Contemporary Concise Review 2019: Interstitial lung disease

PETER M. GEORGE1,2 AND ATHOL U. WELLS1,2

1Interstitial Lung Disease Unit, Royal Brompton and Harefield NHS Foundation Trust, London, UK; 2National Heart and Lung Institute, Imperial College London, London, UK

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SUMMARY OF KEY POINTS

- Antifibrotic therapy has been proven to be effective in the treatment of progressive fibrosing lung diseases other than IPF.
- The COLDICE study has demonstrated that transbronchial lung cryobiopsy (TBLC) is an important diagnostic technique with good concordance when compared with surgical lung biopsy (SLB).
- Telomere dysfunction is associated with progressive fibrosis and a poor prognosis in a broad range of ILDs such as IPF, chronic hypersensitivity pneumonitis and autoimmune-related ILD.
- In IPF, large genome-wide association studies have confirmed the importance of the MUC5B promotor variant rs35705950 amongst other novel genetic loci.
- A randomized controlled trial of thrombomodulin for treatment of acute exacerbations of IPF was negative—this proves that trials of this devastating complication of IPF are feasible and required.

INTRODUCTION

Developments in the understanding of the pathogenesis, diagnosis and treatment for patients with interstitial lung disease (ILD) accelerated at pace in 2019. The progressive fibrotic phenotype of ILDs beyond idiopathic pulmonary fibrosis (IPF) took centre stage1,2 and in this context, for the first time antifibrotic therapy has been shown to be effective for the treatment of non-IPF ILD.3-4 This represents arguably the most seismic paradigm shift since the seminal publications of the phase 3 studies of the antifibrotic drugs pirfenidone5 and nintedanib6 for IPF in 2014. Aside from the progressive fibrotic phenotype, advances have been made in understanding the genetics of IPF and biomarker discovery continues to be an area of fruitful research. Telomere dysfunction in ILD has gained prominence as an important pathobiological feature of ILD conferring poorer prognoses and a greater risk of disease progression.7 The diagnosis of ILD produced controversy with conflicting studies regarding the diagnostic accuracy of transbronchial lung cryobiopsy (TBLC).8,9 Artificial intelligence and computer-based imaging algorithms for the assessment of ILD also yielded important publications. Interstitial lung abnormalities (ILA) are imaging patterns which in some individuals represent early ILD—their relevance in the identification of early ILD was investigated further in 2019. The importance of comorbidities and a greater focus on patient-reported outcomes and quality of life have also been key features of the year. In this concise review of ILD, we review the key studies published in 2019 and explore their impact moving into the new decade.

THE DIAGNOSIS OF ILD

KEY POINTS

- In clinical practice, clinicians tend to perform SLB in patients with suspected IPF much less frequently than suggested by international guidance.
- TBLC findings have high concordance with SLB findings and with the final diagnosis made at multidisciplinary team meeting.
- The risk of developing TB is highest in the first year after the diagnosis of pulmonary sarcoidosis.

The Australian IPF registry is a good example of a well-established, prospectively recruited cohort of patients from a geographically diverse population. Part of its unique appeal is that every patient referred into the registry is re-evaluated at a centralized multidisciplinary team panel meeting ensuring standardization of patient data. In a publication by Jo et al.,10...
almost one quarter of the 417 patients referred to the Australian IPF registry did not meet the 2011 IPF diagnostic criteria. Interestingly, despite not meeting IPF diagnostic criteria, these patients experienced identical outcomes to those who did. Some of these patients may indeed not have IPF but instead an IPF-like progressive fibrotic lung disease of alternative aetiology. Consequently, prior to the publication of the INBUILD study of nintedanib in progressive fibrotic ILD which is discussed further below, there had been a view that a relaxation of the IPF diagnostic guidelines might benefit clinicians and patients, allowing access to antifibrotic therapy for a larger pool of patients, with the important caveat that indiscriminate ‘lumping’ of patients with progressive pulmonary fibrosis might hamper the development of more targeted therapies for specific subsets of patients.

The questions of when to do biopsy and the preferred biopsy modality remain areas of debate. In the study by Jo et al., 63 of the 417 patients studied (15%) had a surgical lung biopsy (SLB). In a study by Walsh et al., 414 physicians reviewed clinical and computed tomography (CT) data from 60 patients and made statements in each case on the need for SLB and the preferred management strategy. Diagnostic likelihoods were designated and were analysed in likelihood bands using the Ryerson et al.’s classification. SLB was recommended in 34.7% of patients with a provisional diagnosis of IPF (between 50% and 90% of diagnostic confidence), despite the conditional positive recommendation in the 2018 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society (ATS/ERS/JRS/ALAT) clinical practice IPF guideline for SLB in such cases. This disparity reflects concerns shared by clinicians and patients with regard to the risks associated with SLB.

TBLC is considered to be safer than SLB. In two prospective studies, concordance between TBLC and SLB for the diagnosis of ILD yielded differing results. In the study of Romagnoli et al., histopathological features from paired lung samples taken from the same patient sequentially, utilizing both biopsy techniques, were assessed by a pathologist blinded to the biopsy procedure. In this under-powered study of 21 patients, the authors concluded that TBLC and SLB are poorly concordant, raising doubts about the use of TBLC in ILD diagnosis. However, when this question was evaluated in a meaningfully powered cohort in the COLDICE study, a very different picture emerged; 65 prospectively recruited patients underwent TBLC and SLB. The co-primary endpoints were histopathological concordance and the agreement between the histological diagnosis and the consensus clinical diagnosis made at multidisciplinary team meeting, with each case discussed twice using samples from the two biopsy techniques. Histopathological concordance between the two biopsy techniques in this study was high at 70.8% with a weighted κ of 0.70 and diagnostic agreement at multidisciplinary team meeting was high at 76.9%. Importantly, histological concordance between SLB and TBLC was strikingly high in the majority of patients with a confident TBLC diagnosis. The findings in the COLDICE study appear to show clearly that the conclusions drawn from the earlier study were highly misleading, due to under-powering and failure to compare the two procedures against multidisciplinary team diagnosis as the widely accepted gold standard for a diagnostic test in ILD.

In hypothesis-generating work, Salaün et al. reported data on the use of probe-based confocal laser endomicroscopy (pCLE) to allow direct visualization of the alveoli and terminal bronchioles of patients with ILD, identifying specific features associated with disease groups. Interestingly, these changes correlated with CT appearances, suggesting that this technique might have clinical utility by providing additional diagnostic information to inform the multidisciplinary team. Further work assessing the clinical utility of this technique should provide information as to whether the observations are specific to individual diseases, or are merely markers of differences in disease severity between individual disorders.

Tuberculosis (TB) and pulmonary sarcoidosis are sometimes challenging to distinguish from one another due to similarities in the clinical presentation, imaging and pathology. Wang et al. utilized the Taiwan National Health Insurance Database to perform a retrospective longitudinal cohort study and demonstrated that TB and sarcoidosis are often bed-fellows. Patients with TB have a >8-fold increased risk of developing sarcoidosis and patients with sarcoidosis have a 1.85-fold increased risk of developing TB. While the increased risk of sarcoidosis in patients with TB persisted throughout the 15-year follow-up period, the risk of developing TB in sarcoid patients was increased only in the first year after diagnosis.

Silicosis, a severe occupational lung disease, is sometimes misdiagnosed as sarcoidosis due to imaging similarities, including centrilobular nodularity, bilateral airspace opacification (albeit unlike sarcoid often lower predominately) and calcified lymphadenopathy. There remain no effective treatment options for this entirely avoidable lung disease, now a source of growing international concern.

IMPACT OF ILD ON QUALITY OF LIFE

KEY POINTS

- Patients continue to report deficiencies in the quality of their care with specific reference to provision of information, drug side effect management and access to specialist care.
- Polypharmacy is a common burden in patients with ILD, with the greatest increase seen in IPF patients following initiation of antifibrotic therapy.
- In healthcare settings where eligibility for antifibrotic therapy is dictated by lung function parameters, the lack of standardized reference range equations influences access to therapy.
- Combining two easily accessible parameters (peripheral oxygen saturation and the DlCO), the DeOX score is a reliable predictor of the risk of oxygen desaturation on 6-min walk test.
ILD has a major impact on quality of life with patients and healthcare professionals reporting that a greater focus is required on symptom-centred management.20 In a survey of 100 patients with IPF, participants reported that specific areas requiring improvement include more accurate and timely provision of information, better access to specialist care and improved support for managing the side effects of antifibrotic therapy.20 The provision of high-quality, holistically oriented, patient-centred care, coordinated at specialist high-volume centres but delivered at the convenience of the patient, should now be considered the minimum standard of care26 with early consideration of lung transplantation vital.26 Polypharmacy is common in patients with ILD at diagnosis and becomes an increasing burden as therapies are introduced to treat the lung disease and/or associated systemic manifestations. In a study of 214 ILD patients, 75 (35%) of whom had IPF, the Medication Regimen Complexity Index (MRCI), a validated score of treatment regimen complexity, increased from 8 to 22.5 in IPF patients and from 14.5 to 21.5 in patients with inflammatory ILD.29 Whether and by how much a raised MRCI negatively impacts patients’ quality of life and whether this is can be judged as acceptable by patients when held up against the benefits of antifibrotic therapy is explored in the linked editorial.30 In this editorial, Dr Kass also cites a Twitter conversation regarding the different clinical practices when considering timing of initiation of antifibrotic therapy (https://twitter.com/IPFdoc/status/10873169806856194)—an example of how, over the past decade, social media has influenced the scientific arena, allowing the rapid dissemination of newly published work, peer review and robust journal club discussion.31

The tweet cited above has relevance when considering the timing of antifibrotic therapy in different countries. In some countries such as the UK and Australia, reimbursement for antifibrotic therapy is allowed only for patients fulfilling specific lung function criteria. In an Australian study published by Burgess et al., it was demonstrated that depending on the reference equations used for the calculation of percentage predicted values, eligibility for antifibrotic therapy varied from 73.6% to 82.8% of patients.32 Thus, there is an urgent need for standardization of reference range equations to ensure equitable access to treatment.33

The King’s Brief Interstitial Lung Disease (KBILD) questionnaire is a validated quality of life questionnaire, shown in 209 patients with ILD (of whom 105 (50%) had IPF), to be responsive to intervention with an estimated minimum clinically important difference of 3.9 points for the total score.34 Supplemental ambulatory oxygen therapy has been shown to improve quality of life in patients with fibrotic ILD, desaturating to 88% or less during a 6-min walk test.35 In a retrospective study of 300 patients with ILD, of whom 112 (37.3%) had IPF, two easily accessible parameters—the diffusion capacity of the lung for carbon monoxide (DLCO) and peripheral oxygen saturation on air at rest—were combined to form the ‘DeOx score’, shown to reliably quantify the risk of oxygen desaturation on 6-min walk test.36

**THE ASSOCIATION BETWEEN COMORBIDITIES AND OUTCOMES**

**KEY POINTS**

- Hiatus hernia is highly prevalent and associated with worse survival and more rapid lung function decline in patients with IPF treated with antifibrotic therapy.
- Nocturnal hypoxaemia is associated with pulmonary hypertension and mortality in patients with mild to moderate fibrotic ILD.
- The ratio of the right ventricle to left ventricle in patients with ILD and confirmed pulmonary hypertension is a better predictor of mortality than invasive haemodynamic parameters.

Comorbidities are frequent in patients with ILD and impact outcomes as well as quality of life.26,29,37,38 The comorbidity which has generated the most controversy over recent years is gastro-oesophageal reflux disease.39 In a study by Macintosh et al., the impact of hiatus hernia was examined in a cohort of IPF patients treated with pirfenidone.40 Hiatus hernia was highly prevalent at 42% and its presence was associated with more rapid lung function decline, including an annual forced vital capacity (FVC) decline of 250 mL compared with a decline of 36 mL in those without hiatus hernia. Furthermore, patients with a hiatus hernia had a significantly reduced survival of 31 months compared with 55 months in those without.

Troy et al. added to a growing body of work in prospectively confirming the association between obstructive sleep apnoea in patients with ILD and documenting a prevalence of 65% in a cohort of patients with mild to moderate fibrotic ILD.41 Those with significant nocturnal hypoxaemia, defined as spending at least 10% of total sleep time with an oxygen saturation <90%, had an increased risk of developing pulmonary hypertension and were at increased risk of death. It is not known whether treatment of nocturnal hypoxaemia in patients with ILD might delay or prevent the development of pulmonary hypertension, thereby improving survival—further dedicated studies are now warranted.42 Pulmonary hypertension is common and associated with adverse outcomes in ILD but can be difficult to detect clinically and is often underestimated on echocardiogram.43 In 92 patients with ILD and pulmonary hypertension confirmed at right heart catheter, Bax et al. found that the right ventricle to left ventricle ratio was a stronger predictor of mortality and lung transplant (hazard ratio: 3.26; 95% CI: 1.49–7.13; P = 0.003) than invasive haemodynamic parameters.44
BIOMARKERS – IMAGING, SERUM AND BREATH

KEY POINTS
- Biomarkers relevant to accurate ILD diagnosis and management remain highly sought after and continue to be explored using imaging, breath and blood.

Effective biomarkers to guide treatment response are highly sought after in the care of patients with IPF. The current approach, which requires evidence of irreversible disease progression despite therapy as evidence of treatment failure, is clearly suboptimal. Furthermore, there is no means of determining which of the two antifibrotic agents to use in IPF patients, based on likely efficacy in individual patients. Taking a proteomic approach to biomarker discovery, Moodley et al. identified five plasma proteins differentially expressed between IPF patients and healthy controls. Amongst these, antithrombin III was downregulated in patients with IPF and positively correlated with FVC levels, suggesting that it might have added value as a prognostic biomarker, in keeping with the previous observation that it is an independent predictor of mortality. Gaugg et al. used mass spectrometry from exhaled breath condensate to demonstrate elevation of a group of amino acids when compared with healthy controls, although, as stated in the linked editorial, the ‘acid test’ (no pun intended) of whether these amino acids represent a useful biomarker panel will be whether their levels change with disease progression and/or response to antifibrotic therapy.

Yoon et al. applied a texture-based automated quantification system to establish the extent of concomitant emphysema in 209 patients with IPF patients and analysed the effect of emphysema on the rate of lung function decline and mortality. The authors suggest that 10% extent of emphysema should be the cut off for a diagnosis of combined pulmonary fibrosis and emphysema at which point FVC no longer reflects extent of ILD and is unlikely to decline with subclinical progression of fibrosis.

CALIPER is an example of a computer tool that can quantify various CT parameters including vessel-related volume which has previously been shown to powerfully predict outcomes in patients with ILD. Jacob et al. have added to this body of work by exploring the utility of a new vessel quantification tool, the Chest Imaging Platform, which was able to replicate the association between pulmonary vessel volume and disease severity in patients with IPF. In a separate study of IPF patients, CALIPER was also sensitive to change in vessel-related structures over time, independently predicting mortality and correlating weakly with FVC change (thus providing new progression signal validated against survival), leading the authors to speculate that this technology could be used as an IPF drug trial co-endpoint. The clinical utility of CALIPER assessment of vessel-related structures extends beyond IPF; this technology also predicted outcomes in a cohort of patients with rheumatoid arthritis-associated ILD.

TELOMERE DYSFUNCTION AND GENETICS

KEY POINTS
- Telomere dysfunction is associated with progressive fibrosis in a broad range of ILD including IPF, chronic hypersensitivity pneumonitis and autoimmune-related ILD.
- Large genome wide association studies of patients with IPF confirm the importance of the MUC5B promotor variant rs3570950 amongst other novel genetic loci.

Telomere dysfunction is an established risk factor for familial and spontaneous pulmonary fibrosis. Conventional assessment of telomere function comprises measurement of peripheral blood leucocyte telomere length and/or testing for germline mutations through DNA extraction from blood. Planas-Cerezales et al. were able to reliably measure telomere length from buccal cells from oral swabs, finding a good correlation with blood measurement. They also found that patients presenting under the age of 60 years with IPF had a high pre-test probability for short telomeres as did those with subtle immunological abnormalities—namely low titre antinuclear antibodies, thrombocytopenia and anaemia. The authors did not report on the presence of telomerase gene mutations, leaving it open to debate as to whether clinicians should consider measuring for both gene mutations and telomere length and which patients should be prioritized for assessment of telomere dysfunction.

An important study in 2019 suggested that patients with IPF who came to harm as a result of combination immunosuppression with prednisolone and azathioprine may have done so as a result of shortened telomeres. The pathological role of telomere dysfunction extends beyond IPF: short telomeres have also been associated with more rapid lung function decline in patients with chronic hypersensitivity pneumonitis and autoimmune-related ILD, suggesting that telomere-related pathways might be a unifying pathogenetic factor across progressive fibrotic lung diseases of differing aetiology.

Vast genetic sequencing studies in IPF have confirmed the importance of mutations in the MUC5B promotor variant rs3570950, identified novel genome-wide significant associations with altered gene expression of KIF15, MAD1L1 and DEPTOR and implicated host defence and telomerase-regulating genes. In a study of 494 asymptomatic relatives of patients with familial pulmonary fibrosis, 15.6% were found to have early changes suggestive of early pulmonary fibrosis, termed by the authors ‘Preclinical pulmonary fibrosis (PrePF)’. Those with PrePF were more likely to be older, male and have the MUC5B promoter variant

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rs35705950 and those with the MUC5B promoter variant had a greater extent of fibrosis on CT. ILA are patterns of density on CT scan which in some individuals represent the early stages of pulmonary fibrosis. Hobbs et al. performed a genome-wide association study across six different screening cohorts. They found that the MUC5B promoter variant rs35705950 was strongly associated with both ILA and subpleural ILA and an additional four genetic loci previously described in IPF were also significantly associated with ILA (DPP9, DSP, FAM13A and IVD).

**ACUTE EXACERBATIONS**

| KEY POINTS |
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| Thrombomodulin was initially considered to have been a potentially useful treatment for acute exacerbations of ILD—a prospective controlled trial in IPF was subsequently negative. |
| An elevated pulmonary artery:aorta ratio is a poor prognostic indicator for patient experiencing an acute exacerbation of ILD. |

Acute exacerbations are the most feared complication of fibrotic lung diseases, particularly IPF, with high levels of morbidity and mortality and no effective treatments. In a retrospective study, Hozumi et al. explored the effect of adding intravenous cyclophosphamide to high-dose corticosteroids in patients with IPF. The 90-day survival rate of the entire cohort was 64.7%, with no benefit gained through combination therapy over corticosteroid monotherapy. This suggests that despite the retrospective study, intravenous cyclophosphamide is unlikely to be an effective therapy for acute exacerbations of IPF.

Thrombomodulin is a key regulator of clotting and inflammation, so there is biological plausibility for this as a potential therapy for acute exacerbations of ILD where endothelial and epithelial cell dysfunction play an important role. Arai et al. prospectively studied recombinant human thrombomodulin in patients with acute exacerbations of idiopathic interstitial pneumonia, comparing outcomes with a retrospectively identified cohort of patients receiving conventional therapy. They found that recombinant human thrombomodulin was associated with an improved 90-day mortality from 66.7% to 47.5%. However, apparently impressive retrospective treatment data have failed to stand up to prospective scrutiny in past ILD evaluations. This has proven to be the case again in the subsequent placebo-controlled trial, where treatment with thrombomodulin did not confer a survival benefit in patients with acute exacerbation of IPF.

From these studies and others, it is well established that acute exacerbations are associated with a poor outcome. Kogo et al. use the ratio of the pulmonary artery to aorta to prognosticate and report that a ratio of ≥1 predicts a greater risk of mortality associated with acute exacerbations.

**THE PROGRESSIVE FIBROTIC PHENOTYPE AND ANTIFIBROTIC THERAPY BEYOND IPF**

**KEY POINTS**

- Antifibrotic therapy has therapeutic efficacy in fibrotic lung diseases beyond IPF.
- Patients should be assessed for the presence of the progressive fibrotic phenotype as antifibrotic therapy is effective in slowing the rate of lung function decline in this group.

Perhaps, the most exciting development of 2019 was the advent of antifibrotic therapy for indications beyond IPF. The SENSICS study revealed that nintedanib is an effective treatment in patients with systemic sclerosis-associated ILD, significantly attenuating the rate of lung function decline. 2019 was the year that the “progressive fibrotic phenotype” of ILD came to prominence with the publication of the seminal INBUILD study. Nintedanib was shown to be effective in slowing the rate of lung function decline in a range of progressively fibrotic lung diseases regardless of the underlying pattern of pulmonary fibrosis. Although not meeting its primary endpoint, pirfenidone was also shown to be effective in the treatment of unclassifiable progressive fibrotic lung diseases. These advances will change the outlook for patients with progressive fibrosis and as we enter the new decade, this area is likely to be a key focus of future research.

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Interstitial lung disease 2019

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