Welcome to issue 140 of Respiratory Research Review. It is a privilege to be practicing respiratory medicine during a decade where treatment for ILD (interstitial lung disease), and in particular its most aggressive form, IPF (idiopathic pulmonary fibrosis), is becoming available. It is a challenge attempting to prioritise only ten articles for this September issue of Respiratory Research Review.

‘Treatment of idiopathic pulmonary fibrosis in Australia and New Zealand: a position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia’ (Respirology 2017) is a great way to gain an overview of the current standards in diagnosis and management of IPF. Fernando Martinez and colleagues echo the Australian/NZ approach, highlight limitations and summarise new research initiatives that will probably enter our clinical practice, including new imaging interpretation, cryobiopsies and the use of multidisciplinary meetings to reach a consensus diagnosis (Lancet Respir Med). Two of these ideas we pick up on in our selection; a study to diagnose IPF without lung biopsy or honeycombing (Thorax) and the clinical impact of an ILD multidisciplinary service (Respirology). For the ‘nuts and bolts’ including online forms and proforma see the brand new publications ‘The interstitial lung disease multidisciplinary meeting: a position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia’ (Respirology).

Until recently the lack of treatment for IPF has been frustrating; at this stage both pirfenidone and nintedanib are licensed for treatment in NZ but only pirfenidone is currently funded. All major journals have published evidence-based and very readable reviews; here we highlight three. The first is ‘Therapeutic approach to adult fibrotic lung disease’ by Adegunsoye and Strek (Chest), an up-to-date and pragmatic approach on how to diagnose, treat and manage the side effects of most ILDs. They also have a comprehensive table of 19 ongoing randomised trials. The second is ‘Idiopathic pulmonary fibrosis: effects and optimal management of comorbidities’ (Lancet Respir Med), a practical review of the incidence and management of the most common comorbidities in patients with IPF like diabetes, sleep apnoea, depression, heart failure, lung cancer and others. Thirdly, ‘Should all patients with idiopathic pulmonary fibrosis, even those with more than moderate impairment, be treated with nintedanib or pirfenidone?’ (Chest) is an evidence-based, entertaining and passionate read; if you wish to become up-to-date with the current debate on the treatment options, limitations, and indications it is highly recommended reading.

‘Shall we call them telomere-mediated? Penaming the idiopathic after the cause is found’ is the title of the editorial reviewing the genetic mutations in telomere related genes leading to ILD (Eur Respir J). This article may be seen as a placeholder for a whole section of research of TERT mutation, biomarkers and promising diagnostic and possible therapeutic strategies, which will undoubtedly become important. However, the ten articles selected will focus half on the hot topic of IPF and half on other ILDs. Although there are many more interesting articles that we could have included in this review, we still hope you enjoy the selection. As always feedback and comments are welcome.

Kind regards,

Professor Lutz Beckert
luitzbeckert@researchreview.co.nz

Independent commentary by Professor Lutz Beckert.
Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or with the view of future collaborations.
Accuracy and reliability of internet resources for information on idiopathic pulmonary fibrosis
Authors: Fisher JH et al.
Summary: These authors searched for ‘idiopathic pulmonary fibrosis’ using common internet search engines and analysed the first 200 hits for content on IPF features and treatments that are discussed in clinical guidelines. 181 of these websites, with a median reading level of 12, met their eligibility criteria. Scientific resources and foundation/advocacy organisation sites included more content than personal commentary sites, although the information provided was incomplete and/or inaccurate for most websites. Almost half of the websites included nonindicated and/or harmful pharmacotherapies as potential treatments for IPF; mostly the foundation/advocacy organisation websites. Among 98 websites with up-to-date information, 13.3% and 30.6% discussed azathioprine and corticosteroids, respectively, as potential chronic treatments. All types of websites scored poorly on the DISCERN scale, particularly news/media and personal commentary websites.
Comment: At times, it is challenging for us to stay on top of diagnostic, prognostic and therapeutic changes in IPF. Most New Zealanders have internet access and it is likely that your patients or their whanau will have searched IPF on the internet. These Canadian authors applied a standard evaluation tool to 181 freely available, unique websites on IPF. Overall the content and quality of these websites was poor, many items were inadequately covered, nearly half suggested at least one unproven treatment and most sites had not been updated for 1.3 years. Bottom line: patient information on IPF is frequently incomplete, inaccurate and outdated.

Clinical impact of the interstitial lung disease multidisciplinary service
Authors: Jo HE et al.
Summary: Ninety patients with suspected ILD attended a standard ILD clinic visit and underwent multidisciplinary diagnostic review. Changes in ILD diagnosis and management at referral were compared with those following the multidisciplinary discussions. Specific ILD diagnoses were changed following multidisciplinary discussions in 53% of the patients. Among patients referred with an IPF diagnosis (n=27), ten had their diagnosis changed as the result of the multidisciplinary discussions, while seven of the remaining patients had their diagnosis changed to IPF. A significant reduction was also seen in ‘unclassifiable’ diseases, and disease behaviour classifications provided information beyond the ILD diagnosis.
Comment: Simon Walsh and colleagues have just published an article suggesting that more than 20 years of experience or access to a multidisciplinary team meeting improves diagnostic accuracy in diagnosing IPF. Our Australian colleagues report on the clinical impact of a dedicated ILD multidisciplinary team meeting on the diagnosis and management of 90 patients. The article provides graphic representation of the 53% of patients whose diagnosis was altered by the multidisciplinary team meeting. This article also provides a flow diagram of the ILD multidisciplinary team pathway, including possible outcomes. Bottom line: this article is the primer for the position statement, including an online toolbox on how to run an ILD multidisciplinary team meeting.

The use of pretest probability increases the value of high-resolution CT in diagnosing usual interstitial pneumonia
Authors: Brownell R et al.
Summary: These researchers investigated test characteristics of nondefinitive HRCT patterns for identifying histopathological usual interstitial pneumonia. They studied a derivation cohort of 385 patients, of whom 17% were found to have a possible usual interstitial pneumonia pattern on HRCT; 29% had a histopathological usual interstitial pneumonia pattern. A possible usual interstitial pneumonia pattern was associated with specificity of 91.2% and a PPV (positive predictive value) of 62.5% for a usual interstitial pneumonia pattern on surgical lung biopsy; the PPV improved when age, sex and total traction bronchiectasis score were added. Inconsistency with a usual interstitial pneumonia pattern had a low PPV (22.7%). In a validation cohort, the specificity of an HRCT pattern was nearly identical at 92.7%, and the PPV improved when age, sex and total traction bronchiectasis score were added. Inconsistency with a usual interstitial pneumonia pattern had a low PPV (22.7%). In a validation cohort, the specificity of an HRCT pattern was nearly identical at 92.7%, and the PPV was improved due to a higher prevalence of usual interstitial pneumonia patterns.
Comment: This may be the paper with the greatest clinical impact. Collectively we are not too bad at diagnosing IPF with established honeycombing on the HRCT scan. However, clinically that means this progressive illness is already well established. It would be beneficial to diagnose IPF earlier, so our treatment can have more impact. In this study, the authors use a simple clinical score (age above 60 years, male) and HRCT findings of possible usual interstitial pneumonia and traction bronchiectasis to identify IPF with 92% accuracy. Robert Homer and David Lederer’s editorial gives us the bottom line: “diagnosing idiopathic pulmonary fibrosis without a lung biopsy: honeycombing not required”.

Upgrade your COPD patients to SPIOLTO® RESPIMAT®
www.turnopenpress.co.nz
Freedom to breathe.

Fully funded inhalers without special authority.

**Rexair, Salair, Floair and Meterol**

- The first fully-funded dose counters on pMDIs for Fluticasone Inhalers and Salmeterol Inhaler in New Zealand
- Clearly embossed actuators for patient safety
- Proudly marketed by REX Medical, 100% New Zealand owned company
- Multilingual patient brochures and poster in English, Māori, Chinese, Tongan, and Samoan available upon request. To request, please email admin@rexmed.co.nz

---

**The evidence of benefits of exercise training in interstitial lung disease**

**Authors:** Dowman LM et al.

**Summary:** Patients with IPF (n=61), asbestosis (n=22), connective tissue disease-related ILD (n=23) or other ILD aetiology (n=38) were randomised to undergo 8 weeks of supervised exercise training or usual care. 6MWD was increased by 25m and health-related QOL improved in the exercise group, with a greater effect seen in participants with asbestosis and IPF than those with connective tissue disease-related ILD. All participants except those with connective tissue disease-related ILD showed a decline in the benefits at 6 months. Greater benefits for 6MWD and symptoms were seen in participants with a lower 6MWD and worse symptoms at baseline, and in those who successfully adhered to the exercise protocol. Sustained improvements in 6MWD and symptoms at 6 months were associated with better lung function at baseline and less pulmonary hypertension.

**Comment:** Our Australian colleagues are leading the way in treatment options beyond drug therapy. Patients with ILD are often deconditioned, have a reduced exercise tolerance, are fatigued and suffer an impaired QOL. These researchers report the outcome of a twice weekly supervised exercise programme across three academic centres in Melbourne. The cohort of 142 participants is large enough to comment on the impact of the underlying lung disease on the outcome.

**Bottom line:** pulmonary rehabilitation for patients with ILD improves 6MWD, shortness of breath and health-related QOL.

**Reference:** Thorax 2017;72(7):610–9

**Abstract**

---

**Occupational pesticide exposure and respiratory health: a large-scale cross-sectional study in three commercial farming systems in Ethiopia**

**Authors:** Negatu B et al.

**Summary:** The impact of occupational pesticide exposure on the respiratory health of farmers and farm workers from commercial farming systems was explored in two cross-sectional surveys. The first survey included 601 subjects occupationally exposed to pesticides and 503 unexposed individuals, and the second survey, which was conducted 2 years later in the same farming regions and also included lung function measurements, included 206 occupationally exposed individuals and 180 unexposed individuals. Compared with nonexposed individuals, those with pesticide exposure had greater likelihoods of chronic cough and shortness of breath (respective odds ratios 3.15 [95% CI 1.56, 6.36] and 6.67 [2.60, 17.58]) in the first survey. The second survey showed similar results for these outcomes, along with reductions in FEV₁ and symptoms at 6 months were associated with better lung function at baseline and less pulmonary hypertension.

**Comment:** One of my colleagues drew my attention to this potentially preventable cause of ILD secondary to pesticide exposure. In this fascinating study from Holland and Ethiopia, I have learned about Ethiopians’ large-scale greenhouses and intensely irrigated farms for the cut flower industry. With this the application of organophosphates, organochlorines and phosphonoglycines has also increased. K Mortimer and J Feary nicely frame this work in their outstanding editorial. Bottom line: after only 4 years of exposure to pesticides, even young workers report cough, shortness of breath and a loss of 140mL in their FEV₁.

**Reference:** Thorax 2017;72(6):498–9

**Abstract**

---

For more information, please go to [www.medsafe.govt.nz](http://www.medsafe.govt.nz)
Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II)

Authors: Tashkin DP et al., for the Scleroderma Lung Study II Investigators

Summary: Patients with scleroderma-related ILD were randomised to receive mycophenolate mofetil at a target dosage of 1500mg twice daily for 24 months (available n=63) or oral cyclophosphamide at a target dosage of 2.0 mg/kg/day for 12 months followed by placebo for 12 months (evaluable n=63). Significant improvements from baseline in percent predicted FVC at 24 months were seen in the mycophenolate mofetil and cyclophosphamide arms, but they did not differ between the two treatments (2.19 vs. 2.88 [p=0.24]); the respective mortality rates were 7% and 15%, with most deaths attributable to progressive ILD. Cyclophosphamide recipients had more leucopenia (30 vs. 4 participants) and thrombocytopenia (4 vs. 0) than mycophenolate mofetil recipients, and there were more premature study withdrawals (32 vs. 20) and treatment failures (2 vs. 0) in the cyclophosphamide arm.

Comment: Just about 10 years ago, Donald Tashkin and colleagues reported that the use of cyclophosphamide in the management of scleroderma-related lung disease was beneficial in maintaining lung function; however, the effect was small and of dubious clinical relevance, given the toxicity of oral cyclophosphamide. Now, Donald Tashkin and colleagues report a further trial with a complex and innovative patient recruitment system comparing cyclophosphamide with mycophenolate mofetil. Christopher Denton acknowledges this landmark trial in his comment and gives us the bottom line: mycophenolate mofetil is tolerable, has a similar efficacy to cyclophosphamide and could be valuable in treating lung fibrosis in scleroderma.


Characteristics of sarcoidosis in Maori and Pacific Islanders

Authors: Wilsher ML et al.

Summary: This retrospective medical record review of 406 patients attending specialist ILD clinics in NZ sought to identify differences in clinical characteristics of those who were of Maori or Pacific Island descent (n=69) versus those of European descent; only patients of Indian ethnicity were over-represented in the cohort. Parenchymal lung involvement was uncommon in Maori and Pacific Islander patients, and no patient had extensive pulmonary fibrosis. Maori and Pacific Islander patients were less likely to have CT patterns of sarcoid parenchymal lung involvement. No difference was seen for Maori/Pacific Island versus European ethnicity for baseline lung function or requirement for treatment. Maori and Pacific Islanders were significantly more likely to have ocular or skin involvement and to have CT patterns of extra-pulmonary sarcoidosis. Maori and Pacific Islanders tend to have more extrapulmonary sarcoidosis and less erythema nodosum.

Comment: Margaret Wilsher and colleagues keep NZ internationally visible in the world of ILD. They had previously published that IFP affects Maori and Pacific Islanders less frequently than NZ Europeans. In this study, they report that the incidence of sarcoidosis generally matches the general census, suggesting a similar incidence. Maori patients can have very disfiguring lupus pernio with associated sinonasal disease, and clinicians need to be cognisant of sarcoidosis without classical pulmonary features. Bottom line: Maori and Pacific Islanders tend to have more extrapulmonary sarcoidosis and less erythema nodosum. Parenchymal lung involvement is uncommon.

Reference: Respiratory 2017;22(2):360–3

Daily home spirometry: an effective tool for detecting progression in idiopathic pulmonary fibrosis

Authors: Russell A-M et al.

Summary: The feasibility and reliability of daily administered lung function measurements in patients with IPF were evaluated in this research involving 50 participants provided with handheld spirometers and instructions regarding spirometry self-administration. The participants obtained daily spirometry measurements for a median of 279 days. During the study period, 18 participants died. Excellent correlations were seen between the home spirometry data and those obtained at hospital. The rate of FVC decline predicted outcomes and subsequent mortality at 3, 6 and 12 months (respectively hazard ratios 1.040 [95% CI 1.021, 1.062], 1.024 [1.014, 1.033] and 1.012 [1.007, 1.016]).

Comment: The loss of FVC is a marker for the progression of IPF, and slowing the decline in FVC translates into improved survival. These authors report that daily home monitoring is feasible, reliable and potentially adds value to patient management; this is well reflected in the Editorial “What gets measured gets managed”. Key insights are: a) the rate of FVC decline was even more predictive of outcome than in retrospective studies; b) no meaningful signal can be seen within 28 days; and c) our bottom line: while home spirometry doesn’t change individual treatment as yet, it has the potential to transform clinical trials.


New Zealand Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.
Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients
Authors: Delaunay M et al.

Summary: These authors analysed retrospective data from centres with experience in the use of immune-checkpoint inhibitors to describe the main features of immune-checkpoint inhibitor-associated ILD. Of 1826 patients with cancer, 64 (3.5%) had developed immune-checkpoint inhibitor-associated ILD: most had received programmed cell death-1 inhibitors. Males and former or current smokers were particularly affected, and the median age was 59 years. The respective rates of grade 2–3, grade 4 and fatal ILD were 65.6%, 9.4% and 9.4%. The median time between starting immunotherapy and the development of ILD was 2.3 months; ILD developed significantly earlier in patients with lung cancer than those with melanoma (2.1 vs. 5.2 months [p=0.02]). The predominant lesions were ground-glass opacities (81.3%), followed by consolidations (53.1%), and the most common patterns were organising pneumonia (23.4%) and hypersensitivity pneumonitis (15.6%). The 6-month overall survival rate was 58.1%.

Comment: In this excellent study and editorial, the authors summarised their experience of almost 2000 patients on immunotherapy for cancer and applied a strict definition of immune-checkpoint inhibitor-associated ILD. Some key findings are: i) the overall incidence of immune-checkpoint inhibitor-associated ILD was 3.5%; however, 75% of patients had received immune-checkpoint inhibitors for lung cancer; ii) the median onset of immune-checkpoint inhibitor-associated ILD was after 2.3 months; iii) most cases were of severity grade 2–3; and iv) the most common radiological findings were organising pneumonia, hypersensitivity pneumonitis and bronchiolitis. In the absence of validated recommendations, the authors suggest our bottom line: in suspected immune-checkpoint inhibitor-associated ILD, perform a contrast CT chest, bronchoalveolar lavage and transbronchial lung biopsy. Consider a treatment pause and steroid initiation.

Reference: Eur Respir J 2017;50(2):1700050
Abstract

Palliative care for patients with advanced fibrotic lung disease: a randomised controlled phase II and feasibility trial of a community case conference intervention
Authors: Bajwah S et al.

Summary: These researchers set out to determine how Hospital2Home, a case conference intervention delivered in the home, impacts on palliative care concerns of patients and their carers, and to evaluate the programme’s feasibility and acceptability. A phase 2 fast-track randomised controlled trial with qualitative interviews was conducted in 33 patients (26 fast-track; 7 control) from a specialist centre. Compared with controls, the fast-track group had a significantly greater impact on Palliative Care Outcome Scale scores at 4 weeks (primary outcome; –5.7 vs. –0.4 [p=0.02]), as well as superior outcomes for QOL, anxiety and depression.

Comment: This is a slightly complex phase 2 randomised controlled trial that is becoming topical now that we are starting to organise multidisciplinary meetings for the management of ILD. We have previously reported (Respiratory Research Review, issue 128) that patient organisations identify a lack of holistic IPF care, and have articulated a need for better access to palliative and end-of-life care. The Brompton group developed an intervention addressing some of these needs and performed a proof-of-concept trial. This is a very data-rich paper with intriguing qualitative data. Bottom line: early discussion about disease prognosis and progression significantly improved patients’ anxiety and overall QOL.

Reference: Thorax 2015;70(9):830–9
Abstract