEG
Immunomodulation							
Raghu <i>et al</i> ¹⁹¹	2004	IFN- γ	immunomodulation	330	58	Disease progression	NEG
Raghu <i>et al</i> ¹⁹²	2008	Etanercept	immunomodulation	88	48	FVC DLco and P(A-a)O ₂ change	NEG
INPSPIRE ¹⁹³	2009	IFN- γ	immunomodulation	826	64	Mortality	NEG
Daniels <i>et al</i> ¹⁹⁴	2010	imatnib	immunomodulation	119	96	Disease progression	NEG
Combination treatments							
PANTHER ⁵⁶	2012	Prednisone, azathioprine, NAC	Immunomodulation, antioxidant	155	32	FVC change	Harmful
PANORMA ⁵⁸	2016	Pirfenidone and NAC	Anti-fibrotic and antioxidant	123	24	FVC, DLco and 6MWT change	NEG
Other							
Horton <i>et al</i> ¹⁶⁴	2012	thalidomide		24	12	cough	POS
ACE-IPF ⁶⁰	2012	warfarin	anticoagulant	145	28	death, hospitalisation, FVC10%	NEG

* Overall pooled results were positive, although CAPACITY 006 was negative for primary outcome



Table 2. Current trials for the treatment of Idiopathic Pulmonary Fibrosis

Study	intervention	Mode of action	phase	Primary outcome	Company/ Countries
Mechanism : Blockade of inflammation and Fibrosis					
NCT01766817	BMS-986020	Lysophosphaticdic acid (LPA) antagonist	2	Safety and efficacy	Bristol Myers Squibb
NCT02257177	TD 139	Galacetin-3 inhibitor	2	Safety and tolerability	Galecto Bitotec, Scotland
NCT02688647	KD025	ROCK2 inhibitor	2	Safety, tolerability, activity	Kadmon Corperation
NCT02036580	Tralokinumab	IL-13 blocker	2	Safety, tolerability, dose finding	AstraZeneca. Japan
NCT02874989	Dasatinib + Quercetin	Tyrosine kinase inhibitor + anti-inflammatory	1	safety	Wake Forest School of Medicine
Mechanism: Blockade of inflammation					
(NHLBI) NCT02315586	Apolipoprotein A1 mimetics	Anti-inflammtory	1	safety	
NCT02397005	ZL2102	anti-inflammatory	1	safety	Perth
NCT02173145	Azithromycin	Immunomodulation/ anti-inflammatory	2	Efficacy against cough	Berne
NCT00262405	Zileuton	Anti-inflammatory	2	Compared to azathioprine/ prednisolone	University of Michigan
NCT00786201	CNTO 888 Carlumab	immunomodulation	2	Evaluate the Safety and Effectiveness.	Centocor Inc
NCT02345070	SAR156597	immunomodulation	2	Safety and efficacy	Sanofi
NCT02085018	Omeprazole	Attenuate acid reflux	2	Efficacy	Newcastle-upon-Tyne hospitals
NCT02759120	Doxycycline or co-trimoxazole	immunomodulation	3	Efficacy	Weill-Cornell
EUDRACT 2014-004058-32	Co-trimaxazole	immunomodulation	2	Efficacy	Norfolk and Norwich University
Mechanism: Blockade of Fibrosis					
NCT01890265	FG-3019	Antibody against CTGF	2	Safety and efficacy	Fibrogen
NCT00463983	SOM230	Octreatide	1	safety	France
NCT00189176	Tetrathiomolybdate	Copper chelator reduces collagen-1	2	Safety and efficacy in patients who failed previous treatment	Uni Michigan
NCT01872689	Lebrikizumab	inhibits (IL-13), periostin	2	Safety and efficacy	Hoffman La Roche USA
NCT02648048	Vismodegib	antagonist of hedgehog signaling	P1b	safety and tolerability in combination with pirfenidone	Hoffman La Roche USA
NCT01619085	BIBF 1120	tyrosine kinase inhibitor	2	long term safety	Boehringer Ingelheim
NCT02538536	PBI-4050	reduces TGF, CTGF),		Safety and Tolerability	Prometic biosciences
NCT01462006	Sirolimus	mTOR inhibitor	2	Test if drug reduces circulating fibrocytes	University of Virginia
NCT02738801	GLPG1690	autotaxin inhibitor	2	exploratory phase IIa study.	Galapagos
NCT01254409	PRM-151	Pentraxin-2 Serum amyloid P, monocyte and macrophage differentiation	2	Efficacy	Promedior, USA
NCT02612051	GSK3008348	Integrin avb6 antagonist	1	safety	GlaxoSmithKline
NCT00203697	Minocycline	inhibits angiogenesis and fibrosis	3	safety and efficacy	University of California, Los Angeles
NCT01371305	STX100	Antibody to Integrin avb6	2	efficacy	Biogen



Table 3. Contraindications to lung transplantation

Absolute contraindications	Relative contraindications
Malignancy within the last 2-5 years	Age >65 with low physiologic reserve
Other untreatable major organ dysfunction	Mechanical ventilation and/or extracorporeal life support
Uncorrectable atherosclerotic disease with end organ dysfunction	Progressive or severe malnutrition
Acute medical instability or bleeding diathesis	Severe, symptomatic osteoporosis
Chronic infection with highly virulent and/or resistant microbes including active mycobacterium tuberculosis infection	Colonisation or infection with highly resistant or virulent microbes
BMI >35.0 kg/m ²	BMI >30
Non-adherence to medical therapy	Extensive prior chest surgery with lung resection
Psychiatric or psychological conditions associated with inability to co-operate with health care team	Hepatitis B and/or C
Absence of social support system	HIV infection
Severely limited functional status with poor rehabilitation potential	Suboptimal treatment of diseases with potential for end organ damage
Substance abuse/dependence	



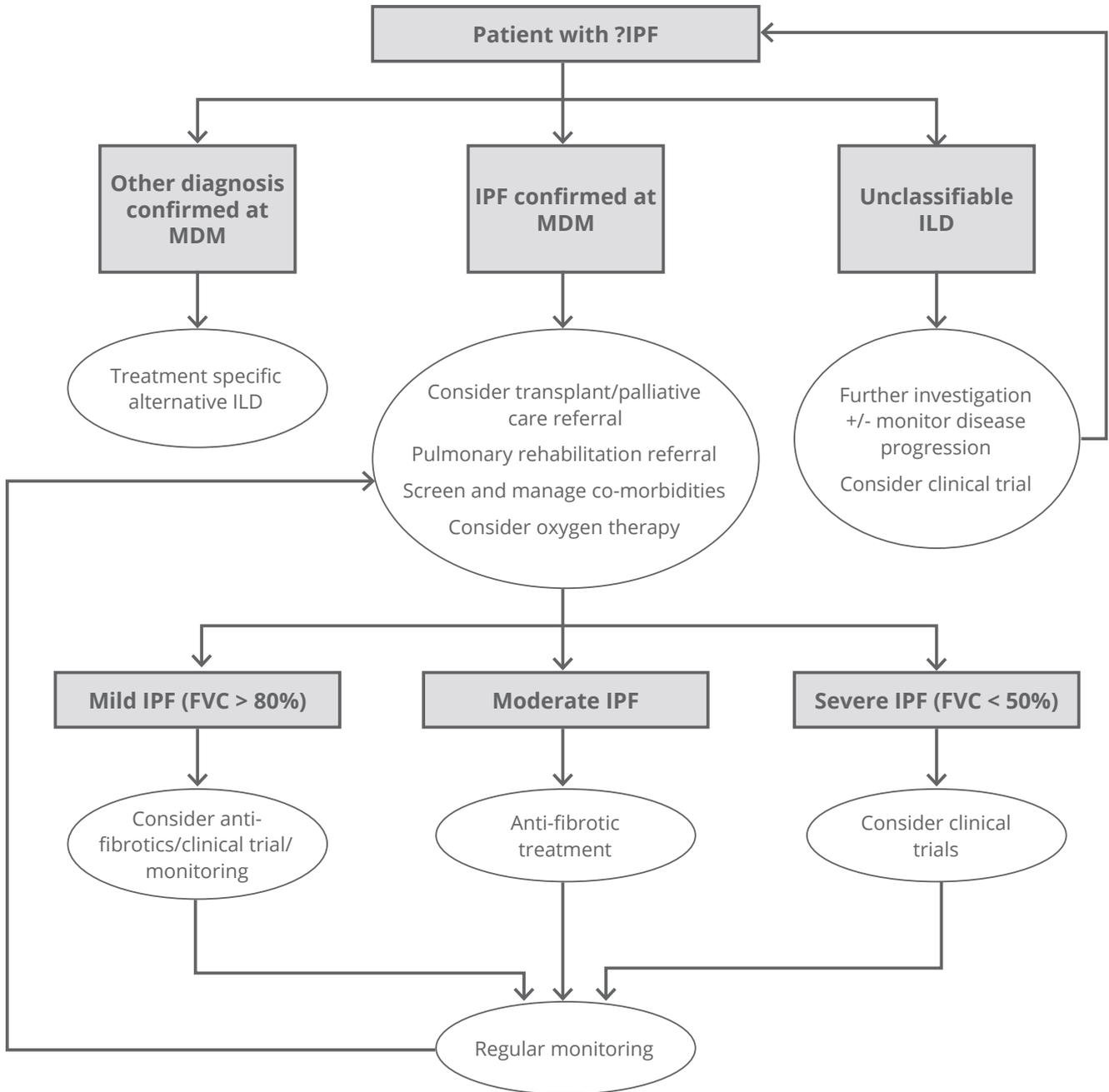
Table 4. National criteria for funded anti-fibrotic therapy

Australia (PBS)	New Zealand (PHARMAC)*
Multidisciplinary diagnosis of IPF	Physician diagnosis of IPF, confirmed by CT or biopsy
HRCT consistent with UIP within 12 months	
FVC \geq 50%	FVC between 50-80%
FEV1/FVC ratio $>$ 0.7	
DLCO \geq 30%	
ILD not due to other known cause	
	Funding discontinued if disease progression (fall in FVC \geq 10% in 12 months)

*has only approved pirfenidone

FIGURE LEGENDS

Figure 1. Suggested algorithm for the management of patients with Idiopathic Pulmonary Fibrosis



REFERENCES

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE, Jr., Kondoh Y, Myers J, Muller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schunemann HJ, Fibrosis AEJACoIP. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *American journal of respiratory and critical care medicine*. 2011; **183**: 788-824.
2. Nalysnyk L, Cid-Ruzafa J, Rotella P, Esser D. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. *European respiratory review : an official journal of the European Respiratory Society*. 2012; **21**: 355-61.
3. Ley B, Collard HR, King TE, Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*. 2011; **183**: 431-40.
4. Raghu G, Rochweg B, Zhang Y, Garcia CA, Azuma A, Behr J, Brozek JL, Collard HR, Cunningham W, Homma S, Johkoh T, Martinez FJ, Myers J, Protzko SL, Richeldi L, Rind D, Selman M, Theodore A, Wells AU, Hoogsteden H, Schunemann HJ, Ats EJ, Alar. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *American journal of respiratory and critical care medicine*. 2015; **192**: e3-e19.
5. Jo HE, Randhawa S, Corte TJ, Moodley Y. Idiopathic Pulmonary Fibrosis and the Elderly: Diagnosis and Management Considerations. *Drugs Aging*. 2016; **33**: 321-34.
6. De Vries J, Kessels BL, Drent M. Quality of life of idiopathic pulmonary fibrosis patients. *The European respiratory journal*. 2001; **17**: 954-61.
7. Ryerson CJ, Berkeley J, Carrieri-Kohlman VL, Pantilat SZ, Landefeld CS, Collard HR. DEpression and functional status are strongly associated with dyspnea in interstitial lung disease. *Chest*. 2011; **139**: 609-16.
8. Raghu G, Johnson WC, Lockhart D, Mageto Y. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label Phase II study. *American journal of respiratory and critical care medicine*. 1999; **159**: 1061-9.
9. Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, Taguchi Y, Takahashi H, Nakata K, Sato A, Takeuchi M, Raghu G, Kudoh S, Nukiwa T, Pirfenidone Clinical Study Group in J. Pirfenidone in idiopathic pulmonary fibrosis. *The European respiratory journal*. 2010; **35**: 821-9.
10. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE, Jr., Lancaster L, Sahn SA, Swartzberg J, Valeyre D, du Bois RM. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet*. 2011; **377**: 1760-9.
11. King TE, Jr., Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW. A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. *N Engl J Med*. 2014.
12. Noble PW, Albera C, Bradford WZ, Costabel U, du Bois RM, Fagan EA, Fishman RS, Glaspole I, Glassberg MK, Lancaster L, Lederer DJ, Leff JA, Nathan SD, Pereira CA, Swigris JJ, Valeyre D, King TE, Jr. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. *The European respiratory journal*. 2016; **47**: 243-53.
13. Lancaster L, Albera C, Bradford WZ, Costabel U, du Bois RM, Fagan EA, Fishman RS, Glaspole I, Glassberg MK, King TE, Lederer DJ, Lin Z, Nathan SD, Pereira CA, Swigris JJ, Valeyre D, Noble PW. Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: integrated analysis of cumulative data from 5 clinical trials. *BMJ open respiratory research*. 2016; **3**.
14. Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, Kolb M. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *The European respiratory journal*. 2015.
15. Hostettler KE, Zhong J, Papakonstantinou E, Karakiulakis G, Tamm M, Seidel P, Sun Q, Mandal J, Lardinois D, Lambers C, Roth M. Anti-fibrotic effects of nintedanib in lung fibroblasts derived from patients with idiopathic pulmonary fibrosis. *Respiratory research*. 2014; **15**: 157.
16. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *New England Journal of Medicine*. 2011; **365**: 1079-87.
17. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, Le Maulf F, Girard M, Stowasser S, Schlenker-Herceg R, Disse B, Collard HR, Investigators IT. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *The New England journal of medicine*. 2014; **370**: 2071-82.
18. Costabel U, Inoue Y, Richeldi L, Collard HR, Tschoepe I, Stowasser S, Azuma A. Efficacy of nintedanib in idiopathic pulmonary fibrosis across prespecified subgroups in INPULSIS. *American journal of respiratory and critical care medicine*. 2016; **193**: 178-85.
19. Raghu G, Wells AU, Nicholson AG, Richeldi L, Flaherty KR, Le Maulf F, Stowasser S, Schlenker-Herceg R, Hansell DM. Effect of Nintedanib in Subgroups of Idiopathic Pulmonary Fibrosis by Diagnostic Criteria. *American journal of respiratory and critical care medicine*. 2016.



20. Koschel D, Cottin V, Skold M, Tomassetti S, Azuma A, Giot C, Yocum D, Hamza S, Maher TM. Pirfenidone post-authorization safety registry (PASSPORT) – Interim analysis of IPF treatment. *European Respiratory Journal*. 2014; **44**.
21. Crestani B, Ogura T, Pelling K, Coeck C, Quaresma M, Kreuter M, Kaye M. P7 Interim analysis of nintedanib in an open-label extension of the INPULSIS® trials (INPULSIS®-ON). *Thorax*. 2015; **70**: A77-A8.
22. Bonella F, Kreuter M, Hagemeyer L, Neurohr C, Keller C, Kohlhaeuff MJ, Muller-Quernheim J, Milger K, Prasse A. Insights from the German Compassionate Use Program of Nintedanib for the Treatment of Idiopathic Pulmonary Fibrosis. *Respiration; international review of thoracic diseases*. 2016; **92**: 98-106.
23. Wijnenbeek MS, Grutters JC, Wuyts WA. Early Experience of Pirfenidone in Daily Clinical Practice in Belgium and The Netherlands: a Retrospective Cohort Analysis. *Advances in therapy*. 2015; **32**: 691-704.
24. Harari S, Caminati A, Albera C, Vancheri C, Poletti V, Pesci A, Luppi F, Saltini C, Agostini C, Bargagli E, Sebastiani A, Sanduzzi A, Giunta V, Della Porta R, Bandelli GP, Puglisi S, Tomassetti S, Biffi A, Cerri S, Mari A, Cinetto F, Tirelli F, Farinelli G, Bocchino M, Specchia C, Confalonieri M. Efficacy of pirfenidone for idiopathic pulmonary fibrosis: An Italian real life study. *Respiratory medicine*. 2015; **109**: 904-13.
25. Hughes G, Toellner H, Morris H, Leonard C, Chaudhuri N. Real World Experiences: Pirfenidone and Nintedanib are Effective and Well Tolerated Treatments for Idiopathic Pulmonary Fibrosis. *Journal of clinical medicine*. 2016; **5**.
26. Ogura T, Taniguchi H, Azuma A, Inoue Y, Kondoh Y, Hasegawa Y, Bando M, Abe S, Mochizuki Y, Chida K, Klüglich M, Fujimoto T, Okazaki K, Tadayasu Y, Sakamoto W, Sugiyama Y. Safety and pharmacokinetics of nintedanib and pirfenidone in idiopathic pulmonary fibrosis. *European Respiratory Journal*. 2015; **45**: 1382-92.
27. ClinicalTrials.gov. 2017. <https://clinicaltrials.gov>. Accessed: May 2017.
28. Albera C, Bradford WZ, Costabel U, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Kardatzke D, King TE, Lancaster L. Pirfenidone is efficacious in patients with idiopathic pulmonary fibrosis (IPF) and mild restrictive disease. *A15 THE LONG AND WINDING ROAD TO IPF TREATMENT: EXPANDED ANALYSES OF PIRFENIDONE AND NINTEDANIB*. *Am Thoracic Soc*, 2015; A1018-A.
29. Kolb M, Richeldi L, Behr J, Maher TM. Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. 2017; **72**: 340-6.
30. Arai T, Inoue Y, Sasaki Y, Tachibana K, Nakao K, Sugimoto C, Okuma T, Akira M, Kitaichi M, Hayashi S. Predictors of the clinical effects of pirfenidone on idiopathic pulmonary fibrosis. *Respiratory investigation*. 2014; **52**: 136-43.
31. Sakamoto S, Itoh T, Muramatsu Y, Satoh K, Ishida F, Sugino K, Isobe K, Homma S. Efficacy of pirfenidone in patients with advanced-stage idiopathic pulmonary fibrosis. *Internal medicine*. 2013; **52**: 2495-501.
32. Okuda R, Hagiwara E, Baba T, Kitamura H, Kato T, Ogura T. Safety and efficacy of pirfenidone in idiopathic pulmonary fibrosis in clinical practice. *Respiratory medicine*. 2013; **107**: 1431-7.
33. Nathan SD, Albera C, Bradford WZ, Costabel U, du Bois RM, Fagan EA, Fishman RS, Glaspole I, Glassberg MK, Glasscock KF, King TE, Lancaster L, Lederer DJ, Lin Z, Pereira CA, Swigris JJ, Valeyre D, Noble PW, Wells AU. Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis. *Thorax*. 2016.
34. Richeldi L, Azuma A, Selman M, Tang W, Capapey J, Stowasser S, Cottin V. Twenty-four week decline in forced vital capacity predicts mortality at week 52 in the INPULSIS® trials. *European Respiratory Journal*. 2016; **48**.
35. Raghu G, Rochwerg B, Zhang Y, Garcia CAC, Azuma A, Behr J, Brozek JL, Collard HR, Cunningham W, Homma S, Johkoh T, Martinez FJ, Myers J, Protzko SL, Richeldi L, Rind D, Selman M, Theodore A, Wells AU, Hoogsteden H, Schünemann HJ. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *American journal of respiratory and critical care medicine*. 2015; **192**: e3-e19.
36. Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, Poletti V, Bucciolli M, Elicker BM, Jones KD, King TE, Jr., Collard HR. A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Annals of internal medicine*. 2012; **156**: 684-91.
37. Wells AU, Desai SR, Rubens MB, Goh NS, Cramer D, Nicholson AG, Colby TV, du Bois RM, Hansell DM. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. *American journal of respiratory and critical care medicine*. 2003; **167**: 962-9.
38. Kondoh S, Chiba H, Nishikiori H, Umeda Y, Kuronuma K, Otsuka M, Yamada G, Ohnishi H, Mori M, Kondoh Y, Taniguchi H, Homma S, Takahashi H. Validation of the Japanese disease severity classification and the GAP model in Japanese patients with idiopathic pulmonary fibrosis. *Respiratory investigation*. 2016; **54**: 327-33.
39. Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis—FDA review of pirfenidone and nintedanib. *The New England journal of medicine*. 2015; **372**: 1189-91.
40. Loeh B, Drakopanagiotakis F, Bandelli GP, von der Beck D, Tello S, Cordani E, Rizza E, Barrocu L, Markart P, Seeger W, Guenther A, Albera C. Intra-individual response to treatment with pirfenidone in idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*. 2015; **191**: 110-3.



41. Rotolo N, Imperatori A, Dominionioni L, Facchini A, Conti V, Castiglioni M, Spanevello A. Efficacy and safety of surgical lung biopsy for interstitial disease. Experience of 161 consecutive patients from a single institution in Italy. *Sarcoidosis Vasc Diffuse Lung Dis.* 2015; **32**: 251-8.
42. Chung JH, Chawla A, Peljto AL, Cool CD, Groshong SD, Talbert JL, McKean DF, Brown KK, Fingerlin TE, Schwarz MI, Schwartz DA, Lynch DA. CT scan findings of probable usual interstitial pneumonitis have a high predictive value for histologic usual interstitial pneumonitis. *Chest.* 2015; **147**: 450-9.
43. Flaherty KR, Thwaite EL, Kazerooni EA, Gross BH, Toews GB, Colby TV, Travis WD, Mumford JA, Murray S, Flint A, Lynch JP, 3rd, Martinez FJ. Radiological versus histological diagnosis in UIP and NSIP: survival implications. *Thorax.* 2003; **58**: 143-8.
44. Elliot TL, Lynch DA, Newell JD, Jr., Cool C, Tuder R, Markopoulou K, Veve R, Brown KK. High-resolution computed tomography features of nonspecific interstitial pneumonia and usual interstitial pneumonia. *Journal of computer assisted tomography.* 2005; **29**: 339-45.
45. Silva CI, Muller NL, Hansell DM, Lee KS, Nicholson AG, Wells AU. Nonspecific interstitial pneumonia and idiopathic pulmonary fibrosis: changes in pattern and distribution of disease over time. *Radiology.* 2008; **247**: 251-9.
46. Oltmanns U, Kahn N, Palmowski K, Trager A, Wenz H, Heussel CP, Schnabel PA, Puderbach M, Wiebel M, Ehlers-Tenenbaum S, Warth A, Herth FJ, Kreuter M. Pirfenidone in idiopathic pulmonary fibrosis: real-life experience from a German tertiary referral center for interstitial lung diseases. *Respiration; international review of thoracic diseases.* 2014; **88**: 199-207.
47. Prasad JDL, Fiona; Corte, Tamera J; Chambers, Daniel C; Hopkins, Peter; Glaspole, Ian. Interstitial Lung Disease Multidisciplinary Meeting: A position statement from the Thoracic Society of Australian and New Zealand and the Lung Foundation Australia. *Respirology (Carlton, Vic).* 2017.
48. Jee AS, Adelstein S, Bleasel J, Keir GJ, Nguyen M, Sahhar J, Youssef P, Corte TJ. Role of Autoantibodies in the Diagnosis of Connective-Tissue Disease ILD (CTD-ILD) and Interstitial Pneumonia with Autoimmune Features (IPAF). *Journal of clinical medicine.* 2017; **6**.
49. Ryerson CJ, Urbania TH, Richeldi L, Mooney JJ, Lee JS, Jones KD, Elicker BM, Koth LL, King TE, Jr., Wolters PJ, Collard HR. Prevalence and prognosis of unclassifiable interstitial lung disease. *The European respiratory journal.* 2013; **42**: 750-7.
50. Troy L, Glaspole I, Goh N, Zappala C, Hopkins P, Wilsher M, Moodley Y, Corte T. Prevalence and prognosis of unclassifiable interstitial lung disease. *The European respiratory journal.* 2014; **43**: 1529-30.
51. Peikert T, Daniels CE, Beebe TJ, Meyer KC, Ryu JH, Interstitial Lung Diseases Network of the American College of Chest P. Assessment of current practice in the diagnosis and therapy of idiopathic pulmonary fibrosis. *Respiratory medicine.* 2008; **102**: 1342-8.
52. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *American journal of respiratory and critical care medicine.* 2000; **161**: 646-64.
53. Demedts M, Behr J, Buhl R, Costabel U, Dekhuijzen R, Jansen HM, MacNee W, Thomeer M, Wallaert B, Laurent F, Nicholson AG, Verbeke EK, Verschakelen J, Flower CD, Capron F, Petruzzelli S, De Vuyst P, van den Bosch JM, Rodriguez-Becerra E, Corvasce G, Lankhorst I, Sardina M, Montanari M, Group IS. High-dose acetylcysteine in idiopathic pulmonary fibrosis. *The New England journal of medicine.* 2005; **353**: 2229-42.
54. Raghu G, Depaso WJ, Cain K, Hammar SP, Wetzel CE, Dreis DF, Hutchinson J, Pardee NE, Winterbauer RH. Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. *The American review of respiratory disease.* 1991; **144**: 291-6.
55. Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: response to corticosteroid treatment and its effect on survival. *Thorax.* 1980; **35**: 593-9.
56. Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis. *New England Journal of Medicine.* 2012; **366**: 1968-77.
57. Idiopathic Pulmonary Fibrosis Clinical Research N, Martinez FJ, de Andrade JA, Anstrom KJ, King TE, Jr., Raghu G. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. *The New England journal of medicine.* 2014; **370**: 2093-101.
58. Behr J, Bendstrup E, Crestani B, Günther A, Olschewski H, Sköld CM, Wells A, Wuyts W, Koschel D, Kreuter M, Wallaert B, Lin C-Y, Beck J, Albera C. Safety and tolerability of acetylcysteine and pirfenidone combination therapy in idiopathic pulmonary fibrosis: a randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet Respiratory Medicine.* 2016; **4**: 445-53.
59. Kubo H, Nakayama K, Yanai M, Suzuki T, Yamaya M, Watanabe M, Sasaki H. Anticoagulant therapy for idiopathic pulmonary fibrosis. *Chest.* 2005; **128**: 1475-82.
60. Noth I, Anstrom KJ, Calvert SB, de Andrade J, Flaherty KR, Glazer C, Kaner RJ, Olman MA, Idiopathic Pulmonary Fibrosis Clinical Research N. A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine.* 2012; **186**: 88-95.
61. Hyldgaard C, Hilberg O, Bendstrup E. How does comorbidity influence survival in idiopathic pulmonary fibrosis? *Respiratory medicine.* 2014; **108**: 647-53.
62. Tomassetti S, Ruy JH, Gurioli C, et al. The effect of anticoagulant therapy for idiopathic pulmonary fibrosis in real life practice. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG / World Association of Sarcoidosis and Other Granulomatous Disorders.* 2013; **30**: 121-7.



63. Kreuter M, Wijsenbeek MS, Vasakova M, Spagnolo P, Kolb M, Costabel U, Weycker D, Kirchgaessler K-U, Maher TM. Unfavourable effects of medically indicated oral anticoagulants on survival in idiopathic pulmonary fibrosis. *European Respiratory Journal*. 2016.
64. Raghu G, Freudenberger TD, Yang S, Curtis JR, Spada C, Hayes J, Sillery JK, Pope CE, 2nd, Pellegrini CA. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. *The European respiratory journal*. 2006; **27**: 136-42.
65. Tobin RW, Pope CE, 2nd, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*. 1998; **158**: 1804-8.
66. Brunner E, Oltmanns U, Piel S, Herth F, Kreuter M. Evaluation of laryngopharyngeal reflux in patients with interstitial lung disease (ILD) by a pharyngeal pH-probe. *European Respiratory Journal*. 2016; **48**.
67. Noth I, Zangan SM, Soares RV, Forsythe A, Demchuk C, Takahashi SM, Patel SB, Streck ME, Krishnan JA, Patti MG, Macmahon H. Prevalence of hiatal hernia by blinded multidetector CT in patients with idiopathic pulmonary fibrosis. *The European respiratory journal*. 2012; **39**: 344-51.
68. Raghu G, Yang ST, Spada C, Hayes J, Pellegrini CA. Sole treatment of acid gastroesophageal reflux in idiopathic pulmonary fibrosis: a case series. *Chest*. 2006; **129**: 794-800.
69. Linden PA, Gilbert RJ, Yeap BY, Boyle K, Deykin A, Jaklitsch MT, Sugarbaker DJ, Bueno R. Laparoscopic fundoplication in patients with end-stage lung disease awaiting transplantation. *The Journal of thoracic and cardiovascular surgery*. 2006; **131**: 438-46.
70. Lee JS, Collard HR, Anstrom KJ, Martinez FJ, Noth I, Roberts RS, Yow E, Raghu G, Investigators IP. Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. *The Lancet Respiratory medicine*. 2013; **1**: 369-76.
71. Kreuter M, Wuyts W, Renzoni E, Koschel D, Maher TM, Kolb M, Weycker D, Spagnolo P, Kirchgaessler K-U, Herth FJF, Costabel U. Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis. *The Lancet Respiratory Medicine*. 2016; **4**: 381-9.
72. Raghu G, Crestani B, Bailes Z, Schlenker-Herceg R, Costabel U. Effect of anti-acid medication on reduction in FVC decline with nintedanib. *European Respiratory Journal*. 2015; **46**.
73. ClinicalTrials.com. www.clinicaltrials.com. Accessed: May 2017.
74. Chambers DC, Enever D, Ilic N, Sparks L, Whitelaw K, Ayres J, Yerkovich ST, Khalil D, Atkinson KM, Hopkins PM. A phase 1b study of placenta-derived mesenchymal stromal cells in patients with idiopathic pulmonary fibrosis. *Respirology*. 2014; **19**: 1013-8.
75. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, Lee JS, Maher TM, Wells AU, Antoniou KM, Behr J, Brown KK, Cottin V, Flaherty KR, Fukuoka J, Hansell DM, Johkoh T, Kaminski N, Kim DS, Kolb M, Lynch DA, Myers JL, Raghu G, Richeldi L, Taniguchi H, Martinez FJ. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. *American journal of respiratory and critical care medicine*. 2016; **194**: 265-75.
76. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *The European respiratory journal*. 2011; **37**: 356-63.
77. Collard HR, Yow E, Richeldi L, Anstrom KJ, Glazer C, investigators IP. Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials. *Respiratory research*. 2013; **14**: 73.
78. Kondoh Y, Taniguchi H, Katsuta T, Kataoka K, Kimura T, Nishiyama O, Sakamoto K, Johkoh T, Nishimura M, Ono K, Kitaichi M. Risk factors of acute exacerbation of idiopathic pulmonary fibrosis. Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG / World Association of Sarcoidosis and Other Granulomatous Disorders. 2010; **27**: 103-10.
79. Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. *The European respiratory journal*. 2006; **27**: 143-50.
80. Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. *The European respiratory journal*. 2015; **46**: 1113-30.
81. Behr J, Kreuter M, Hoepfer MM, Wirtz H, Klotsche J, Koschel D, Andreas S, Claussen M, Grohe C, Wilkens H, Randerath W, Skowasch D, Meyer FJ, Kirschner J, Glaser S, Herth FJ, Welte T, Huber RM, Neurohr C, Schwaiblmair M, Kohlhaufl M, Hoffken G, Held M, Koch A, Bahmer T, Pittrow D. Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. *The European respiratory journal*. 2015; **46**: 186-96.
82. Lancaster LH, Mason WR, Parnell JA, Rice TW, Loyd JE, Milstone AP, Collard HR, Malow BA. Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. *Chest*. 2009; **136**: 772-8.
83. Collard HR, Ward AJ, Lanes S, Cortney Hayflinger D, Rosenberg DM, Hunsche E. Burden of illness in idiopathic pulmonary fibrosis. *Journal of medical economics*. 2012; **15**: 829-35.



84. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE, Jr., Kondoh Y, Myers J, Muller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schunemann HJ. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *American journal of respiratory and critical care medicine*. 2011; **183**: 788-824.
85. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest*. 2006; **129**: 746-52.
86. Patel NM, Lederer DJ, Borczuk AC, Kawut SM. Pulmonary hypertension in idiopathic pulmonary fibrosis. *Chest*. 2007; **132**: 998-1006.
87. Shorr AF, Wainright JL, Cors CS, Lettieri CJ, Nathan SD. Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. *The European respiratory journal*. 2007; **30**: 715-21.
88. Authors/Task Force M, Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Authors/Task Force M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *European heart journal*. 2015.
89. Idiopathic Pulmonary Fibrosis Clinical Research N, Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *The New England journal of medicine*. 2010; **363**: 620-8.
90. Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, Martinez FJ, Nathan SD, Wells AU, Collard HR, Costabel U, Richeldi L, de Andrade J, Khalil N, Morrison LD, Lederer DJ, Shao L, Li X, Pedersen PS, Montgomery AB, Chien JW, O'Riordan TG, Investigators* A-I. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. *Annals of internal medicine*. 2013; **158**: 641-9.
91. King TE, Jr., Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stahler G, Leconte I, Roux S, Raghu G. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*. 2008; **177**: 75-81.
92. Raghu G, Million-Rousseau R, Morganti A, Perchenet L, Behr J, Group MS. Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial. *The European respiratory journal*. 2013; **42**: 1622-32.
93. Corte TJ, Keir GJ, Dimopoulos K, Howard L, Corris PA, Parfitt L, Foley C, Yanez-Lopez M, Babalis D, Marino P, Maher TM, Renzoni EA, Spencer L, Elliot CA, Birring SS, O'Reilly K, Gatzoulis MA, Wells AU, Wort SJ, Group BS. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *American journal of respiratory and critical care medicine*. 2014; **190**: 208-17.
94. King CS, Nathan SD. Idiopathic pulmonary fibrosis: effects and optimal management of comorbidities. *Lancet Respir Med*. 2016.
95. Mermigkis C, Stagaki E, Tryfon S, Schiza S, Amfilochiou A, Polychronopoulos V, Panagou P, Galanis N, Kallianos A, Mermigkis D, Kopanakis A, Varouchakis G, Kapsimalis F, Bouros D. How common is sleep-disordered breathing in patients with idiopathic pulmonary fibrosis? *Sleep & breathing = Schlaf & Atmung*. 2010; **14**: 387-90.
96. Aydogdu M, Ciftci B, Firat Guven S, Ulukavak Ciftci T, Erdogan Y. [Assessment of sleep with polysomnography in patients with interstitial lung disease]. *Tuberkuloz ve toraks*. 2006; **54**: 213-21.
97. Kolilekas L, Manali E, Vlami KA, Lyberopoulos P, Triantafyllidou C, Kagouridis K, Baou K, Gyftopoulos S, Vougas KN, Karakatsani A, Alchanatis M, Papiiris S. Sleep oxygen desaturation predicts survival in idiopathic pulmonary fibrosis. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2013; **9**: 593-601.
98. Corte TJ, Wort SJ, Talbot S, Macdonald PM, Hansel DM, Polkey M, Renzoni E, Maher TM, Nicholson AG, Wells AU. Elevated nocturnal desaturation index predicts mortality in interstitial lung disease. Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG / World Association of Sarcoidosis and Other Granulomatous Disorders. 2012; **29**: 41-50.
99. Troy LK, Corte TJ. Sleep disordered breathing in interstitial lung disease: A review. *World journal of clinical cases*. 2014; **2**: 828-34.
100. Trakada G, Nikolaou E, Pouli A, Tsiamita M, Spiropoulos K. Endothelin-1 levels in interstitial lung disease patients during sleep. *Sleep & breathing = Schlaf & Atmung*. 2003; **7**: 111-8.
101. Clark M, Cooper B, Singh S, Cooper M, Carr A, Hubbard R. A survey of nocturnal hypoxaemia and health related quality of life in patients with cryptogenic fibrosing alveolitis. *Thorax*. 2001; **56**: 482-6.
102. Minai OA, Ricaurte B, Kaw R, Hammel J, Mansour M, McCarthy K, Golish JA, Stoller JK. Frequency and impact of pulmonary hypertension in patients with obstructive sleep apnea syndrome. *The American journal of cardiology*. 2009; **104**: 1300-6.
103. Krishnan V, McCormack MC, Mathai SC, Agarwal S, Richardson B, Horton MR, Polito AJ, Collop NA, Danoff SK. Sleep quality and health-related quality of life in idiopathic pulmonary fibrosis. *Chest*. 2008; **134**: 693-8.
104. Pihtili A, Bingol Z, Kiyan E, Cuhadaroglu C, Issever H, Gulbaran Z. Obstructive sleep apnea is common in patients with interstitial lung disease. *Sleep & breathing = Schlaf & Atmung*. 2013; **17**: 1281-8.



105. Mermigkis C, Bouloukaki I, Antoniou K, Papadogiannis G, Giannarakis I, Varouchakis G, Sifakas N, Schiza SE. Obstructive sleep apnea should be treated in patients with idiopathic pulmonary fibrosis. *Sleep & breathing = Schlaf & Atmung*. 2015; **19**: 385-91.
106. Cottin V, Cordier JF. Combined pulmonary fibrosis and emphysema: an experimental and clinically relevant phenotype. *American journal of respiratory and critical care medicine*. 2005; **172**: 1605; author reply -6.
107. Jankowich MD, Polsky M, Klein M, Rounds S. Heterogeneity in combined pulmonary fibrosis and emphysema. *Respiration; international review of thoracic diseases*. 2008; **75**: 411-7.
108. Kitaguchi Y, Fujimoto K, Hanaoka M, Honda T, Hotta J, Hirayama J. Pulmonary function impairment in patients with combined pulmonary fibrosis and emphysema with and without airflow obstruction. *Int J Chron Obstruct Pulmon Dis*. 2014; **9**: 805-11.
109. Jankowich MD, Rounds S. Combined pulmonary fibrosis and emphysema alters physiology but has similar mortality to pulmonary fibrosis without emphysema. *Lung*. 2010; **188**: 365-73.
110. Mejia M, Carrillo G, Rojas-Serrano J, Estrada A, Suarez T, Alonso D, Barrientos E, Gaxiola M, Navarro C, Selman M. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. *Chest*. 2009; **136**: 10-5.
111. Cottin V, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I, Israel-Biet D, Court-Fortune I, Valeyre D, Cordier JF, Groupe d'Etude et de Recherche sur les Maladies Orphelines P. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *The European respiratory journal*. 2005; **26**: 586-93.
112. Kwak N, Park CM, Lee J, Park YS, Lee SM, Yim JJ, Yoo CG, Kim YW, Han SK, Lee CH. Lung cancer risk among patients with combined pulmonary fibrosis and emphysema. *Respiratory medicine*. 2014; **108**: 524-30.
113. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, Le Maulf F, Girard M, Stowasser S, Schlenker-Herceg R, Disse B, Collard HR. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. *The New England journal of medicine*. 2014.
114. Corte T, Cottin V, Taniguchi H, Richeldi L, Collard H, Kaye M, Hansell D, Bailes Z, Schlenker-Herceg R, Raghu G. Effect of baseline emphysema on reduction in FVC decline with nintedanib in the INPULSIS trials. *Respirology*. 2015; **20**: 57.
115. Seeger W, Adir Y, Barbera JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galie N, Ghio S, Gibbs S, Martinez FJ, Semigran MJ, Simonneau G, Wells AU, Vachiery JL. Pulmonary hypertension in chronic lung diseases. *Journal of the American College of Cardiology*. 2013; **62**: D109-16.
116. Hook JL, Arcasoy SM, Zimmel D, Bartels MN, Kawut SM, Lederer DJ. Titrated oxygen requirement and prognostication in idiopathic pulmonary fibrosis. *The European respiratory journal*. 2012; **39**: 359-65.
117. Collard HR, King TE, Jr., Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*. 2003; **168**: 538-42.
118. Egan TM, Murray S, Bustami RT, Shearon TH, McCullough KP, Edwards LB, Coke MA, Garrity ER, Sweet SC, Heiney DA, Grover FL. Development of the new lung allocation system in the United States. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2006; **6**: 1212-27.
119. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet*. 1981; **1**: 681-6.
120. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Annals of internal medicine*. 1980; **93**: 391-8.
121. McDonald CF, Crockett AJ, Young IH. Adult domiciliary oxygen therapy. Position statement of the Thoracic Society of Australia and New Zealand. *The Medical journal of Australia*. 2005; **182**: 621-6.
122. McDonald CF, Whyte K, Jenkins S, Serginson J, Frith P. Clinical Practice Guideline on Adult Domiciliary Oxygen Therapy: Executive summary from the Thoracic Society of Australia and New Zealand. *Respirology*. 2016; **21**: 76-8.
123. Bye PT, Anderson SD, Woolcock AJ, Young IH, Alison JA. Bicycle endurance performance of patients with interstitial lung disease breathing air and oxygen. *The American review of respiratory disease*. 1982; **126**: 1005-12.
124. Harris-Eze AO, Sridhar G, Clemens RE, Gallagher CG, Marciniuk DD. Oxygen improves maximal exercise performance in interstitial lung disease. *American journal of respiratory and critical care medicine*. 1994; **150**: 1616-22.
125. Visca D, Montgomery A, de Lauretis A, Sestini P, Soteriou H, Maher TM, Wells AU, Renzoni EA. Ambulatory oxygen in interstitial lung disease. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology*. 2011; **38**: 987-90.
126. Frank RC, Hicks S, Duck AM, Spencer L, Leonard CT, Barnett E. Ambulatory oxygen in idiopathic pulmonary fibrosis: of what benefit? *The European respiratory journal*. 2012; **40**: 269-70.
127. Nishiyama O, Miyajima H, Fukai Y, Yamazaki R, Satoh R, Yamagata T, Sano H, Iwanaga T, Higashimoto Y, Nakajima H, Kume H, Tohda Y. Effect of ambulatory oxygen on exertional dyspnea in IPF patients without resting hypoxemia. *Respiratory medicine*. 2013; **107**: 1241-6.



128. Chaouat A, Weitzenblum E, Kessler R, Charpentier C, Enhart M, Schott R, Levi-Valensi P, Zielinski J, Delaunois L, Cornudella R, Moutinho dos Santos J. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. *The European respiratory journal*. 1999; **14**: 1002-8.
129. Fletcher EC, Lockett RA, Goodnight-White S, Miller CC, Qian W, Costarangos-Galarza C. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO₂ above 60 mm Hg. *The American review of respiratory disease*. 1992; **145**: 1070-6.
130. Shea SA, Winning AJ, McKenzie E, Guz A. Does the abnormal pattern of breathing in patients with interstitial lung disease persist in deep, non-rapid eye movement sleep? *The American review of respiratory disease*. 1989; **139**: 653-8.
131. Vazquez JC, Perez-Padilla R. Effect of oxygen on sleep and breathing in patients with interstitial lung disease at moderate altitude. *Respiration; international review of thoracic diseases*. 2001; **68**: 584-9.
132. Crockett AJ, Cranston JM, Antic N. Domiciliary oxygen for interstitial lung disease. *Cochrane Database Syst Rev*. 2001: CD002883.
133. Braghiroli A, Donner CF. A multicentre randomised controlled trial on long term oxygen therapy in pulmonary fibrosis. Personal communication, 2000.
134. King TE, Jr., Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW, Group AS. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *The New England journal of medicine*. 2014; **370**: 2083-92.
135. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. *The Cochrane database of systematic reviews*. 2014; **10**: Cd006322.
136. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. *Thorax*. 2008; **63**: 549-54.
137. Vainshelboim B, Oliveira J, Fox BD, Soreck Y, Fruchter O, Kramer MR. Long-Term Effects of a 12-Week Exercise Training Program on Clinical Outcomes in Idiopathic Pulmonary Fibrosis. *Lung*. 2015; **193**: 345-54.
138. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease. *Respiratory medicine*. 2012; **106**: 429-35.
139. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, Pitta F, Sewell L, Raskin J, Bourbeau J, Crouch R, Franssen FM, Casaburi R, Vercoulen JH, Vogiatzis I, Gosselink R, Clini EM, Effing TW, Maltais F, van der Palen J, Troosters T, Janssen DJ, Collins E, Garcia-Aymerich J, Brooks D, Fahy BF, Puhan MA, Hoogendoorn M, Garrod R, Schols AM, Carlin B, Benzo R, Meek P, Morgan M, Rutten-van Molken MP, Ries AL, Make B, Goldstein RS, Dowson CA, Brozek JL, Donner CF, Wouters EF. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine*. 2013; **188**: e13-64.
140. Alison JA, McKeough ZJ, Johnston K, McNamara RJ, Spencer LM, Jenkins SC, Hill CJ, McDonald VM, Frith P, Cafarella P, Brooke M, Cameron-Tucker HL, Candy S, Cecins N, Chan ASL, Dale MT, Dowman LM, Granger C, Halloran S, Jung P, Lee AL, Leung R, Matulick T, Osadnik C, Roberts M, Walsh J, Wootton S, Holland AE, on behalf of the Lung Foundation A, the Thoracic Society of A, New Z. Australian and New Zealand Pulmonary Rehabilitation Guidelines. *Respirology*. 2017; **22**: 800-19.
141. Keating A, Lee A, Holland AE. What prevents people with chronic obstructive pulmonary disease from attending pulmonary rehabilitation? A systematic review. *Chronic respiratory disease*. 2011; **8**: 89-99.
142. Holland AE, Fiore JF, Jr., Goh N, Symons K, Dowman L, Westall G, Hazard A, Glaspole I. Be honest and help me prepare for the future: What people with interstitial lung disease want from education in pulmonary rehabilitation. *Chronic respiratory disease*. 2015; **12**: 93-101.
143. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, Lederer DJ, Mulligan MJ, Patterson GA, Singer LG, Snell GI, Verleden GM, Zamora MR, Glanville AR. A consensus document for the selection of lung transplant candidates: 2014—An update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *The Journal of Heart and Lung Transplantation*. 2015; **34**: 1-15.
144. 2016. OPTN data. <http://optn.transplant.hrsa.gov/latestData/rptData.asp>.
145. Bennett D, Fossi A, Bargagli E, Refini RM, Pieroni M, Luzzi L, Ghiribelli C, Paladini P, Voltolini L, Rottoli P. Mortality on the Waiting List for Lung Transplantation in Patients with Idiopathic Pulmonary Fibrosis: A Single-Centre Experience. *Lung*. 2015; **193**: 677-81.
146. Yusef RD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Goldfarb SB, Levvey BJ, Lund LH, Meiser B, Rossano JW, Stehlik J. The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Lung and Heart-Lung Transplantation Report—2015; Focus Theme: Early Graft Failure. *The Journal of Heart and Lung Transplantation*. 2015; **34**: 1264-77.
147. Grimm JC, Valero V, 3rd, Magruder JT, Kilic A, Dungan SP, Silhan LL, Shah PD, Kim BS, Merlo CA, Sciortino CM, Shah AS. A novel risk score that incorporates recipient and donor variables to predict 1-year mortality in the current era of lung transplantation. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2015; **34**: 1449-54.
148. Thabut G, Christie JD, Ravaud P, Castier Y, Dauriat G, Jebrak G, Fournier M, Leseche G, Porcher R, Mal H. Survival after bilateral versus single-lung transplantation for idiopathic pulmonary fibrosis. *Annals of internal medicine*. 2009; **151**: 767-74.



149. Schaffer JM, Singh SK, Reitz BA, Zamanian RT, Mallidi HR. Single- vs double-lung transplantation in patients with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis since the implementation of lung allocation based on medical need. *Jama*. 2015; **313**: 936-48.
150. Bajwah S, Higginson IJ, Ross JR, Wells AU, Biring SS, Riley J, Koffman J. The palliative care needs for fibrotic interstitial lung disease: a qualitative study of patients, informal caregivers and health professionals. *Palliative medicine*. 2013; **27**: 869-76.
151. Danoff SK, Schonhoft EH. Role of support measures and palliative care. *Current opinion in pulmonary medicine*. 2013; **19**: 480-4.
152. Lanken PN, Terry PB, Delisser HM, Fahy BF, Hansen-Flaschen J, Heffner JE, Levy M, Mularski RA, Osborne ML, Prendergast TJ, Rocker G, Sibbald WJ, Wilfond B, Yankaskas JR. An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. *American journal of respiratory and critical care medicine*. 2008; **177**: 912-27.
153. Bajwah S, Ross JR, Wells AU, Mohammed K, Oyebode C, Biring SS, Patel AS, Koffman J, Higginson IJ, Riley J. Palliative care for patients with advanced fibrotic lung disease: a randomised controlled phase II and feasibility trial of a community case conference intervention. *Thorax*. 2015; **70**: 830-9.
154. Garibaldi BT, Danoff SK. Symptom-based management of the idiopathic interstitial pneumonia. *Respirology*. 2016; **21**: 1357-65.
155. Jennings AL, Davies AN, Higgins JP, Gibbs JS, Broadley KE. A systematic review of the use of opioids in the management of dyspnoea. *Thorax*. 2002; **57**: 939-44.
156. Abernethy AP, Currow DC, Frith P, Fazekas BS, McHugh A, Bui C. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *Bmj*. 2003; **327**: 523-8.
157. Kohberg C, Andersen CU, Bendstrup E. Opioids: an unexplored option for treatment of dyspnea in IPF. *European clinical respiratory journal*. 2016; **3**: 30629.
158. Ekstrom MP, Abernethy AP, Currow DC. The management of chronic breathlessness in patients with advanced and terminal illness. *Bmj*. 2015; **349**: g7617.
159. Simon ST, Higginson IJ, Booth S, Harding R, Weingartner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *The Cochrane database of systematic reviews*. 2016; **10**: Cd007354.
160. Abernethy AP, McDonald CF, Frith PA, Clark K, Herndon JE, 2nd, Marcello J, Young IH, Bull J, Wilcock A, Booth S, Wheeler JL, Tulsy JA, Crockett AJ, Currow DC. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet*. 2010; **376**: 784-93.
161. Campbell ML, Yarandi H, Dove-Medows E. Oxygen is nonbeneficial for most patients who are near death. *Journal of pain and symptom management*. 2013; **45**: 517-23.
162. Brown KK. Chronic cough due to chronic interstitial pulmonary diseases: ACCP evidence-based clinical practice guidelines. *Chest*. 2006; **129**: 180s-5s.
163. Lee JS, McLaughlin S, Collard HR. Comprehensive care of the patient with idiopathic pulmonary fibrosis. *Current opinion in pulmonary medicine*. 2011; **17**: 348-54.
164. Horton MR, Santopietro V, Mathew L, Horton KM, Polito AJ, Liu MC, Danoff SK, Lechtzin N. Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: a randomized trial. *Annals of internal medicine*. 2012; **157**: 398-406.
165. Horton MR, Danoff SK, Lechtzin N. Thalidomide inhibits the intractable cough of idiopathic pulmonary fibrosis. *Thorax*. 2008; **63**: 749.
166. Bajwah S, Koffman J, Higginson IJ, Ross JR, Wells AU, Biring SS, Riley J. 'I wish I knew more ...' the end-of-life planning and information needs for end-stage fibrotic interstitial lung disease: views of patients, carers and health professionals. *BMJ supportive & palliative care*. 2013; **3**: 84-90.
167. Bajwah S, Higginson IJ, Ross JR, Wells AU, Biring SS, Patel A, Riley J. Specialist palliative care is more than drugs: a retrospective study of ILD patients. *Lung*. 2012; **190**: 215-20.
168. Lindell KO, Liang Z, Hoffman LA, Rosenzweig MQ, Saul MI, Pilewski JM, Gibson KF, Kaminski N. Palliative care and location of death in decedents with idiopathic pulmonary fibrosis. *Chest*. 2015; **147**: 423-9.
169. Ahmadi Z, Wysham NG, Lundstrom S, Janson C, Currow DC, Ekstrom M. End-of-life care in oxygen-dependent ILD compared with lung cancer: a national population-based study. *Thorax*. 2016; **71**: 510-6.
170. Beernaert K, Cohen J, Deliens L, Devroey D, Vanthomme K, Pardon K, Van den Block L. Referral to palliative care in COPD and other chronic diseases: a population-based study. *Respiratory medicine*. 2013; **107**: 1731-9.
171. Brown CE, Jecker NS, Curtis JR. Inadequate Palliative Care in Chronic Lung Disease. An Issue of Health Care Inequality. *Annals of the American Thoracic Society*. 2016; **13**: 311-6.
172. Wachterman MW, Pilver C, Smith D, Ersek M, Lipsitz SR, Keating NL. Quality of End-of-Life Care Provided to Patients With Different Serious Illnesses. *JAMA internal medicine*. 2016; **176**: 1095-102.



173. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF, Billings JA, Lynch TJ. Early palliative care for patients with metastatic non-small-cell lung cancer. *The New England journal of medicine*. 2010; **363**: 733-42.
174. Duck A, Spencer LG, Bailey S, Leonard C, Ormes J, Caress AL. Perceptions, experiences and needs of patients with idiopathic pulmonary fibrosis. *Journal of advanced nursing*. 2015; **71**: 1055-65.
175. Collard HR, Tino G, Noble PW, Shreve MA, Michaels M, Carlson B, Schwarz MI. Patient experiences with pulmonary fibrosis. *Respiratory medicine*. 2007; **101**: 1350-4.
176. Schoenheit G, Becattelli I, Cohen AH. Living with idiopathic pulmonary fibrosis: an in-depth qualitative survey of European patients. *Chronic respiratory disease*. 2011; **8**: 225-31.
177. Morisset J, Dube BP, Garvey C, Bourbeau J, Collard HR, Swigris JJ, Lee JS. The Unmet Educational Needs of Patients with Interstitial Lung Disease. Setting the Stage for Tailored Pulmonary Rehabilitation. *Annals of the American Thoracic Society*. 2016; **13**: 1026-33.
178. Lindell KO, Olshansky E, Song MK, Zullo TG, Gibson KF, Kaminski N, Hoffman LA. Impact of a disease-management program on symptom burden and health-related quality of life in patients with idiopathic pulmonary fibrosis and their care partners. *Heart & lung : the journal of critical care*. 2010; **39**: 304-13.
179. Duck A, Pigram L, Errhalt P, Ahmed D, Chaudhuri N. IPF Care: A Support Program for Patients with Idiopathic Pulmonary Fibrosis Treated with Pirfenidone in Europe. *Advances in therapy*. 2015; **32**: 87-107.
180. Australia LF. Patient Support - Idiopathic Pulmonary Fibrosis. <http://lungfoundation.com.au/patient-support/other-lung-conditions/idiopathic-pulmonary-fibrosis-ipf/>. Accessed: 16th September 2016.
181. Rosas IO, Richards TJ, Konishi K, Zhang Y, Gibson K, Lokshin AE, Lindell KO, Cisneros J, Macdonald SD, Pardo A, Sciruba F, Dauber J, Selman M, Gochuico BR, Kaminski N. MMP1 and MMP7 as potential peripheral blood biomarkers in idiopathic pulmonary fibrosis. *PLoS medicine*. 2008; **5**: e93.
182. Kropski JA, Blackwell TS, Loyd JE. The genetic basis of idiopathic pulmonary fibrosis. *The European respiratory journal*. 2015.
183. Peljto AL, Zhang Y, Fingerlin TE, Ma SF, Garcia JG, Richards TJ, Silveira LJ, Lindell KO, Steele MP, Loyd JE, Gibson KF, Seibold MA, Brown KK, Talbert JL, Markin C, Kossen K, Seiwert SD, Murphy E, Noth I, Schwarz MI, Kaminski N, Schwartz DA. Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. *Jama*. 2013; **309**: 2232-9.
184. Stuart BD, Lee JS, Kozlitina J, Noth I, Devine MS, Glazer CS, Torres F, Kaza V, Girod CE, Jones KD, Elicker BM, Ma SF, Vij R, Collard HR, Wolters PJ, Garcia CK. Effect of telomere length on survival in patients with idiopathic pulmonary fibrosis: an observational cohort study with independent validation. *The Lancet Respiratory medicine*. 2014; **2**: 557-65.
185. Newton CA, Batra K, Torrealba J, Kozlitina J, Glazer CS, Aravena C, Meyer K, Raghu G, Collard HR, Garcia CK. Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive. *Eur Respir J*. 2016; **48**: 1710-20.
186. Oldham JM, Ma SF, Martinez FJ, Anstrom KJ, Raghu G, Schwartz DA, Valenzi E, Witt L, Lee C, Vij R, Huang Y, Streck ME, Noth I. TOLLIP, MUC5B, and the Response to N-Acetylcysteine among Individuals with Idiopathic Pulmonary Fibrosis. *American journal of respiratory and critical care medicine*. 2015; **192**: 1475-82.
187. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, Taguchi Y, Nagai S, Itoh H, Ohi M, Sato A, Kudoh S. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*. 2005; **171**: 1040-7.
188. King TE, Jr., Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez F, Valeyre D, Leconte I, Morganti A, Roux S, Behr J. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*. 2011; **184**: 92-9.
189. Homma S, Azuma A, Taniguchi H, Ogura T, Mochiduki Y, Sugiyama Y, Nakata K, Yoshimura K, Takeuchi M, Kudoh S. Japan NACCSG. Efficacy of inhaled N-acetylcysteine monotherapy in patients with early stage idiopathic pulmonary fibrosis. *Respirology*. 2012; **17**: 467-77.
190. Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis. *New England Journal of Medicine*. 2014; **370**: 2093-101.
191. Raghu G, Brown KK, Bradford WZ, Starko K, Noble PW, Schwartz DA, King TE, Jr., Idiopathic Pulmonary Fibrosis Study G. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. *The New England journal of medicine*. 2004; **350**: 125-33.
192. Raghu G, Brown KK, Costabel U, Cottin V, du Bois RM, Lasky JA, Thomeer M, Utz JP, Khandker RK, McDermott L, Fatenejad S. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. *American journal of respiratory and critical care medicine*. 2008; **178**: 948-55.
193. King TE, Jr., Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, Noble PW, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, du Bois RM, Group IS. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2009; **374**: 222-8.
194. Daniels CE, Lasky JA, Limper AH, Mieras K, Gabor E, Schroeder DR, Imatinib IPFSI. Imatinib treatment for idiopathic pulmonary fibrosis: Randomized placebo-controlled trial results. *American journal of respiratory and critical care medicine*. 2010; **181**: 604-10.





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