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Clinical networks for ILD: casting light on diffuse lung shadows

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The terms interstitial lung disease (ILD) and diffuse parenchymal lung disease are often used synonymously to refer to a disparate group of pulmonary disorders affecting the alveoli and/or respiratory bronchioles. Whilst many ILDs are rare disorders, as a group they account for ~15% of the workload for an average respiratory physician.[1]

Despite this, and unlike diseases of the airway or lung cancer, the approach to diagnosis and management of ILD has not yet embraced multidisciplinary or shared, pathway-driven models of care. This, together with a paucity of treatments and the aggressive nature of some ILDs, casts a dim light on an already murky field where definitions are changing and even the pathogenesis remains unclear.

It is noteworthy that in idiopathic pulmonary fibrosis (IPF), the most common ILD,[2] there have been no prospective randomised therapeutic trials undertaken in the UK for almost 20 years, and indeed there have only been two placebo-controlled randomised trials in this disease.[3 4] However, there is no justification for this nihilism. Rather, the recent publication of the new BTS Guideline on ILD, published by the BTS in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society, is a timely reminder of our current state of knowledge, or perhaps ignorance, regarding diagnosis and management of ILDs.[5] It is now appropriate to look beyond the Guideline and consider opportunities for improving care for patients with ILDs and in particular IPF. In the absence of promising new pharmaceuticals, such improvements can only be achieved through improvements to the organisation of care.

A study from Michigan examined the effect a multidisciplinary team (MDT), composed of specialist respiratory physicians, radiologists and pathologists, had on diagnosis of ILDs.[6] It was found that whilst the addition of pathological information had the greatest impact on an individual MDT member's diagnostic confidence, this was consolidated when the team was permitted to reach a consensus. This provided support for the notion that surgical lung biopsy is no longer the diagnostic gold standard for ILD; but rather the new standard is consensus decision making. The same authors have demonstrated that diagnostic advice provided by MDTs in specialist (academic) centres differed significantly from that derived from community respiratory physicians.[7] So, for the diagnosis of ILD, consensus opinions would appear to be more robust than those of individuals, and experts are more accurate than generalists.

As if to emphasise these conclusions, recent surveys examining clinical practice of respiratory physicians in both the UK and USA identified considerable variance in the way idiopathic interstitial pneumonias were diagnosed and treated.[8 9] Whilst the Michigan data require validation in other healthcare settings and with other idiopathic interstitial pneumonias, they nonetheless raise serious concerns about diagnostic accuracy and hence appropriateness of decision making as currently practised by respiratory physicians, frequently in isolation and without expert opinion.

If reorganisation of the care pathway is required, which model will best suit the needs of patients and their physicians?

Patients with cystic fibrosis have been managed by a partnership of local and specialist centres for >25 years, although proof that such a configuration of service actually improves outcome took a long time to emerge. However, it is now widely accepted that a 'shared care' model, combining best local management with access to specialist centres, prolongs survival and improves quality of life for people with this disease.[10] The Greater Manchester Lung Fibrosis Consortium was established in the early 1990s—an era that pre-dated digital image transfer and telemedicine. Its remit was to offer the facilities of a dedicated ILD clinic with a multidisciplinary approach to a wider area of North-West England and North Wales. It is almost 10 years since this group reported a retrospective study suggesting their model of care improved survival for patients with IPF under the age of 60.[11] An integrated regional and community services model has recently been described for the management of patients with lung cancer in the Greater Toronto area.[12] In this model, clinical resources were deployed to restructure services along patient-centred lines to devise a non-hierarchical clinical network with improved access to the specialist lung cancer team.

We can draw from these models to develop a paradigm of clinical networks which deliver a comprehensive package of high quality diagnostic services and patient information together with clear

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advice on best supportive care, possible treatments, the choice to enter a clinical trial, referral for lung transplantation and, ultimately, palliative care.[13 14]

Such networks will need to be non-hierarchical, multi-institutional and multidisciplinary. This would allow an integrated team of specialists including the local respiratory physician, the subspecialised respiratory physicians, radiologists and pathologists with an interest in ILD, plus specialist respiratory nurses and allied health professionals to deliver high quality care and improved opportunities for teaching whilst maximising the utilisation of (particularly human) resources, through the use of electronic image transfer and telemedicine. It should also permit the gathering of data to assess impact on patient outcomes as well as identifying deficiencies (predictably expertise in radiology and pathology) and variations in care which may need to be addressed. This type of configuration also has wider implications for the future collection of accurate epidemiological information as well as providing better opportunities to support basic "omics" research through the development of biobanks and identification of biomarkers on patients who will have been carefully phenotyped.

Guidelines for referral to a specialist centre within a network should not be proscriptive and should generally remain at the discretion of the secondary care physician. The recent section on 'Care Pathway for ILD' in the Guideline makes clear and helpful recommendations in this respect. In general, patient groups likely to benefit include:

- Patients in whom there is diagnostic uncertainty
- Patients who may be considered for transplantation
- Patients with rare or complex multisystem disease (eg, interstitial pneumonias associated with connective tissue disease) in whom extensive investigation will be required
- Patients with pulmonary sarcoidosis complicated by vascular disease such as pulmonary hypertension or pulmonary veno-occlusive disease
- Patients requesting a second opinion or seeking the opportunity to enter a clinical trial.[15]

It is also worth emphasising that referral to a Specialist Centre should not be synonymous with long-term follow-up by that Centre, and it is possible, indeed desirable, that the majority of referrals should return to local follow-up unless the Specialist Centre can provide ongoing benefits unavailable locally.

There are compelling reasons why the present climate offers the best opportunities for research into ILDs for over two decades. The last 5 years has seen the publication of an unprecedented number of therapeutic trials in patients with IPF. Whilst some treatments, such as interferon γ-1β, the antifibrotic agent pirfenidone, the endothelin-1 antagonist bosentan and the tumour necrosis factor α (TNFα) receptor antagonist etanercept, have failed to demonstrate any beneficial effects,[3 4 16 17] others offer real hope for the future. These include the antioxidant, *N*-acetyl cysteine[18] and warfarin.[19] The latter was investigated in a study from Japan, which compared the combined effects of warfarin and corticosteroids with corticosteroids alone and is the first to demonstrate improved survival from a pharmacological intervention in IPF. There are also interesting preliminary data on the possible benefits of co-trimoxazole on survival and thalidomide on cough.[20 21]

Such findings are encouraging and, taken together with the accumulating evidence of an association between gastro-oesophageal reflux and IPF,[22 23] should stimulate a study of antireflux treatment. The recent call for a formal study of pulmonary rehabilitation in IPF[24] and the urgency to establish the palliative care needs of these patients also highlight the requirement for a networked approach to care, presenting patients with opportunities to participate in trials and in turn facilitating recruitment.

There have been considerable changes to the way clinical research is organised in the UK over the last 2 years, with the development of the National Institute for Health Research. The 25 newly emerging comprehensive Local Clinical Research Networks in England and their equivalents in Scotland, Wales and Northern Ireland will provide an infrastructure within which it should be possible to undertake large clinical trials, assuming that Respiratory Physicians are prepared to work together and funding can be obtained. It would greatly facilitate such endeavours if evolving clinical networks for patients with ILD could be superimposed on these newly establishing Local Clinical Research Networks. Once the infrastructure for delivery of care is in place it must be recognised that funding is available for such research. The Medical Research Council, appreciating that its portfolio of grants for respiratory research is small relative to the mortality and morbidity caused by respiratory disease in the UK, is currently calling for grant applications on mechanisms of chronic inflammatory lung diseases including ILDs, as a priority area in respiratory research.

The recently published BTS/TSANZ/ITS Guideline provides a stepping stone to the reorganisation of care for patients with ILDs, particularly IPF. A shared-care model coordinated through networks potentially offers patients and their physicians access to expert and consensus opinion, opportunities for trial participation with improved accumulation of data. In the absence of any immediate pharmaceutical promise, gains in quality of life from improvements in the pathway of care are likely to be immeasurably greater and much appreciated by our patients.

Competing interests NKH and MW were members of the British Thoracic Society Interstitial Lung Disease Guideline Group. NJ was Chair of the British Thoracic Society Standards of Care Committee.

Provenance and peer review Commissioned; not externally peer reviewed.

Thorax 2010;**65**:466–468.
doi:10.1136/thx.2009.122135

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New options for bronchodilator treatment in COPD

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Although the definition of chronic obstructive pulmonary disease (COPD) is now more elaborate than in the past,[1] the presence of persistent airflow obstruction is still a cardinal feature of this illness, and improved lung emptying, usually expressed as an increase in forced expiratory volume in 1 s (FEV_1), is a key goal of chronic disease management. This can be achieved in several ways, ranging from lung volume reduction surgery[2] to anti-inflammatory treatments such as inhaled corticosteroids or phosphodiesterase type IV (PDE IV) inhibition[3 4] even on a background of existing inhaled bronchodilators.[5] However, for most patients, inhaled bronchodilator drugs remain the cornerstone of drug treatment for this disease. Historically, shorter acting bronchodilators, and especially the antimuscarinic agent ipratropium, were the mainstay of treatment. Although these drugs were initially recommended for use twice or three times per day, later data based on the time course of FEV_1 change showed that their effects only lasted for 4–6 h at best. Combining β-agonists with antimuscarinic drugs increased the peak values for FEV_1 change without greatly changing this limited period of activity.[6] The development of long-acting inhaled β-agonists, such as salmeterol[7] and formoterol,[8] showed that it was possible to improve lung function and health status, although their effects on exacerbation frequency were less impressive.[9 10] When the first truly 24 h bronchodilator drug, the antimuscarinic agent tiotropium, became available, it soon became obvious that this drug could produce significant improvements in morning FEV_1[11] together with better health status and fewer exacerbations than had proved possible with regular ipratropium treatment,[12] findings shown to occur on a background of multiple other treatments in the recent UPLIFT trial.[13] Previous randomised direct comparisons between tiotropium and salmeterol suggested that lung function tended to be better with tiotropium treatment, with non-significant differences in health status and exacerbations tending to favour the antimuscarinic drug.[14] Whether these differences represent an important clinical effect or, specifically, a more favourable response resulting from blockade of muscarinic receptors remained unclear, particularly since the duration of action of the drugs was quite different.

Recently, the first once-daily inhaled β-agonist indacaterol has been tested in healthy subjects, patients with asthma and subjects with COPD. Dose-ranging trials have been reported in patients with COPD which showed benefits at some doses comparable with those seen in a tiotropium comparator group.[15] In this issue of *Thorax* (***see page 473***), Dahl and colleagues (the same first author who reported the early beneficial effects or formoterol 8 years ago) present the results of a large randomised prospective double-blind placebo-controlled study that compares two doses of indacaterol (300 and 600 mg) given once daily with formoterol 12 μg twice daily and placebo in 1732 stable patients with COPD.[16] The primary outcome was the change in trough FEV_1—that is, the value before the morning dose of medication, which was 170 ml greater than placebo when indacaterol was given and 100 ml greater than formoterol at 12 weeks into the study. Both these comparisons were statistically significant and were supported by significant improvements in other prespecified pulmonary function outcomes in favour of indacaterol. These changes were maintained throughout the study and were independent of concomitant medication including inhaled corticosteroids. Clinically, the patients receiving the inhaled β-agonists fared better, with more of them completing the 1 year trial. All three β-agonist regimes were associated with better clinical outcomes such as reductions in the exacerbation rate, the total St Georges Respiratory Questionnaire (SGRQ) score and in reported dyspnoea relative to placebo-treated patients. Numerically, greater improvements in SGRQ and dyspnoea scores (but not exacerbation rate) were observed when compared with formoterol. However, these differences in clinical outcomes were not statistically significant when directly compared. Overall, there were no worrying safety concerns with the new drug and no excess episodes of tachycardia or evidence of ECG changes in the indacaterol-treated patients. However, tremor was reported slightly more often in patients receiving the higher dose of indacaterol, whilst transient cough after using the inhaled treatment was an issue in almost 1 in 5 of indacaterol-treated participants. Although

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