Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society

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1. INTRODUCTION

1.1 An overview of the ILD guideline

Since the publication of the first BTS guidelines for diffuse lung disease nearly 10 years ago,[1] the specialty has seen considerable change. The early discussions of the Guideline Group centred upon whether the revised document might consist of the 1999 document with minor adaptations. However, it was considered that too much change had taken place in the intervening years to justify a simple editorial approach. The last decade had seen the development of a new consensus terminology for the idiopathic interstitial pneumonias (IIP)[2] stimulated, in part, by the identification of non-specific interstitial pneumonia (NSIP) as a discrete histological pattern with increasingly recognised clinical correlates.[3] The better prognosis seen in fibrotic NSIP than in idiopathic pulmonary fibrosis (IPF)[4 5] fuelled a more intense approach to diagnosis in cases of suspected IPF. This in turn has led to a radical change in accepted diagnostic gold standards, which have become increasingly multidisciplinary and dependent equally upon the skills of pathologists, radiologists and clinicians.[6] NSIP, as a new entity, has posed particular difficulties. With more detailed studies of outcome specific to individual IIPs, especially IPF and fibrotic NSIP, the prognostic weighting given to pulmonary function impairment has been refined, especially with regard to longitudinal functional trends.[7] Most important, with the standardisation of terminology, it became possible to recruit patients into multicentre treatment studies.[8–10] With regard to IPF in particular, the last 3 years have seen more studies of treatment than in the previous history of the speciality, yet there is no universally accepted "best current treatment".

1.2 Methodology for constructing guidelines and making recommendations

The overall process for generating BTS guidelines has been addressed in numerous recently published documents (available at http://www.brit-thoracic.org.uk/guidelines.html). The methodology applied herein is broadly similar and is not therefore described in detail. However, there are specific aspects in the process of writing the ILD guidelines that merit explanation.

1. These are the first BTS guidelines to have been written in conjunction with other international bodies, namely the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. It is hoped that, by broadening the collaborative base, the quality and credibility of the guidelines has been enhanced and the document will reach a wider readership. Inevitably certain aspects of the guidelines—for example, delivery of specific healthcare resources—are written with the UK in mind, but may be equally applicable internationally.
2. At a very early stage the Guideline Committee canvassed the views of colleagues (chest physicians, radiologists and pathologists) via focus groups. The aim was to determine the spread of opinions with regard to the ideal content of a new guideline and specifically on the more controversial aspects of ILD including nomenclature, delivery of care and optimum management in the absence of evidence.
3. The diagnosis and management of common interstitial lung diseases—but not rare conditions—are comprehensively addressed in these guidelines. Conditions such as Langerhan's cell histiocytosis (LAH), lymphangioleiomoyomatosis (LAM), pulmonary vasculitis and alveolar proteinosis are being addressed by the BTS-endorsed British Orphan Lung Disease project (http://www.brit-thoracic.org.uk/rare_lung_diseases.html)
4. A comprehensive search of major databases (Medline, PubMed, EmBase and CINAHL) was performed, focusing principally on peer-reviewed articles generated since the publication of the previous guidelines in 1999. Where possible, searches were performed in response to a specific question (eg, "What is the evidence that pulmonary rehabilitation is beneficial in ILD?").
5. The levels of evidence and the grading of recommendations are summarised in table 1. The grading of recommendations A–D will be very familiar to the reader. However, in the course of writing the guidelines it became apparent that there are many areas of ILD

Table 1 Grading system for recommendations[11]

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews or RCTs or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (eg, case reports, case series)
4	Expert opinion
Grades of recommendations	
A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+

management for which there is, at best, sparse data upon which to base recommendations. This is highlighted where appropriate and should act as a spur for more research. In other areas—such as the management of acute ILD in the intensive care unit or the management of fibrotic NSIP—it is clear that controlled clinical trials may never be feasible. The Committee, based on the discussions with focus groups, felt compelled to offer some form of guidance in those areas that impact regularly on clinical practice, are immensely challenging, but for which there is little or no evidence base. Also, in the course of guideline development, there has been a discussion in the literature on the usefulness of guideline recommendations for everyday practice.[11] Treatment decisions involve a trade-off between the potential benefits and risks, and these decisions need to be individualised on a case-by-case basis after discussion with the patient. This model of recommendations is embodied in the GRADE system[12] in which the quality of evidence is qualified by strength of recommendation (either weak or strong). This allows, for example, a strong recommendation to be made even if the evidence base is weak and visa versa. The Committee felt that this resonated strongly with several management areas in the guideline, best exemplified in the management of IPF. Here there are examples of discordance between the strength of recommendation and level of evidence; interferon-γ (IFNγ)-1b is not recommended for the treatment of IPF (pending further data) although there is a published meta-analysis suggesting survival benefit. For this reason, some of the statements for the "management and treatment of IPF" are qualified where appropriate with a "weak" or "strong" recommendation.

6. There are some proposed recommendations in the guideline that were subject to intense debate within the Committee and upon which "consensus" could not be achieved. Again, this is exemplified in the management of IPF with specific drugs and, in such cases, a final statement was derived by anonymous voting within the Committee, removing the exercise of undue influence by any single committee member.

In the remainder of the introduction the recent key contentious issues in ILD are considered in turn. A constant theme that permeates through the entire guideline is that regional centres are now required to effectively manage ILD, a strong recommendation reached unanimously by the Guideline Group.

1.3 Terminology of interstitial lung disease

The term "interstitial lung disease" is synonymous with "diffuse parenchymal lung disease" and, while the latter was used in the 1999 BTS guideline, a decision was made to adopt interstitial lung disease in the current document, consistent with other international guidelines. A more difficult issue arose with the terminology embracing subgroups of ILD. Traditionally, in the UK, the term "cryptogenic fibrosing alveolitis" (CFA) corresponds to a characteristic clinical presentation seen typically in IPF but common also to many patients with other idiopathic interstitial pneumonias and some cases of hypersensitivity pneumonitis. The use of "CFA" as an umbrella term in the 1999 BTS guideline reflected the fact that it was not then clear that distinctions between IIP subsets were of any true clinical value other than the very crude distinction between predominantly inflammatory and predominantly fibrotic disease; in short, the historical distinction between desquamative interstitial pneumonia (DIP) and usual interstitial pneumonia (UIP).

However, within 2 years of the publication of the first BTS guidelines, a new consensus classification had been proposed by a joint American Thoracic Society (ATS) and European Respiratory Society (ERS) committee.[2] The new ATS/ERS terminology captured outcome differences in a number of studies comparing subsets of patients with IIP.[2–4 13–18] The historical outcome distinctions between predominantly fibrotic disease and inflammatory disorders (the latter now expanded to include cryptogenic organising pneumonia (COP), lymphocytic interstitial pneumonia (LIP), cellular NSIP, respiratory bronchiolitis with associated interstitial lung disease (RBILD) and desquamative interstitial pneumonia (DIP)) were exactly as reported previously. However, the important new "outcome subgroup" to emerge was the entity of fibrotic NSIP. These patients made up 20–35% of patients previously diagnosed as IPF or CFA and their long-term survival was substantially better than that seen with a histological pattern of UIP. On this basis, the core entity of IPF was redefined: characteristic clinical features were required in association with a histological pattern of UIP at surgical biopsy or a high resolution CT (HRCT) pattern typical of UIP. In addition, the absence of a lymphocytosis on bronchoalveolar lavage (BAL) or the absence of features of an alternative diagnosis on transbronchial biopsy were required in patients not undergoing a surgical biopsy (table 2).[19] These non-biopsy ATS/ERS criteria remain the internationally accepted standard by which to make a diagnosis of IPF in the absence of a surgical lung biopsy. However, for pragmatic reasons, many elderly patients, those with significant co-morbidity and patients seen outside referral centres often do not undergo transbronchial lung biopsy or BAL. The role of BAL and transbronchial biopsy is thus currently under review.

The ATS/ERS consensus statement explicitly stated that CFA and IPF were synonymous terms.[2] The Committee therefore faced a choice between adopting the ATS/ERS terminology and persisting with the use of CFA as an umbrella term as used in the first BTS guidelines. In an initial consultative process in

Table 2 ATS/ERS criteria for diagnosis of idiopathic pulmonary fibrosis (IPF) in the absence of surgical lung biopsy*†

Major criteria	Minor criteria
► Exclusion of other known causes of ILD such as certain drug toxicities, environmental exposures and connective tissue diseases	► Age >50 years
► Abnormal pulmonary function studies that include evidence of restriction (reduced VC, often with an increased FEV_1/FVC ratio) and impaired gas exchange (increased $P(A–a)O_2$, decreased Pa_{O_2} with rest or exercise or decreased T_{LCO})	► Bibasilar, inspiratory crackles (dry or "Velcro"-type in quality)
► Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans	► Insidious onset of otherwise unexplained dyspnoea on exertion
► Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis‡	► Duration of illness >3 months

BAL, bronchoalveolar lavage; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high resolution computed tomography; ILD, interstitial lung disease; $P(A–a)O_2$, difference between alveolar and arterial pressure; Pa_{O_2}, arterial oxygen tension; T_{LCO}, carbon monoxide transfer factor; VC, vital capacity.
*Modified from American Thoracic Society/European Respiratory Society recommendations.[2]
†In the immunocompetent adult the presence of all of the major diagnostic criteria as well as at least three of the four minor criteria increases the likelihood of a correct clinical diagnosis of IPF.
‡The requirement for transbronchial lung biopsy/bronchoalveolar lavage within the diagnostic criteria for IPF is currently under review.

which over 35 chest physicians were canvassed for their opinions, the majority favoured the adoption of the ATS/ERS classification with a significant minority (at least 20–25%) stating a preference for the historical UK definition of CFA. It is worth summarising the rationales for these differing points of view.

Those in favour of the new classification tended to stress the advantages of a true international consensus on terminology that had previously been contentious; workers in diffuse lung disease now understand each other better than previously. Furthermore, international agreement on the definition of IPF was thought by some to have catalysed recruitment into large multinational treatment studies. However, the most consistent argument in favour of the new classification was the prognostic separation between IPF, as redefined, and other forms of fibrosing lung disease. A new syndrome or classification can be justified if it provides added prognostic value to previous terminology; in essence, diagnosis informs prognosis. The diagnostic separation between IPF and fibrotic NSIP in patients presenting with a clinical picture of "CFA" provides a prognostic distinction between 5-year survival rates of 10–15% and >50%, respectively.

Those in favour of retaining the umbrella term "CFA" argued, for the most part, from clinical pragmatism. For many experienced chest physicians the clinical entity of "CFA" was, and is, a key part of their personal diagnostic algorithms—a highly useful starting point in distinguishing between idiopathic interstitial pneumonias and other diffuse lung processes, especially sarcoidosis. Some also questioned whether fibrotic NSIP was sufficiently prevalent in older non-referred patients with a clinical presentation of "CFA" to be a clinically useful diagnosis, although the actual prevalence of fibrotic NSIP is not known. Furthermore, epidemiological work demanded a clinical definition of "CFA" if the true spectrum of disease was to be studied. Requirements that full ATS/ERS criteria be met for a diagnosis of IPF, including bronchoscopic criteria, effectively excludes the elderly, those with major co-morbidity and many patients not studied at referral centres. This is likely to remain true to some extent in epidemiological studies in the foreseeable future. Although HRCT scanning may eventually be used to validate diagnostic labels in patient subsets, this has yet to be attempted despite the widespread availability of HRCT for 15 years or more.

While cognisant of the debate within the UK, the current guideline has adopted the ATS/ERS classification, and perhaps the most compelling argument for doing so is that the ATS/ERS system has now been almost universally adopted around the world. However, the term "CFA" is recognised internationally as being synonymous with IPF as defined in the ATS/ERS classification; the continued use of the term "CFA" in its historical sense would have flown in the face of a growing international consensus and would have invalidated the current guidelines in many eyes. Other considerations aside, the use of the term "CFA" to describe two separate entities could not have been sustained on the grounds of common sense. Consequently, the ATS/ERS system has been adopted throughout the guidelines, except in the section on epidemiology in which more inclusive terminology was required: solely for epidemiological statements, the term "CFA clinical syndrome" was sanctioned.[20]

1.4 Diagnostic standards in interstitial lung disease

The recent change in classification has led to a reappraisal of the way in which diagnoses are, and should be, reached in clinical practice. In the last century it was widely accepted that the diagnostic "gold standard" for ILD was a histological diagnosis made on a surgical biopsy. Clinical and radiological diagnostic information were seen by many as deeply unsatisfactory surrogates for histology.

However, the limitations of diagnoses relying solely on histology are increasingly recognised. In many patients the disease is too advanced or co-morbidity too severe to allow a surgical biopsy to be performed. The procedure is highly unattractive to patients and physicians alike in the elderly. Furthermore, as with all other diagnostic tests, there is significant interobserver variation. In a study undertaken by the UK histopathological panel[21] the level of agreement on a first choice diagnosis was at the lower limit of what would be accepted as clinically useful. In many cases, histological appearances were "intermediate" (ie, features were compatible with two or more diagnoses). It should be stressed that interobserver diagnostic variation is equally problematic between experienced HRCT radiologists, particularly in more difficult cases referred for surgical biopsy. A further confounding factor in the histological evaluation of lung biopsies is the problem of "sampling error": the possibility that a biopsy specimen was taken from an area not representative of the predominant disease process. This problem applies particularly to the distinction between UIP and NSIP and is discussed in Sections 7.3 and 10.5.

No test can be regarded as a diagnostic "gold standard" if it (1) cannot be performed in a large proportion of patients; (2) is subject to major interobserver variation; and (3) provides non-representative information in a significant minority of cases. However, there are additional grounds for questioning the assertion that all patients with IIP should undergo a surgical biopsy whenever possible. As discussed in the body of the guidelines, a diagnosis of IPF can be reasonably based upon typical HRCT appearances and a compatible clinical setting in approximately 70% of cases and, in this context, a surgical biopsy adds no useful information.[5 6 22–24] However, a surgical biopsy is often invaluable in the remaining patients with less

typical radiological features. With further experience it is likely that the repertoire of "classical" clinicoradiological profiles that obviate diagnostic surgical biopsy will be expanded. For example, it is increasingly accepted that a diagnosis of RBILD is secure when based upon typical HRCT findings in a current smoker, especially when BAL findings are also compatible.[25]

Surgical biopsy may also be misleading if considered in isolation and without the integration of clinical and radiological information. In hypersensitivity pneumonitis (HP) it is now known that the typical histological appearances are absent in a significant minority of cases, with both UIP- and NSIP-type patterns of disease encountered.[3 26 27] UIP may occur in connective tissue disease but the outcome, in contrast to IPF, is not uniformly poor.[28 29] Thus, it is increasingly accepted that diagnosis of diffuse lung disease requires a multidisciplinary approach with the reconciliation of clinical, radiological and histological information. Such an approach was first formally evaluated in a study of over 50 patients with suspected IPF involving leading clinicians, radiologists and pathologists.[6] Key conclusions relate to comparisons between clinicoradiological diagnoses made by clinicians and radiologists, histological diagnoses made by pathologists and final diagnoses reached after joint discussion of all information by all participants. In patients without typical clinical and HRCT features of IPF, the clinicoradiological diagnosis changed approximately half the time and the histological diagnosis changed in 25% of cases compared with the final consensus diagnosis. Thus, while histological information was more influential, no single mode of evaluation was uniformly pre-eminent. This study accords with widespread anecdotal experience that, when clinical, HRCT and histological information are examined together, the final diagnosis is often a matter of negotiation and consensus formation with a frequent need to reconcile apparently contradictory findings.

The multidisciplinary approach is now considered the "gold standard" for diagnosing diffuse lung disease. This has profound implications for routine clinical practice. Historically in the UK and in other healthcare systems represented in these BTS guidelines, diffuse lung disease has largely been managed locally with occasional referral of difficult cases to tertiary centres. The provision of a multidisciplinary approach will require an expansion of expert centres in diffuse lung disease with the fostering of regional expertise in clinical, HRCT and histopathological skills alike, as discussed later.

1.5 The problem of NSIP

A good deal of diagnostic difficulty in the last few years has related to the entity of NSIP, currently identified in the ATS/ERS classification as a single disorder. Herein lies the problem. A confident diagnosis of idiopathic NSIP requires a surgical biopsy. However, based upon multidisciplinary evaluation and, to some extent, upon genetic fingerprinting,[30 31] it is increasingly recognised that the term "NSIP" covers a number of separate clinicoradiological entities expressed as a common histological pattern of NSIP. Hence, without a multidisciplinary approach, little sense can be made of NSIP as a single disorder. A careful perusal of clinical and HRCT statements on NSIP reveals a true diversity of clinicoradiological profiles associated with a histological diagnosis of NSIP.[4 5 7 13–16 18 30 32–34]

Although it is tempting to conclude that NSIP is not a true entity but merely a "waste-basket" term to cover unclassifiable histological appearances, there are now sufficient data to justify the concept of several clinicoradiological syndromes of NSIP; these include NSIP with an IPF-like profile or overlap (NSIP/IPF), NSIP with an organising pneumonia profile (NSIP/OP) and NSIP with a hypersensitivity profile (NSIP/HP). This concept has been broadly recognised by an ATS/ERS expert group which has yet to submit a final report and, for this reason, no final statement of the subclassification of idiopathic NSIP can be made in current guidelines, including the definition of a core entity for NSIP. Nonetheless, a framework for managing NSIP in the current era is required. Conceptualising NSIP as most closely resembling IPF, COP or HP may help to rationalise treatment, but this can only be achieved in a multidisciplinary forum. This integrated approach should facilitate realistic therapeutic goals and treatment strategies to be set in individual cases. As such, a dogmatic guideline-centred approach, laying down a single treatment strategy for NSIP, will inevitably prove to be too inflexible and will fail to meet the needs of many patients. Guidance on the management of NSIP, based on categorising cases with a histological pattern of NSIP into NSIP/IPF, NSIP/OP and NSIP/HP profiles, is provided in Section 14.

1.6 Staging the severity and progression of disease

Evaluation of the chest radiograph provides, at best, a crude approximation of disease extent in ILD. Pulmonary function tests usually reflect the severity of disease more accurately than chest radiography. However, the wide variation in the normal range of pulmonary function tests (generally ranging from 80% to 120% of values predicted from age, sex, race and height) is a major constraint in the staging of mild disease. For example, apparently minor impairment in levels of forced vital capacity (FVC) to 75% of predicted can represent anything from a 5% to 45% decline from premorbid values. Moreover, pulmonary function tests are readily confounded by concurrent disease processes. The most widely studied example is the frequent admixture of emphysema and fibrosis seen in up to 40% of patients with IPF in some series, and producing a spurious preservation in spirometric and plethysmographic lung volumes but a disproportionate reduction in gas transfer.[35 36] In the connective tissue diseases a variety of abnormal processes, including interstitial, pulmonary vascular, pleural and muscle disease, commonly coexist but, without an independent means of evaluating the morphological extent of each, clinicians face difficulty in understanding and deconstructing patterns of lung function impairment.

The advent and application of HRCT scanning has provided clinicians with a sensitive means of staging disease severity in diffuse lung diseases but has its own limitations. The formal scoring of disease extent applied in clinical research is not "user friendly" in routine practice. The clinical significance of subtle HRCT abnormalities is often uncertain, especially in patients with connective tissue disease and minor lung function impairment. In other cases it is difficult to distinguish between normal HRCT appearances and subtle diffuse ground glass attenuation. In all these scenarios pulmonary function tests complement HRCT, helping the clinician to discount trivial disease on HRCT scans but to recognise—especially with estimation of gas transfer—that HRCT may underestimate widespread and clinically important pulmonary infiltration. Much the same principle applies to the interpretation of serial changes in pulmonary function tests. The prognostic value of short-term serial functional change has been widely investigated in IPF and fibrotic NSIP.[7 37–40] However, serial data need to be integrated with baseline clinical, HRCT and, when applicable, histological information in order to achieve the most accurate estimation of the likely long-term outcome. Thus, the reconciliation of HRCT findings and pulmonary function tests

is an important part of the multidisciplinary process and repetition of the multidisciplinary process, integrating longitudinal observations, may be as informative as initial evaluation.

1.7 Advances in the treatment of diffuse lung disease

Historically there has been a paucity of therapeutic clinical trials for ILDs and, in particular, IPF. However, recent studies, although inconclusive, have indicated possible therapeutic benefits in IPF with the use of IFNγ-1b,[41] pirfenidone,[8] bosentan (unpublished at the time of writing), warfarin[42] and, more convincingly, with the use of N-acetylcysteine in combination with low dose prednisolone and azathioprine.[9] These and other data are reviewed in detail later in this document. However, three points deserve particular emphasis.

First, these guidelines were written during a time of rapid change, making it difficult to distil recommendations on best current treatment. The role of antioxidant therapy is a good example of this problem. There was a wide range of strongly held views within the group, ranging from scepticism to optimism and reflecting the current range of views in editorial statements.[43 44] The amicable reconciliation of these differences was greatly helped by an anonymised vote on key recommendations.

Second, at present there is no specific therapy that can be considered "best current treatment" for IPF, the most prevalent of the chronic fibrosing lung diseases and that with the poorest prognosis. However, confirmation and extension of current data on, for example, antioxidant therapy, perhaps emerging from a large imminent study in the USA, might make it increasingly difficult to undertake placebo controlled studies in the face of increasing acceptance of a "best current regimen". The Guideline Committee felt that that point has not yet been reached, but the implications are potentially profound. IPF has an outcome similar to lung cancer and is more prevalent than many of the less frequent malignancies. If a real difference in outcome can be achieved with treatment, there is likely to be an increasing perception that the disease should be managed in specialist clinics, exactly as has occurred in the oncological world. If more than one beneficial treatment emerges, best management may require therapies to be combined to achieve therapeutic synergism, and this also is likely to require specialist expertise.

Finally, clinicians currently face a therapeutic division between IPF—in which the pathogenetic role of inflammation has been questioned and an epithelial-fibrotic model is increasingly favoured[45]—and other fibrosing lung diseases in which inflammation is believed to precede and induce fibrosis. High-dose corticosteroid therapy, now considered to be contraindicated in IPF, may have an important role in some of the other diseases presenting with the traditional clinical picture of "CFA clinical syndrome" (discussed in Section 13.2). The optimal use of traditional therapies therefore requires accurate multidisciplinary diagnosis.

1.8 Structure of healthcare delivery for interstitial lung disease

The importance of multidisciplinary evaluation by expert clinicians, radiologists and pathologists is a constant theme throughout this document. In particular, multidisciplinary evaluation allows a more accurate application of disease classification, diagnosis, staging, prognosis and a more informed application of therapeutic advances. Historically, most patients with ILD have been managed by respiratory physicians in general respiratory clinics. Within this model, each physician looks after relatively few patients with ILD and accrues clinical experience only slowly. The accumulation of clinical, radiological and histopathological expertise will require the development of designated ILD clinics using a model similar to that in cystic fibrosis or lung cancer. The multidisciplinary team (MDT) model requires that a clinic dedicated to patients with ILD should be led by a consultant chest physician with a specialist interest in ILD and supported by a regular local multidisciplinary meeting with a consultant radiologist and, ideally, a consultant pathologist with an interest in ILD. In most cases the team would work closely with a thoracic surgeon and with local palliative care, rheumatology and primary care services using models reminiscent of those developed for lung cancer and cystic fibrosis. Such a system should allow equality of access to common standards of high quality care while allowing local chest physicians to retain ownership of day-to-day patient management. An essential requirement would be close collaboration between local and specialist centres as well as rapid and effective communication (including image transfer) between the two.

It is envisaged that some regional clinics will evolve into specialist (tertiary) centres, coordinating regional clinics and collaborating with other centres to form a national ILD network able to deliver the large-scale studies urgently required in this field. Streamlining of the referral, diagnostic and management pathway of patients with ILD may be enhanced through the development of regional "do once and share" programmes, a process already underway in many parts of the UK for a number of clinical conditions (www.connectingforhealth.nhs.uk/engagement/clinical/doas).

At present, few studies have addressed the utility of the multidisciplinary regional clinic model of care in ILD.[6 46] There is therefore an urgent need to demonstrate the value of this model to patients and to commissioners and those involved in research and teaching. The precise nature and number of regional ILD clinics is likely to be dictated by local needs. However, the observation that there are a growing number of regional ILD clinics already established in the UK bears testimony to their perceived need. Recommendations for referral to regional ILD clinics are provided in Section 11.

2. SUMMARY OF RECOMMENDATIONS FOR ILD

History and clinical examination in ILD

- Detailed history taking is required to identify respiratory risk factors both past and present. [D]

Lung function testing in ILD

- All patients with ILD should have resting spirometric and gas transfer measurement at presentation, which together provide a reasonable measure of disease severity. [C]
- In idiopathic pulmonary fibrosis (IPF) and fibrotic non-specific interstitial pneumonia (NSIP), carbon monoxide transfer factor (TLCO) levels at presentation are a more reliable guide to outcome than other resting lung function variables. A TLCO level of less than 40% is indicative of advanced disease in fibrotic idiopathic interstitial pneumonia (IIP). [B]
- In IPF a fall from baseline of ≥10% in forced vital capacity (FVC) or ≥15% in TLCO in the first 6–12 months identifies patients with a much higher mortality. [B]
- Desaturation during the 6 minute walk test at presentation is a stronger prognostic determinant in IPF than resting lung

function. [C]. However, additional studies are required to define the role of exercise testing in routine staging and follow-up both in IPF and other ILDs.

- Maximal exercise data probably add little to resting lung function in assessing the severity of ILD but are sometimes useful, when normal, in excluding clinically significant diffuse lung disease. [C]

Chest radiography and HRCT

- Radiologists with an interest in thoracic imaging and respiratory physicians should meet regularly to evaluate imaging in patients with ILD. [D]
- In patients for whom the diagnosis is uncertain after chest radiography and clinical assessment, HRCT scanning is the next investigation of choice. [C]
- HRCT is valuable in detecting ILD in patients with a normal chest radiograph. [B]
- In the appropriate clinical setting, appearances on the HRCT scan may be sufficiently characteristic to preclude the need for BAL or lung biopsy and histopathological confirmation. [B]
- Radiologists involved with determining the protocol and interpretation of HRCT scans should have expertise in the technique, be responsible for quality assurance and ensure that an appropriate radiation dose protocol is used. At least one radiologist in any department should have a declared interest and be trained in chest radiology and HRCT. [D]
- Consideration should be given to establishing a reference panel of radiologists with particular expertise in HRCT. [D]

Initial blood and other tests

- Initial tests in all cases of suspected ILD should include a urine dipstick, full differential blood cell count, serum urea, electrolytes and creatinine, and liver function tests. Other tests are largely dependent upon clinical context. [D]
- The serum angiotensin-converting enzyme (ACE) level has only a limited role in diagnosis and does not contribute to monitoring patients with pulmonary sarcoidosis when added to serial lung function and imaging. [D]

Bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB)

- BAL or TBLB, when required, should be performed before the initiation of treatment. [D]
- BAL should be considered in all patients with suspected infection, malignancy and some rare ILDs. In such cases, BAL may be diagnostic. [C]
- BAL is not required as a diagnostic tool in patients with clinical features and HRCT appearances typical of IPF. [C]
- In patients for whom the diagnosis is uncertain after clinical assessment and HRCT scanning, typical BAL cellular profiles may allow a diagnosis of hypersensitivity pneumonitis or sarcoidosis to be made with greater confidence. [C]
- In cases in which the diagnosis is uncertain and BAL is considered, the procedure should be performed in a regional centre with technical expertise in the procedure and the analysis of the BAL samples. [D]
- BAL should be performed in all patients undergoing TBLB. [D]
- TBLB is the initial procedure of choice in those patients likely to have ILDs in which small samples may be diagnostic, particularly if the disease has a tendency for bronchocentric involvement. HRCT should be used to guide the biopsy site. [D]
- Four to six TBLB specimens should be taken. [D]
- In suspected sarcoidosis, endobronchial biopsy samples in addition to TBLB are recommended since they are frequently positive, are associated with low morbidity and increase the diagnostic yield. [C]
- TBLB is not recommended as the initial biopsy option in cases of suspected IPF and is unreliable in the diagnosis of rare lung disease (other than alveolar proteinosis). [C]

Surgical lung biopsy in ILD

- Surgical lung biopsy, when required, should be performed before the initiation of treatment. [D]
- A confident pathological diagnosis of IPF or the other interstitial pneumonias can only be made if a surgical lung biopsy is obtained. [C]
- A confident clinical diagnosis of IPF can be reliably made in the presence of characteristic HRCT and clinical findings. [C]
- If a surgical biopsy is performed in cases of suspected interstitial pneumonia, more than one biopsy specimen must be taken from more than one site, preferably from different lobes. [C]
- Multiple multilobe lung biopsies are technically easier by video-assisted thoracoscopy (VATS) than by open lung biopsy [D]. VATS is also associated with less early postoperative pain than open lung biopsy. [B]
- It is recommended that the precise biopsy sites are based on HRCT appearances [D]. In patients with suspected IIP, areas of intermediate abnormality or comparatively normal lung adjacent to areas of established honeycombing should be targeted with the specific aim of identifying UIP if present. [D]

Care pathway and general management strategies for ILD

- All patients with ILD should have access to a multidisciplinary team based in a regional centre with expertise in ILD. [C]
- Referral to a regional ILD clinic should be made if there are perceived difficulties in diagnosis and/or management, but a tailored shared care model is advocated. [D]
- Patients with ILD who are current smokers should receive opportunistic smoking cessation advice from healthcare professionals and this advice should be recorded in the clinical notes. Current smokers should be offered specialist support and nicotine replacement therapy or bupropion on NHS prescription. [B]
- Patients with ILD should have access to a local pulmonary rehabilitation programme. [C]

Management and treatment of IPF

- Best supportive care should be considered a specific and important treatment strategy in all patients with IPF. It is a proactive approach to symptomatic treatment and may include oxygen therapy, pulmonary rehabilitation, opiates, antireflux therapy, withdrawal of steroids and other immunosuppressants, early recognition of terminal decline and liaison with palliative care specialists. [D]
- To date there is no therapy proven to improve survival or otherwise significantly modify the clinical course of IPF. As such, it is recommended that all patients be considered for

recruitment to high quality clinical trials of therapy and/or for lung transplantation if appropriate. [C]

- High-dose steroid monotherapy (0.5–1 mg/kg) does not improve survival or otherwise modify the clinical course of the disease and is associated with significant morbidity. It is therefore strongly recommended that high-dose steroids not be used to treat patients with IPF. [C]
- Prednisolone (tapering from 0.5 mg/day to 10–20 mg/day) with azathioprine (2 mg/kg, maximum150 mg/day) and N-acetylcysteine (NAC, 600 mg three times a day) has been shown to have a significantly better treatment effect than prednisolone and azathioprine alone. However, further studies are required and this regime currently carries a weak recommendation [C]. Prednisolone and azathioprine without NAC is not recommended.
- Variations from the above regimens, such as lower dose steroids (20 mg or less) or omission of azathioprine are very likely to be better tolerated but are entirely without evidence base. Appropriate counselling should be given to all patients started on specific regimes.
- Treatment, if started, could be equally reasonably initiated at presentation or following objective evidence of disease progression or in moderate/severe disease.

Referral for lung transplantation in patients with IPF

The following apply only to patients who fulfil established selection criteria for transplant, thus generally excluding those over the age of 65 years and/or those with significant co-morbidity.

- Referral to a transplant centre should be made if the disease is advanced (T_{LCO} <40% predicted) or progressive (≥10% decline in FVC or ≥15% decline in FVC during 6 months of follow-up). [C]

Cryptogenic organising pneumonia (COP)

- COP usually responds to corticosteroid therapy but the optimum dose and length of treatment is not known. Initial doses of 0.75–1 mg/kg, weaning over 6–12 months, are reasonable. [C]
- Relapses of COP are common but are only rarely associated with poor outcome. The risk versus benefit of prolonged corticosteroid therapy should be carefully considered in patients with relapsing COP. [D]

Respiratory bronchiolitis ILD (RBILD) and desquamative interstitial pneumonia (DIP)

- Patients with RBILD or DIP should receive appropriate smoking cessation advice and treatment. [C]

Hypersensitivity pneumonitis

- The diagnosis of hypersensitivity pneumonitis requires a high index of suspicion and in difficult cases an integrated multidisciplinary approach is essential. [D]
- Avoidance of the causative antigen, when identified, is the most important and effective aspect of management. [C]
- Corticosteroids may have a role in treating severe or progressive disease. [C]

Connective tissue disease (CTD)-associated ILD

- In general, the threshold for starting treatment in the hope of preventing progression of pulmonary fibrosis in CTD-associated ILD is reduced when disease is severe (as judged by HRCT or pulmonary function tests), recently progressive, or there is a short duration of systemic disease. [C] In many patients the potential benefits of therapy will be outweighed by the risks.
- For the majority of CTD, with the exception of systemic sclerosis (SSc), recommended initial treatment for ILD is oral prednisolone at an initial dose of 0.5–1 mg/kg with the aim of tapering to a maintenance dose of 10 mg/day or less, often in association with an immunosuppressive agent (usually oral or intravenous cyclophosphamide or oral azathioprine). [C]
- ILD associated with polymyositis/dermatomyositis often warrants early treatment with oral prednisolone (0.75–1 mg/kg) and cyclophosphamide or other immunosuppressive therapy to prevent disease progression. [C]
- In SSc-associated ILD, recommended treatment, if required, is with low-dose oral steroids (10 mg/day) and/or cyclophosphamide (oral or intravenous). [C] High-dose corticosteroid treatment (daily prednisolone dose >10 mg) should be avoided if at all possible because of the risk of renal crisis. [C]

Sarcoidosis

- Because of the high rate of spontaneous remission, treatment is not indicated for asymptomatic stage I disease. [B]
- Because of high rates of remission, treatment is not indicated in asymptomatic stage II or III disease with mildly abnormal lung function and stable disease. [D]
- Oral corticosteroids are the first line of therapy in patients with progressive disease determined by radiology or on lung function, significant symptoms or extrapulmonary disease requiring treatment. [B]
- Treatment with prednisolone (or equivalent) 0.5 mg/kg/day for 4 weeks, then reduced to a maintenance dose which will control symptoms and disease progression, should be used for a period of 6–24 months. [D]
- Bisphosphonates should be used to minimise steroid-induced osteoporosis. [D]
- Inhaled corticosteroids, either as initial treatment or maintenance therapy, are not of significant benefit. [B] Inhaled corticosteroids may be considered for symptom control (cough) in a subgroup of patients. [D]
- Other immunosuppressive or anti-inflammatory treatments only have a limited role in sarcoidosis, but should be considered in patients when corticosteroids are not controlling the disease or side effects are intolerable. At present, methotrexate is the treatment of choice. [C]
- Lung transplantation should be considered in end stage pulmonary sarcoidosis. [D]

Pulmonary hypertension

Pulmonary hypertension in ILD

- Pulmonary hypertension should be considered in patients with ILD who have either breathlessness or lung dysfunction (reduced T_{LCO} or desaturation on exercise) that seem disproportionate to the extent of parenchymal lung disease. [D]
- Transthoracic echocardiography is a suitable screening tool for the detection of pulmonary hypertension in patients with ILD. [B]
- Long-term oxygen therapy should be prescribed in patients with ILD, chronic hypoxia (<8 kPa) and cor pulmonale. [D]

- Patients with ILD and pulmonary hypertension that is judged to be contributing to symptoms and is disproportionate to the extent of ILD or is severe (systolic pulmonary artery pressure >50 mm Hg) should be considered for referral to a regional specialist pulmonary hypertension centre for assessment and recruitment to high quality clinical trials. [D]

Pulmonary artery hypertension associated with connective tissue disease

- Patients with systemic sclerosis should have annual lung function testing and transthoracic echocardiography should be performed in those with declining TLCO or TLCO <50% predicted. [C]
- Long-term warfarin therapy should be prescribed in patients with CTD-associated pulmonary artery hypertension. [D]

ILD presenting with acute respiratory failure

- Early accurate and secure diagnosis is critically dependent upon considering a broad differential diagnosis including new-onset ILD and ILD progression, and non-ILD processes such as pulmonary oedema, malignancy, drug-induced lung disease and infection. [D]
- Accurate diagnosis in ILD with borderline respiratory failure often requires BAL to exclude infection and is best performed in selected patients on the intensive care unit (ICU) before ventilation is required, or with ventilatory support immediately available. [D]
- Decisions on transbronchial and surgical lung biopsy must be individualised to the clinical scenario. Both procedures are often justifiable, despite increased risk, if there is a realistic possibility that the additional information will influence management. [D]
- ICU support for patients with IPF and respiratory failure is usually not appropriate due to the very high associated mortality. [C]
- In most rapidly progressive ILDs presenting with respiratory failure, intravenous corticosteroid therapy is the initial treatment of choice. Intravenous cyclophosphamide is the second-line treatment of choice and is usually administered to patients not responding to parenteral corticosteroids. [D]
- In cases of known or suspected vasculitis, intravenous cyclophosphamide should be considered as first-line treatment. [C]

3. EPIDEMIOLOGY

3.1 Idiopathic pulmonary fibrosis (IPF) and cryptogenic fibrosing alveolitis (CFA)

The data available on the epidemiology of IPF are very limited and most of the studies predate the new ATS/ERS reclassification of IIPs and need to be considered in this light. For this reason, we have deliberately retained the term CFA for this section of the guidelines and used it interchangeably with "the CFA clinical syndrome", the entity diagnosed by chest physicians and studied in epidemiological studies prior to the new classification system.

Historically, most studies of CFA have relied on clinical criteria (eg, the presence of basal inspiratory pulmonary crackles, bilateral interstitial shadowing on the chest radiograph, no documented exposure to asbestos or other fibrogens, no evidence of collagen vascular disease and no other coexisting cause of interstitial lung disease).[47] For this reason, it is possible that some misclassification of NSIP as CFA is present in the older epidemiological studies. The extent of this misclassification will depend on the relative incidence of NSIP and IPF in the general population, and this is not currently known. One previous epidemiological study has reported that the median survival of newly diagnosed patients with the CFA clinical syndrome is 3 years, a figure which is similar to that currently reported for patients with IPF. This provides some reassurance that there are unlikely to be extensive problems of misclassification in the historical studies. Future epidemiological studies are likely to include data from HRCT scans, and this should reduce problems of misclassification further.

Information on the frequency of the CFA clinical syndrome comes from a variety of sources including population-based disease registries, computerised general practice data (especially from the UK) and death registrations. In the New Mexico registry,[48] CFA had the highest incidence of all the ILDs (9/100 000 person-years) and similar findings have been reported from European registries.[49 50] Data from computerised UK general practice records[51] suggest that the 12-month period prevalence of CFA is 15–18/100 000 person-years and, based on a median survival from diagnosis in the UK of approximately 3 years,[52 53] this equates with an estimated incidence of 5/100 000 person-years. This, in turn, suggests that there are at least 2000 new cases of CFA each year in England and Wales, which is compatible with death certificate registration data.[47 54] There is evidence from death certificate data that the incidence of the CFA clinical syndrome is increasing in the UK and a number of other countries including Canada, Australia and New Zealand.[47 54]

General population-based data in the UK and the USA suggest that the median age of presentation of the CFA clinical syndrome is 70 years,[47 48 55] with the disease uncommon below the age of 50 years. It is more common in men with a male:female ratio of 1.5–2.0:1.[47 50 51 54–56] The CFA clinical syndrome occurs throughout the world and in most ethnic groups,[47 49 57 58] but there are insufficient data to allow meaningful inter-country comparisons of incidence or prevalence. The median survival is 3 years in the UK[52 53] and 4 years in New Mexico,[59] with patients losing an average of 7 years of life compared with the general population.[53] Patients with the CFA clinical syndrome appear to have a markedly increased risk of developing lung cancer.[60 61]

3.2 Sarcoidosis

Excluding patients with stage I disease, sarcoidosis is the second most common ILD.[48] In the UK, general practice data suggest an incidence of approximately 3/100 000 person-years[51] (assuming a mean disease duration of 2 years), similar to the figure derived from the New Mexico registry[48] and from Japan[62] but lower than other estimates from the USA.[63] The incidence of sarcoidosis appears to be higher in Scandinavian countries and in Afro-Caribbean people, and also marginally higher in women.[51 63–66] In general, incidence peaks between the ages of 20 and 50 years, with a second smaller peak after the age of 60.[64] The lungs are involved in most cases and are affected without other organ disease in approximately 50% of patients; the skin, liver and eyes are the most frequent extrapulmonary sites.[64] The prognosis is generally good, but a few patients die from progressive disease.[67] USA data suggest that females and Afro-Caribbean people have an increased mortality.[68]

3.3 Hypersensitivity pneumonitis (HP)

Data on the frequency of HP are limited, but it is less prevalent than the CFA clinical syndrome or sarcoidosis in disease registry populations.[48 49 69] Some studies have been conducted within

high-risk cohorts with specific antigen exposures; for example, the incidence of HP among Swedish farmers is in the region of 20/100 000 person-years.[70] Bird fancier's lung is the commonest form of HP in the UK.[71] HP appears to be more common in men and during middle age, although it is not known whether this reflects host predisposition or merely frequency of exposure to relevant antigens. The disease is sometimes progressive and the development of lung fibrosis is associated with an increased mortality.[72]

3.4 Interstitial lung disease and connective tissue diseases

Patients with connective tissue diseases made up approximately 20% of patients with a CFA clinical profile in early studies from tertiary referral centres.[61 73] More recently, general practice data have suggested that approximately 10% of patients with a diagnosis of fibrosing alveolitis have an overt connective tissue disease, with rheumatoid arthritis (80%) much more frequent than scleroderma (14%) or polymyositis/dermatomyositis (4%).[53] In a study of consecutive outpatients with rheumatoid arthritis, interstitial abnormalities were present on the HRCT scan in 19%[74] and, after 2 years of follow-up, 34% had deterioration in lung function and 14% died.[75] Survival has been reported to be better in patients with the fibrosing alveolitis of systemic sclerosis than in patients with lone CFA, even after allowing for differences in age, sex, duration of dyspnoea, level of lung function impairment and the extent of disease on HRCT.[76] By contrast, in a general population study of patients with rheumatoid arthritis and fibrosing alveolitis, the mortality was as high as in lone CFA.[53]

4. HISTORY AND EXAMINATION

An aide memoire for the assessment of suspected ILD at a first clinic visit is provided in Appendix 1.

4.1 History

Three main questions require answering from the history:

1. What is the natural history/chronology of the condition to date?
2. Are there any respiratory risk factors/aetiological agents?
3. What is the severity of the symptoms?

Natural history/chronology

This is subdivided into acute (<3 weeks), episodic and chronic. It is important to review all available previous chest radiology if possible as the episodic nature of a condition may become apparent and also because subclinical disease may be present radiologically for some time before symptoms develop. Episodic or ''flitting'' shadows on the chest radiograph focuses the ILD differential diagnosis to include eosinophilic pneumonia, vasculitides/pulmonary haemorrhage, HP or COP.

Respiratory risk factors

Smoking

There are some uncommon ILDs—namely respiratory bronchiolitis interstitial lung disease (RBILD), desquamative interstitial pneumonia (DIP) and Langerhans' cell histiocytosis (LCH)—that occur almost exclusively in smokers. Patients with Goodpasture's syndrome are usually smokers.[77] Smoking is an independent risk factor for IPF with an odds ratio of 1.6–2.9.[47 56 78] A history of smoking may point towards coexistent chronic bronchitis and emphysema, but smokers are less likely to have HP[79] or sarcoidosis.[80]

Occupation

A detailed occupational history needs to be taken in order to establish if there has been occupational exposure, its duration, and whether any respiratory protection was worn.

Hobbies/environment/travel

Any identifiable antigen for HP should be sought. Travel may raise the possibility of infection including tuberculosis and eosinophilic lung disease secondary to parasite infestation.

Family history

A positive family history of respiratory disease should be sought. Both sarcoidosis[81–83] and IPF[84] may be familial, albeit rarely.

HIV risk factors

This is particularly important in acute onset ILD, which may represent opportunistic infection, although the latter may also occur in known ILD treated with immunosuppressant therapy.

Rheumatological symptoms

These may point to a specific underlying rheumatological diagnosis. In particular, enquiries should be made about Raynaud's phenomenon, skin thickening, dysphagia and acid reflux, arthralgia, rashes, ocular symptoms, sicca symptoms (dry eyes and mouth), myalgia and proximal muscle weakness. In addition, information on constitutional symptoms of fever, sweats, malaise and weight loss should be sought.

Past medical history

Previous history may suggest a particular ILD, eg, haematuria (vasculitis), asthma/rhinitis (Churg-Strauss syndrome) or a previous malignancy that may have been treated with chemotherapy or radiotherapy. Although radiation pneumonitis usually develops within a few weeks or months of treatment, pulmonary fibrosis may evolve and present several months or years later. A history of pneumothorax may suggest cystic lung disease associated with LCH or lymphangioleiomyomatosis (LAM).

Drug history

It is vital to obtain a detailed history of all previous drug therapy including intermittent courses of drugs. This should include dose and duration of treatment as some drugs are toxic because of the cumulative dose. Specific enquiry should also be made of ''over the counter'' and herbal remedies. Many classes of drugs possess adverse pulmonary effects[85 86] which may be checked on the internet website www.pneumotox.com. A list of drugs associated with ILD is presented in Appendix 2 available in the online data supplement.

Assessment of disease severity

This should include an assessment of exercise tolerance on both the flat and on increased exertion (eg, walking up stairs or inclines). It is important to record whether the patient is limited by breathlessness or because of some other symptom(s) such as joint pains because the latter may mask respiratory symptoms if the patient cannot exercise sufficiently to precipitate breathlessness.

Elucidation of specific symptoms may help to discriminate between different diseases.

Cough

Cough is usually an "airway-centred" symptom which is more likely in bronchocentric diseases such as sarcoidosis, HP and COP. A dry cough is also common in IPF although the mechanism is unclear. Productive cough occurs when there are excessive secretions in the tracheobronchial tree—for example, associated with chronic bronchitis or bronchiectasis coexisting with ILD.

Wheeze

Wheeze is also an "airway-centred" symptom which may suggest Churg-Strauss syndrome or eosinophilic pneumonia because of associated asthma or large airway narrowing secondary to bronchostenoses in sarcoidosis.

Haemoptysis

Haemoptysis can be a manifestation of pulmonary haemorrhagic syndromes such as Wegener's granulomatosis or Goodpasture's syndrome. However, significant alveolar haemorrhage can occur without haemoptysis. Haemoptysis in IPF should alert the clinician to the possibility of a complication such as lung cancer, pneumonia or pulmonary embolus.

Pleurisy

Pleurisy suggests connective tissue disease (especially rheumatoid arthritis and systemic lupus erythematosus), asbestos-related disease and drug-induced lung disease.

4.2 Physical examination

Relatively few physical signs help to discriminate between ILDs. Clubbing is suggestive of IPF (49–66% of patients)[87] in which it occurs significantly more frequently in men,[88 89] asbestosis (43%),[90] chronic HP[91] or rheumatoid arthritis with ILD. Although ILD occurs in up to 40% patients with PM/DM, clubbing is rarely observed.[92]

Fine basal "velcro-like" inspiratory crackles are characteristically heard in IPF (>90% cases).[73 89] They are also common (60%) in patients with pulmonary fibrosis complicating collagen vascular disease and asbestosis.[93 94] However, crackles occur much less frequently in sarcoidosis[93 95] and HP.[93] Inspiratory squeaks reflect bronchiolitis. They are common in subacute HP[1 96] and may be heard in NSIP.[14] Wheeze may indicate asthma associated with Churg-Strauss syndrome or eosinophilic pneumonia and may be a sign of bronchiolitis.

The presence of specific systemic signs may be helpful in narrowing the differential diagnosis. Lymphadenopathy, hepatomegaly, splenomegaly, uveitis and skin rashes occur in sarcoidosis, although connective tissue disease, malignancy and HIV may all present with one or more of these findings.

Hypoxaemia is reliably detected by pulse oximetry which can be routinely performed in clinic to assess patients with ILD. It is also important to look for physical signs of pulmonary hypertension and right ventricular failure which may reflect hypoxia from severe pulmonary fibrosis for example in IPF,[87 97] or coexistent pulmonary vascular disease particularly in systemic sclerosis or pulmonary vasculitis.

Summary of recommendations for history and clinical examination in ILD

- **Detailed history taking is required to identify respiratory risk factors both past and present. [D]**

5. LUNG FUNCTION TESTING IN ILD

A restrictive defect is the most frequent ventilatory abnormality in patients with pulmonary fibrosis which is a common consequence of many ILDs. It is a typical finding in patients with IPF. The presence of airflow obstruction may reflect coexistent chronic obstructive pulmonary disease (COPD) or asthma. However, in sarcoidosis, bronchial involvement and airflow obstruction are common.[98 99]

Some conditions, such as LCH and LAM, show a mixed but variable picture with airflow obstruction and reduced TLCO but preserved lung volumes.[100–103] Lung volumes may be relatively preserved in smokers with IPF due to coexisting emphysema, with the FEV_1/FVC ratio remaining normal.[35 36 104–106] In systemic sclerosis, an isolated reduction in TLCO may indicate pulmonary vascular disease, especially when TLCO levels are markedly reduced (discussed more fully in Section 21). In subacute HP there may be a mixed picture with restriction, reduced TLCO and reduced $FEV_{25–75}$ reflecting the small airways component of the disease.

The aims of lung function testing in all ILDs are to quantify disease severity, monitor disease progression and, ideally, to identify variables most strongly predictive of mortality. Unfortunately, studies of these important aspects of routine management are largely confined to IPF.

5.1 Baseline lung function as a measure of disease severity in IPF

Most previous studies are limited because they contain heterogeneous groups of patients considered by various criteria to be "IPF" or "CFA". The recent ATS/ERS reclassification of the IIPs has allowed greater precision in prognostic evaluation, especially in IPF and NSIP which should allow future studies to be more informative.

In historical studies of IPF, a poor outcome has been consistently associated with severe lung function impairment. In a study of 74 biopsied patients with "IPF", Schwartz *et al* documented increased mortality with a lower percentage predicted FVC and lower percentage predicted TLCO.[107] A specific lung function threshold, separating outcome in a meaningful way, is highly desirable. The study by Gay *et al* applied receiver operator characteristic (ROC) curve estimates to identify the key thresholds that allow a lung function variable to discriminate between death and survival during a specified period of follow-up.[108] In subsequent studies with larger numbers, Mogulkoc *et al* focused on lung function in the context of transplant referral in 110 patients with IPF aged 45–65 years.[109] A TLCO of <39% of predicted, combined with HRCT scores, had an 80% sensitivity and specificity for death within 2 years. The concept of "advanced disease" was further validated by Latsi *et al* in a study of 104 patients with IPF (n = 61) or fibrotic NSIP (n = 43).[7] TLCO levels of <35% were associated with a mean survival of 24 months, with no difference in outcome between IPF and NSIP. Conversely, there were important long-term survival differences between IPF and NSIP in patients with lesser lung function impairment at presentation. By contrast, although a reduced FVC is associated with increased mortality, a single discriminatory FVC threshold has not been identified. Thus, the severity of IPF is best staged by TLCO estimation. Extended survival is more likely in patients with "limited disease" (TLCO >40% of predicted), and it is in this patient group that prognostic evaluation can be usefully refined using short-term serial lung function trends.[110]

Composite physiological indices have been constructed in the hope of refining prognostic evaluation. The first

clinical-radiological-physiological score of Watters *et al*[111] has recently been revised,[112] but both the original and revised score include findings at maximal exercise testing and need to be integrated with a number of non-physiological variables, limiting their application to routine practice. The composite physiological index[106] which, in effect, removes the confounding effect of concurrent emphysema on lung function requires only the measurement of TLCO, FVC and FEV_1 levels. However, further studies are needed to determine whether composite indices offer major advantages over routine lung function tests in routine prognostic evaluation.

5.2 Serial lung function for disease monitoring in IPF

The existence of heterogeneous patterns of disease progression is well recognised. In the 1999 BTS ILD guideline document the lack of consistency in the literature with respect to lung function monitoring in ILD was acknowledged and the need for prospective studies was highlighted. There have since been important contributions to the literature on this subject.

Change in FVC has emerged as the serial lung function measurement most consistently predictive of mortality. In part, this may reflect the good reproducibility of FVC; thus, a change in FVC of only 10% is needed to identify a true change in disease severity (as opposed to measurement variation). By contrast, a minimum change of 15% is required in TLCO, a less reproducible variable.[113] Thus, serial FVC is likely to be more sensitive to change than serial TLCO.

The prognostic value of serial change in pulmonary function indices was first evaluated by Hanson *et al* in a study of 58 patients, with change defined as a 10% alteration in FVC and a 20% alteration in TLCO.[114] The mortality of patients with a decline in FVC (24% of the total) was significantly higher than in the remaining patients, and the same outcome differences were seen when a decline in TLCO (22% of patients) was evaluated.

Following the reclassification of the IIPs, serial change in lung function variables has been examined against survival in five publications.[7 37–40] Collard *et al*, in a study of 81 patients with UIP, evaluated change in lung function over both 6 and 12 months.[37] Six-month changes in total lung capacity (TLC), FVC and TLCO predicted survival, with serial FVC the strongest prognostic determinant. Flaherty *et al* studied 109 patients (UIP, n = 80; NSIP, n = 29).[38] A decline in FVC within 6 months, seen in 32%, was an independent risk factor for mortality on multivariate analysis and was prognostically superior to change in TLCO. These observations were strongly supported by findings from a large clinical trial of IFNγ; a 10% decline in FVC was associated with a 2.4-fold increase in risk of mortality.[40]

Change in TLCO is an alternative measure of disease progression. Latsi *et al*[7] observed a higher mortality in those patients with a decline in TLCO at 6 and 12 months, whether trends were quantified numerically or categorically. However, repeat TLCO measurements can be difficult to standardise, explaining the need for a greater change in TLCO than in FVC in order to categorise deterioration. In the study by Latsi *et al*[7] serial TLCO trends had only a minimal prognostic advantage over serial FVC trends, and the analysis included a significant subset of patients with "advanced disease". The study by Latsi *et al*,[7] and another study of serial lung function in IIP by Jegal *et al*,[39] were performed in a mixed population of patients with IPF and NSIP. Importantly, both studies demonstrated that the histological diagnosis is irrelevant once lung function change over 12 months has been taken into account.

In patients with "limited disease" the re-evaluation of progression at 1 year remains valuable and may be particularly important in the context of "marginal" declines in FVC (5–10%) or TLCO (10–15%), which may reflect either measurement variation or genuine disease progression.[7 38] Thus, data on the prognostic value of change in pulmonary function tests at 6 months should not obscure the need to refine prognostic evaluation regularly thereafter.

5.3 Lung function testing in sarcoidosis

Abnormal lung function tests are present in approximately one-fifth of patients with stage 1 sarcoidosis and 11–80% of patients with stage 2, 3 and 4 sarcoidosis.[115–117] Airflow obstruction has been reported in 11–57% of patients with sarcoidosis, with probably a lower prevalence in non-smokers.[98 99 118] Lung function impairment correlates only modestly with chest radiography and HRCT scanning.[119–123] Baseline lung function parameters are not generally predictive of long-term mortality.[124 125] In an analysis of the United Network for Organ Sharing (UNOS) registry, outcome was examined in 405 patients with 27% awaiting lung transplantation.[126] Raised pulmonary artery pressure but not routine lung function variables were predictive of mortality. Several studies have reported that measurements of vital capacity are more sensitive than other routine variables in identifying corticosteroid responsiveness,[127–129] and it is unusual for changes in vital capacity to be discordant with changes in TLCO.[130]

The limitations of these studies need to be stressed. Patient numbers are usually—though not invariably—small, a heterogeneity in patterns of functional impairment (including lung restriction, predominant airflow obstruction and a disproportionate reduction in gas transfer) are frequently observed and the criteria for determining "improvement" are not validated for sarcoidosis. Statements about mean lung function in populations of patients with sarcoidosis are often unhelpful in individual cases. Thus, it is appropriate to measure FEV_1, FVC and TLCO routinely and to focus on variables that are most severely impaired or change the most at follow-up.

5.4 Exercise testing in ILD

Maximal exercise testing in the detection of ILD

It has long been accepted that maximal exercise testing is more sensitive than resting lung function tests in the detection of ILD, an increase in the alveolar-arterial oxygen gradient being particularly sensitive.[131–133] However, no formal evaluation of the diagnostic accuracy of exercise testing in ILD has ever been undertaken. With the advent of HRCT, the sensitivity of maximal exercise testing may have become less useful in clinical practice, although no comparison of the sensitivities of exercise testing and HRCT has been attempted. In clinical practice, exercise testing is most often useful when normal, effectively excluding clinically significant ILD in the symptomatic patient with normal lung function tests and chest radiography.[134] Although a similar role for exercise testing appears logical when HRCT abnormalities are trivial and their significance is uncertain, a disease detection algorithm incorporating HRCT findings and exercise testing has yet to be validated.

Maximal exercise testing to determine disease severity and prognosis in ILD

The role of exercise testing in the staging of disease severity in ILD is uncertain owing to the absence of a "gold standard" to quantify disease severity. Exercise indices have been evaluated

against the severity of histological features at lung biopsy in several small studies with conflicting and inconclusive results, probably because small biopsy samples are an inappropriate measure of global disease severity.

Historically, the findings of Fulmer *et al*[135] had the greatest impact on clinical practice; in this single study, maximal exercise data (changes in arterial oxygen tension (Pa_{O_2}) and the alveolar-arterial oxygen gradient) correlated better with histological findings than resting lung function indices in IIP. However, although often cited as a justification for routine exercise testing, this finding was not confirmed in other histological studies and has not stood up to scrutiny in more recent studies of HRCT-functional relationships. The evaluation of disease extent on HRCT allows global macroscopic morphological severity to be quantified, an advantage that is crucially lacking in biopsy evaluation. In patients with IIP[136] and lung fibrosis in systemic sclerosis,[137] disease extent on HRCT scanning correlates best with TLCO, less well with maximal exercise data and poorly with lung volumes. Furthermore, TLCO levels have been highly predictive of maximal exercise data in other studies.[138 139] Based on these findings, maximal exercise testing appears to add little or nothing to TLCO in the routine quantification of the severity of ILD.

The role of maximal exercise data in prognostic evaluation is uncertain. Maximal exercise testing forms a major part of the physiological components of the original and revised clinical-radiological-physiological score.[111 112 139] However, there are few data comparing maximal exercise data and resting variables in the prediction of mortality in either IIP or the pulmonary fibrosis of connective tissue disease. In one study the clinical-radiological-physiological score, in which maximal exercise data has a prominent role, was a less powerful prognostic determinant than HRCT appearances.[108]

The six minute walk test (6MWT) has only recently been applied to ILD but has provided powerful prognostic information in four studies of IPF[140–143] and in a mixed cohort with IPF and fibrotic NSIP.[144] Desaturation to 88% in a baseline 6MWT, either during[140] or at the end of the test,[144] has emerged as a much more powerful predictor of mortality than resting lung function tests. In a recent large study of patients with IPF, desaturation to 88% or below was associated with a median survival of 3.21 years compared with a median survival of 6.63 years in those who did not desaturate to this extent.[140] Even within the subgroup of individuals who maintained saturations of >88%, greater cumulative desaturation was associated with increased mortality. The value of the baseline distance walked as a prognostic indicator in IPF is less certain, with conflicting recent data that probably represent differences in study protocols,[140 141 145] although distance walked is a highly reproducible component of the 6MWT.[144] A composite measure of desaturation and distance walked may represent a novel and useful marker of disease severity and prognosis.[143] The shuttle walk exercise test has also been studied in IPF but has not been evaluated against outcome.[146]

Serial exercise testing to monitor disease progression in ILD

In the only study to report on serial exercise testing and mortality, Flaherty *et al* showed that the value of repeating the 6MWT at 6 months depended on the degree of desaturation observed at baseline.[140] In those who maintained oxygen saturations of >88% at baseline, repeating the 6MWT test was useful in that a greater degree of desaturation on the repeat test was associated with higher mortality. A relative fall in FVC of >10% was also a robust indicator of increased mortality in this subgroup but, interestingly, worsening walking distance or a fall of >15% in TLCO were less discriminatory. In individuals with desaturation to ⩽88% at baseline, repeating the 6MWT was of no added value and, indeed, only a fall of >15% in TLCO and not changes in FVC were of prognostic value in this subgroup. The implication from this single large retrospective study is that a baseline 6MWT not only provides prognostic information per se, but may also stratify patients to determine which lung function variable serves as the best prognostic indicator at 6 months.

Summary of recommendations for lung function testing in ILD

- **All patients with ILD should have resting spirometric and gas transfer measurement at presentation, which together provide a reasonable measure of disease severity. [C]**
- **In IPF and fibrotic NSIP, TLCO levels at presentation are a more reliable guide to outcome than other resting lung function variables. A TLCO level of <40% is indicative of advanced disease in fibrotic IIP. [B]**
- **In IPF a fall from baseline of ⩾10% in FVC or ⩾15% in TLCO in the first 6–12 months identifies patients with a much higher mortality. [B]**
- **Desaturation during the 6 minute walk test at presentation is a stronger prognostic determinant in IPF than resting lung function. [C]. However, additional studies are required to define the role of exercise testing in routine staging and follow-up both in IPF and other ILDs.**
- **Maximal exercise data probably add little to resting lung function in assessing the severity of ILD but are sometimes useful, when normal, in excluding clinically significant diffuse lung disease. [C]**

6. CHEST RADIOGRAPHY

A chest radiograph is almost invariably obtained for patients presenting with suspected or obvious ILD. The overall sensitivity of chest radiography for ILD is difficult to gauge, but one historical series showed that at least 10% of cases with biopsy-proven ILD had an apparently normal chest radiograph.[147] However, in the majority of patients with clinically significant ILD the chest radiograph is abnormal. A further issue is the susceptibility to false positive interpretation of chest radiography.[148] Appearances suggesting ILD are frequent in obese individuals (because of overlying soft tissues and/or under-inflation of the lungs) and in some patients with an airways disease with a radiographic pattern resembling interstitial disease (eg, the nodular pattern of diffuse panbronchiolitis).

The radiographic pattern, distribution of disease and its chronicity based on previous radiographs, if available, may allow a confident diagnosis to be made when corroborative clinical features and laboratory findings are taken into account. Specific examples include sarcoidosis presenting with bilateral hilar lymphadenopathy and erythema nodosum, pulmonary eosinophilia and coal workers' pneumoconiosis. In isolation, however, the radiographic pattern of ILD is often non-specific and the correct diagnosis—on the basis of the radiographic appearances—can be made only in approximately half of patients with ILD.[149 150]

Despite the limitations of chest radiography and the paucity of published evidence to support its use, it is widely used for monitoring patients with ILD. Given its ready availability and the improved reproducibility of digital chest radiography,[151] it

seems that chest radiography will continue to be used, in conjunction with pulmonary function, to document coarse changes in the extent of ILD. Chest radiography can detect supervening complications (eg, pneumothorax, acute exacerbation of IPF, infection, lung cancer and heart failure to which patients with ILD are prone).

In summary, in suspected ILD, the chest radiograph in conjunction with the clinical and laboratory findings may allow a confident diagnosis to be made (eg, sarcoidosis presenting with bilateral hilar lymphadenopathy and erythema nodosum). The chest radiograph is also a useful but often non-specific test for detecting secondary pulmonary complications in patients with ILD.

7. HIGH RESOLUTION COMPUTED TOMOGRAPHY (HRCT)

7.1 Technique and radiation considerations

HRCT provides cross-sectional images of the lungs that possess spatial and contrast resolution such that submillimetre structures in the lungs are clearly visible. The basic modifications to the standard CT technique are the use of thin collimation sections (<1.5 mm width) and image reconstruction with a high spatial frequency algorithm.[152] A standard HRCT protocol is a sampling examination and comprises 1–1.5 mm sections with 10 or 20 mm gaps between sections; it is this interspacing that results in an effective radiation dose of 10%, in the case of 10 mm interspacing, of that of conventional contiguous CT scanning. A standard HRCT protocol employing 1.5 mm sections at 20 mm intervals entails an effective radiation dose of 0.35 mSv, approximately equivalent to seven postero-anterior chest radiographs. In line with the ethos of "as low as reasonably achievable" to keep the radiation burden to the patient to a minimum, ancillary CT imaging (eg, HRCT sections obtained at end expiration) should not be routinely undertaken but performed only when needed to clarify a question not answered by a standard HRCT examination.

With the advent of multidetector CT scanners it is possible to acquire contiguous HRCT images in a single breath hold, but there is the potential for a considerable increase in the radiation burden to the patient; furthermore, several hundred HRCT sections are acquired compared with the usual number of 25–30 images that are obtained with a standard HRCT protocol. From a diagnostic point of view, there is as yet no compelling evidence to suggest that the acquisition of a vast number of HRCT sections, possible on the latest generation of multidetector CT scanners, confers any substantial advantage compared with a standard HRCT. Reports have concluded that coronal reconstructions improve the depiction of zonal distribution of ILD,[153 154] but rigorous evaluation of the incremental benefit of these or other reconstructions has not yet been undertaken. A potentially useful benefit of volumetric HRCT (which provides contiguous imaging with no anatomical discontinuity and thus no sampling difficulties) is that it allows accurate comparisons to be made between baseline and follow-up examinations. With a standard HRCT protocol there is often considerable difficulty in making the judgement about serial change in patients with ILD because of the lack of strictly comparable sections on serial HRCT scans; this problem is overcome with volumetrically acquired HRCT. However, with the current 4–16 channel multidetector CT scans, such image acquisition is at considerable radiation cost to the patient. The latest generation of multidetector CT scanners (64 detector and upwards) will allow the more efficient acquisition of contiguous HRCT images at an acceptable radiation dose, more comparable to that of a standard interspaced HRCT protocol. With single detector or limited multidetector CT scans, efforts need to be maintained to acquire HRCT images at the lowest possible radiation dose.[155]

7.2 Sensitivity of HRCT

The magnitude of the increased sensitivity of HRCT scanning over chest radiography for the detection of ILD is difficult to estimate, partly because differences are largely disease-dependent. Studies of individual diseases report widely differing rates of false negative chest radiographs in the face of a positive HRCT.[156] Nevertheless, a survey combining the results of several studies estimates that the sensitivity of HRCT for ILD is 94% compared with 80% for chest radiography.[157]

Whether or not a patient with clinical features suggestive of ILD has a normal or questionably abnormal chest radiograph, HRCT has a valuable role in confirming or refuting the presence of ILD, particularly given the low false positive rate for HRCT.[158] Although the sensitivity of HRCT for the detection of ILD is high, it is not 100%. HRCT does not consistently demonstrate histopathologically evident early disease evident in all patients—for example, in some cases of HP[159] or occasional cases of IPF.[160] Conversely, the increasing use of HRCT has led to situations in which limited features of ILD are seen in patients in whom the clinical significance is unclear. In some cases these changes may be within the limits of normality.[161] It has been reported that approximately one-third of smokers have parenchymal changes such as patchy ground glass opacification and centrilobular nodules without obvious symptomatic or functional correlates.[162 163] Similar observations of "subclinical disease" have been made in patients with connective tissue disorders. In some cases these findings may be unimportant as judged by symptoms, pulmonary function tests and absence of change over time, but the true significance is unknown due to insufficient data.

To summarise, most patients with clinically significant diffuse lung disease have an abnormal HRCT scan but a normal HRCT scan does not exclude ILD in all cases.

7.3 Pathological specificity of HRCT and observer variation

Many reports have shown that HRCT is significantly more accurate than chest radiography in diagnosing individual ILDs. The first study to show that HRCT enabled observers to give a correct diagnosis of ILD more often than chest radiography was by the Vancouver group in 1989.[149] A confident diagnosis was reached more than twice as often with CT than with chest radiography (49% vs 23%) and, of these observations, a correct diagnosis was reached in 93% of the first choice CT diagnoses compared with 77% of the first choice radiographic diagnoses. With increased experience and, to a lesser extent, technological improvements, the proportion of confident and correct diagnoses achievable with HRCT has increased over the last 15 years.

If the incremental contributions of clinical, radiographic and HRCT findings are combined, Grenier *et al* reported that a correct diagnosis could be made in 61–80% of patients with ILD.[164] However, when interpreting the results of the several studies reporting the performance of observers using HRCT, many factors need to be remembered and these reduce the relevance of the reported results to everyday clinical practice. For example, the study populations do not in general mirror general hospital practice in which there is a higher prevalence of smoking-related diffuse lung disease, heart failure, disseminated malignancy and chronic infection. Furthermore, the observers

used in such studies are often highly specialised. Finally, difficult to characterise or poorly understood conditions tend to be under-represented (eg, NSIP) in the published series.

The diagnostic accuracy of HRCT is highly disease-dependent. For example, the wide range of HRCT patterns of NSIP[165] conspire to make it a difficult diagnosis to make on HRCT scanning. In contrast, several studies have confirmed that, when HRCT appearances are judged to be those of UIP, the diagnosis is correct in >90% of cases[5 6 22 23] such that surgical biopsy confirmation, when clinical and HRCT features are typical of IPF, cannot easily be justified.[24] Several other ILDs can also have more or less pathognomonic HRCT appearances (box 1) and, when clinical features and laboratory findings are all in accord with the HRCT diagnosis, investigation with BAL or biopsy may add little to further increase diagnostic confidence.

In many patients there will remain significant diagnostic uncertainty following clinical and radiological assessment. HRCT provides useful information on the distribution of disease that may be used to guide subsequent BAL, transbronchial biopsy or surgical lung biopsy.

Observer agreement between thoracic radiologists using HRCT to make a histospecific diagnosis of ILD has been shown to be comparable to that achieved by pulmonary pathologists.[166] Observer agreement for cases taken from regional teaching hospitals was good (kappa (κ) = 0.60) compared with cases selected from a tertiary referral centre (κ = 0.34); this lower value reflected the unusual nature of tertiary referral cases. It is noteworthy that NSIP was responsible for disagreements between observers in approximately half of cases.[166] (A κ value of 1 indicates total agreement and a κ value of 0 indicates no agreement other than that which might occur by chance. In general, κ values of >7 indicate a high degree of agreement in clinical studies and values of <4 indicate that there is insufficient agreement for the test to be of clinical value.)

In addition to its "simple" role of assigning a likely diagnosis, HRCT sometimes has a useful arbitrating function in cases in which a unifying diagnosis is elusive. As an example, the scenarios in which the histopathological label of non-specific pneumonia are encountered are many and varied (see section on NSIP) and ancillary features on HRCT such as foci of consolidation or centrilobular nodules, taken in conjunction with clinical information, are likely to influence the final (multidisciplinary consensus) diagnosis.

7.4 HRCT evaluation of disease reversibility

In the specific domain of the IIPs, the ability of HRCT appearances to predict disease reversibility has been extensively investigated. In this context, ground glass opacity on HRCT scans predicts the response to treatment and increased survival compared with patients in whom the predominant HRCT abnormality is a reticular pattern.[167] Despite the general applicability of this observation, there are several important caveats. Dilation of airways within ground glass opacity signals fine retractile fibrosis and, in these cases, the ground glass opacity will not be a reversible phenomenon.[168] Conversely, a reticular pattern and associated architectural distortion does not necessarily equate with irreversible fibrosis,[169] and it needs to be reiterated that the HRCT signs of basic pathological processes are indirect and therefore not wholly reliable. The robustness of various HRCT signs of disease reversibility in ILDs other than the IIPs is much less certain, although honeycomb destruction in advanced fibrosing lung diseases of whatever cause is readily evident on HRCT scanning and a reliable sign of irreversible disease.[170] There is currently no evidence to support the routine use of HRCT for the monitoring of patients with ILD. However, HRCT may be useful in providing an explanation in patients in whom there is a sudden and unexpected deterioration in clinical status.

Box 1 Interstitial lung diseases that may exhibit highly characteristic HRCT appearances

- Idiopathic pulmonary fibrosis
- Sarcoidosis
- Hypersensitivity pneumonitis (subacute)
- Lymphangitis carcinomatosis
- Langerhans' cell histiocytosis
- Lymphangioleiomyomatosis
- Alveolar proteinosis

7.5 HRCT in ILD: conclusions

HRCT is significantly superior to chest radiography in identifying and determining the correct diagnosis of ILD and the optimal site of biopsy for patients requiring a tissue diagnosis.

The combined information from clinical, laboratory and HRCT findings allows a correct diagnosis to be made in the majority of patients with ILD.

The combination of clinical features and HRCT appearances typical of IPF obviates the need for histopathological confirmation of the diagnosis.

A standard HRCT protocol is optimal in most patients with ILD and the need for extra techniques or volumetric HRCT must be carefully justified, given the extra radiation burden to the patient.

HRCT interpretation is a specialised task and requires an understanding of the clinical and pathological aspects of ILD.

Summary of chest radiography and HRCT recommendations

- **Radiologists with an interest in thoracic imaging and respiratory physicians should meet regularly to evaluate imaging in patients with ILD. [D]**
- **In patients for whom the diagnosis is uncertain after chest radiography and clinical assessment, HRCT scanning is the next investigation of choice. [C]**
- **HRCT is valuable in detecting ILD in patients with a normal chest radiograph. [B]**
- **In the appropriate clinical setting, appearances on the HRCT scan may be sufficiently characteristic to preclude the need for BAL or lung biopsy and histopathological confirmation. [B]**
- **Radiologists involved with determining the protocol and interpretation of HRCT scans should have expertise in the technique, be responsible for quality assurance and ensure that an appropriate radiation dose protocol is used. At least one radiologist in any department should have a declared interest and be trained in chest radiology and HRCT. [D]**
- **Consideration should be given to establishing a reference panel of radiologists with particular expertise in HRCT. [D]**

8. INITIAL BLOOD AND OTHER TESTS

Initial tests in cases of suspected ILD should include a urine dipstick, full differential blood cell count, serum urea,

electrolytes and creatinine, and liver function tests. Other tests, including autoantibody testing, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), calcium, serum angiotensin-converting enzyme (ACE), creatine kinase, precipitating antibodies, urinary calcium, baseline cardiac investigations and a tuberculin test should be performed based on the clinical context and differential diagnosis. The significance of all investigations must be interpreted in the light of clinical assessment and radiology.

8.1 Autoantibody testing in suspected interstitial pneumonia

Early studies suggested that up to 50% of patients with "CFA" have raised autoantibodies, but the inclusion of interstitial pneumonias other than UIP in this patient population hampers interpretation of the data. In the patient with suspected interstitial pneumonia, rheumatoid factor and antinuclear antibodies should be requested together with extractable nuclear antigens (Ro and La, RNP, Scl-70, Jo-1 and Sm). In the patient with a raised antinuclear antibody (ANA) titre, lupus anticoagulant and anticardiolipin antibodies should be measured. Smoking appears to be associated with the presence of rheumatoid factor, and most (but not all) studies have shown that smoking and/or the presence of rheumatoid factor is a risk factor for the development of ILD in patients with rheumatoid arthritis.[171–176] The ANA titre, albeit usually raised, bears no relationship to the presence or severity of disease in systemic sclerosis (SSc). However, autoantibody profiles associate strongly with SSc clinical phenotypes and may predate the onset of new symptoms.[177] Antitopisomerase (Scl-70) is associated with diffuse cutaneous SSc and with SSc-associated ILD, and anticentromere (ACA) antibodies are associated with limited cutaneous SSc and SSc-associated pulmonary artery hypertension. These antibodies are usually mutually exclusive. Other connective tissue disorders are also associated with patterns of autoantibody and pulmonary involvement. Anti-histidyl tRNA synthetase (Jo-1) is present in 20–30% of patients with inflammatory myopathy and in 50–100% of patients with polymyositis/dermatomyositis (PM/DM) with diffuse lung disease.[178]

8.2 Initial tests in suspected sarcoidosis

The diagnosis rests on the correct clinical setting, typical chest radiographic or HRCT appearances and a biopsy showing non-caseating granulomas.[179] A number of other tests may be decisive in shifting diagnostic probabilities in marginal cases or in strengthening the clinical probability such that tissue biopsy is unnecessary. Depending on the local prevalence, tuberculosis may be the most likely alternative diagnosis at presentation and patients should have a tuberculin test[180] and appropriate mycobacterial cultures of any biopsied tissues. A peripheral blood lymphopenia is often present in the active phase of sarcoidosis but is not diagnostic.[181] The serum ACE is considered by many to be a useful test but, with a low sensitivity (60%) and poor specificity, it cannot be used as part of the diagnostic algorithm.[182] It does not correlate with chest radiographic stage of disease in sarcoidosis, although it does correlate with the extent of nodules and consolidation on the HRCT scan.[183 184] However, the general consensus is that serum ACE does not add to the predictive value of serial lung function testing and imaging in disease management.[185] The test result needs to be considered in the light of the various polymorphisms of the ACE gene and the resultant variation in peripheral blood ACE levels.[186 187] The cerebrospinal fluid ACE level cannot be used to discriminate between neurosarcoidosis and other disorders.[188]

All patients with sarcoidosis should have baseline liver function tests, serum and urinary calcium analyses, the latter being more commonly abnormal,[189] and an ECG. The most common findings in cardiac sarcoidosis are non-specific ST–T segment abnormalities and conduction block.[190] Where there is evidence of significant extrapulmonary involvement in sarcoidosis (eg, cardiac, hepatic, ophthalmic or neurological disease), prompt referral to a relevant subspecialty team is necessary so that appropriate testing can proceed with expedition.

8.3 Initial tests in suspected HP

Measurement of serum IgG antibodies (precipitins) specific to an identified antigen (if known) should be undertaken. The presence of preciptins only indicates exposure and a humoral response; as such, up to 50% of asymptomatic pigeon breeders and 2–10% of asymptomatic farmers test positive for the relevant precipitating antibody.[191–193] The sensitivity of a positive precipitins test in well characterised diseases such as farmer's lung and pigeon-fancier's lung is probably very high, particularly in the acute and subacute forms. However, the overall sensitivity of precipitins testing across all cases of HP is restricted by the requirement to have an identifiable and testable antigen. While every effort must be made to identify an offending antigen, a presumptive diagnosis of HP may be made when a causative agent cannot be identified.[194] Inhalation challenges may be useful in diagnosing HP to a suspected antigen[195–197] but are generally limited to specific specialist centres, often with a research interest in the disease.

Investigations for suspected ILD-associated pulmonary hypertension (PH)

The diagnosis and management of pulmonary hypertension (PH) in ILD is discussed in detail in Section 23.

Summary of recommendations for initial blood and other tests

- **Initial tests in all cases of suspected ILD should include a urine dipstick, full differential blood cell count, serum urea, electrolytes and creatinine, and liver function tests. Other tests are largely dependent upon clinical context. [D]**
- **The serum ACE level has only limited role in diagnosis and does not contribute to monitoring patients with pulmonary sarcoidosis when added to serial lung function and imaging. [D]**

9. BRONCHOALVEOLAR LAVAGE AND TRANSBRONCHIAL LUNG BIOPSY

Further diagnostic tests may be performed to increase diagnostic confidence, allowing a more informed management plan to be agreed between patient and clinician. This is particularly pertinent in conditions in which the benefits of treatment are contentious, potentially harmful, or both. The principal factors influencing the decision to proceed to a bronchoscopy or surgical biopsy are the degree of confidence in the clinical diagnosis including the HRCT appearances and the patient's age, functional status and wish to proceed once informed of the risks versus benefit of the procedure.

9.1 Bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB)

Safety considerations

Flexible bronchoscopy, BAL and TBLB are safe outpatient procedures. The complications, precautions and contraindications have been comprehensively documented in recent guidelines.[198] Overall mortality and major complication rates following bronchoscopy are of the order of <0.05% and <0.5%, respectively.[199–201] The safety profile for BAL is probably not significantly different from bronchoscopy alone, and higher complication rates are generally associated with the more invasive procedure of TBLB. Pneumothorax has been reported in up to 10% of cases following TBLB but, more generally, the figure is 0.7–2% with about half requiring tube drainage.[201–206] Approximately 1–4% of patients with ILD experience significant haemorrhage (>50 ml) following TBLB.[202 203 206 207] There are numerous studies reporting the risk of bleeding in patients with thrombocytopenia or other bleeding diatheses. Most are retrospective, uncontrolled and of small numbers. For example, in a case series of 25 patients with platelet counts <60 000/mm^3, fatal haemorrhage occurred in one patient.[208] There is no reliable information on what constitutes a "safe" clotting screen. A large prospective study has shown that low-dose aspirin does not increase the risk of bleeding following TBLB.[209] Overall mortality for TBLB is approximately 0.1% with haemorrhage the main cause.[204] There is no convincing evidence that fluoroscopic screening increases safety or diagnostic yield in ILD.[203 204 210]

The optimal BAL technique has been addressed in several guidelines.[211–213]

9.2 Role of BAL and TBLB in diagnosis of ILD

The diagnostic utility of BAL or TBLB has not been re-evaluated since HRCT became a routine diagnostic tool in the investigation of ILD. In general, bronchoscopy is indicated if the patient is fit for the procedure and the clinical and HRCT findings suggest a condition in which BAL and/or TBLB are likely to be diagnostic or significantly increase diagnostic confidence. The conditions in which this applies are malignancy, pulmonary eosinophilia, infection, some rare ILD (alveolar proteinosis, LCH), subacute HP, sarcoidosis and COP. The decision to perform BAL, the more "invasive" TBLB, or both is also informed by the likely differential diagnosis and patient fitness, but also on availability of local expertise in differential BAL cell count.

Traditionally, BAL has been performed in one lobe, either the right middle lobe or one of the basal segments of the right lower lobe. While single-site BAL has been considered to be representative of the lung as a whole based largely on studies comparing the same lobe in either lung,[214 215] there is some evidence that this is not the case.[216] BAL may be more useful if targeted to a segment most affected, as identified by HRCT.[217] Similarly, the optimum site for TBLB should be informed by the HRCT appearance.

There are no studies that have compared the diagnostic utility of performing both BAL and TBLB versus a single procedure in patients with ILD. Furthermore, there are studies that suggest a role for BAL in determining prognosis, as opposed to diagnosis, in specific cases of ILD. For these reasons, it is useful to consider the potential roles of BAL and TBLB separately.

9.3 Diagnostic value of BAL without TBLB in ILD

Bronchoalveolar lavage (BAL) has been variably (and sometimes very) helpful as a diagnostic aid in the ILDs and remains an invaluable research tool providing information regarding immune effector cells that accumulate in the alveolus and their non-cellular products. In conjunction with clinical and HRCT findings, BAL alone may be sufficient to make a confident diagnosis of opportunistic infection,[218] malignancy,[219] acute eosinophilic pneumonia and alveolar proteinosis.[220] In reality, this group of conditions makes up a relatively small proportion of the total ILD population. BAL has been widely studied in the more common ILDs where its diagnostic role is more limited.

In sarcoidosis the BAL lymphocyte count is usually (but not always) raised.[221] However, if other granulomatous diseases—most pertinently HP—are high in the differential diagnosis, a raised lymphocyte count alone will not reliably distinguish between the two conditions. In such cases a raised CD4/CD8 ratio favours a diagnosis of sarcoidosis over HP, the latter often being characterised by a low CD4/CD8 ratio.[222–225] Raised BAL neutrophil counts are also seen in patients with sarcoidosis, and in this context have been shown to correlate with more severe disease on the chest radiograph and need for therapy.[226 227]

BAL has only a limited role in the diagnosis of IPF. BAL is not required to make a confident diagnosis if the clinical and HRCT findings are characteristic of IPF. In patients with ILD in which clinical and HRCT evaluation are inconclusive but in whom IPF remains high in the differential diagnosis, BAL cellular profiles are very unlikely to lead to a confident diagnosis. A finding of raised neutrophils (>4%) and raised eosinophils (>2%) is characteristic of IPF, while a lone increase in BAL lymphocytes is uncommon and these observations may influence diagnostic confidence. Within the IIPs the BAL inflammatory cellular profile may provide an indication of the underlying disease process, but there are insufficient data to support its use in discriminating between IPF and the other entities, particularly NSIP. The prevailing difficulty with NSIP—namely, its clinical heterogeneity—is discussed in the Introduction section. In general, NSIP is characterised by an increase in BAL granulocytes with the "cellular" variant often resulting in a concomitant increase in lymphocytes.[16 228 229] Where the HRCT appearances suggest an organising pneumonia pattern, a BAL yielding raised granulocytes and lymphocytes may be a useful discriminator. However, where the HRCT appearances suggest more fibrosis with a UIP-like pattern, the BAL cell count does not differentiate between fibrotic NSIP and UIP either diagnostically or prognostically.[230]

As with the IIPs, there are only limited data on the role of BAL in patients with connective tissue disease and associated ILD. BAL may reveal an increase in inflammatory cells in patients with subclinical pulmonary involvement.[94 231 232] It has been suggested that subclinical "alveolitis" in patients with SSc heralds an adverse course.[233 234] It is likely, however, that as with IPF, BAL neutrophils—which are strongly linked to the extent of disease on HRCT and the severity of functional impairment—merely reflect disease severity.[235] BAL eosinophil levels are higher in IPF than in SSc-related NSIP (the less progressive disorder) even after adjustment for disease severity.[236] In a recent study, BAL eosinophilia was associated with a significantly higher mortality, despite treatment, in patients with SSc with biopsy-proven NSIP.[28] One might therefore conclude that the neutrophil reflects disease extent whereas the eosinophil reflects disease progressiveness. However, routine BAL in such patients may not be as helpful as serial HRCT and, at least at this point, there is insufficient evidence to support the routine

use of BAL cell counts to determine need for treatment in the interstitial pneumonias.

9.4 Diagnostic value of TBLB

TBLB is a valuable tool in establishing a histological diagnosis in ILD. However, the size of specimen obtained is small and crush artefact and failure to penetrate beyond the peribronchial sheath may all preclude diagnostic histological assessment.[237 238] Furthermore, specific histological classification of ILD in most instances requires assessment of the disease pattern across the lung rather than the identification of specific histological features. Only specimens that contain abnormal alveolar tissue are likely to contribute to diagnosis, although such specimens may still be non-diagnostic. TBLB specimens consisting of normal lung or bronchial tissue or of fibrous tissue should be regarded as diagnostically unhelpful. Although there is no direct evidence to support the practice, it is reasonable to perform BAL in all patients undergoing TBLB.

Studies on unselected groups of patients presenting with the broad spectrum of ILD indicate that TBLB can give a specific diagnosis in 29–79% of cases.[201 206 210 238 239] The highest diagnostic yields are achieved in ILDs with centrilobular accentuation. These include granulomatous and metastatic diseases where the yield may be 65–89%[205 206 240 241] and, to a lesser extent, COP and HP in which the diagnostic yield is generally lower.[242] Multiple TBLBs increase the diagnostic yield from 60% to 90% in stage 2 sarcoidosis[243] and, in general, 4–6 biopsy samples are recommended in ILD.[205 244]

Bronchial mucosal biopsy is positive for non-caseating granuloma in 41–77% of patients with sarcoidosis.[240 241 245] In a prospective cohort study of patients with predominantly stage 1 and 2 sarcoidosis, addition of bronchial biopsy to TBLB increased the diagnostic yield by 21%.[246] Bronchial biopsy is more likely to be positive if abnormal looking mucosa is biopsied, but even macroscopically normal mucosa is diagnostic in 30–35% of cases.[246 247] The clinical significance of positive endobronchial biopsy in sarcoidosis is uncertain. Airway hyperreactivity may be more common in such patients, but it is not known if this is associated with subsequent development of airflow obstruction.[248]

Transbronchial biopsies do not allow a specific diagnosis of IPF or other IIPs, with the possible exception of COP.[237 238 242]

Summary of recommendations for BAL and TBLB in ILD

- **BAL or TBLB, when required, should be performed before the initiation of treatment. [D]**
- **BAL should be considered in all patients with suspected infection, malignancy and some rare ILDs. In such cases, BAL may be diagnostic. [C]**
- **BAL is not required as a diagnostic tool in patients with clinical features and HRCT appearances typical of IPF. [C]**
- **In patients for whom the diagnosis is uncertain after clinical assessment and HRCT scanning, typical BAL cellular profiles may allow a diagnosis of HP or sarcoidosis to be made with greater confidence. [C]**
- **In cases in which the diagnosis is uncertain and BAL is considered, the procedure should be performed in a regional centre with technical expertise in the procedure and the analysis of the BAL samples. [D]**
- **BAL should be performed in all patients undergoing TBLB. [D]**
- **TBLB is the initial procedure of choice in those patients likely to have ILDs in which small samples may be diagnostic, particularly if the disease has a tendency for bronchocentric involvement. HRCT should be used to guide the biopsy site. [D]**
- **Four to six TBLB specimens should be taken. [D]**
- **In suspected sarcoidosis, endobronchial biopsy samples in addition to TBLB are recommended since they are frequently positive, are associated with low morbidity and increase the diagnostic yield. [C]**
- **TBLB is not recommended as the initial biopsy option in cases of suspected IPF and is unreliable in the diagnosis of rare lung disease (other than alveolar proteinosis). [C]**

10. SURGICAL LUNG BIOPSY IN ILD

A surgical approach to lung biopsy provides a significantly larger specimen than TBLB, usually without crush artefacts. In prospective and retrospective studies, surgical lung biopsy has been shown to yield pathological diagnosis in 37–100% of cases.[238 249–252] Two key considerations impact upon the decision to pursue a surgical lung biopsy in a patient with ILD: (1) the risk associated with a surgical approach and (2) the recognition that histological assessment in ILD has limitations and that the multidisciplinary integration of clinical and HRCT data, perhaps with the addition of TBB/BAL data, is often sufficient to yield a confident diagnosis.

10.1 Safety of surgical lung biopsy

The overall complication rate of surgical biopsy is up to 7% with a mortality rate due to the procedure of <1%.[251 252] Postoperative pain (early and late) and persistent air leak are the commonest complications. A retrospective study of 88 patients with diffuse lung disease showed that surgical biopsy had no detrimental effect on lung function 2–6 months after the procedure compared with 48 non-biopsied patients.[253] Recently, a study reported that 10 of 60 patients in whom a diagnosis of UIP was made following surgical biopsy had died within 30 days of operation.[254] All biopsies were performed in patients in whom the clinical and/or HRCT features were not considered typical of IPF. Two subsequent studies from independent centres have reported that postoperative mortality in patients subsequently shown to have a UIP pattern of disease was no different from those with other ILDs.[255 256] Further studies are required to determine if an identifiable subgroup of patients with IPF are at a particularly high risk for surgical lung biopsy.

One measure of clinical benefit following lung biopsy is subsequent change in therapy. Overall, in studies in which "change in therapy" is a reported outcome, surgical lung biopsy resulted in therapy change in 18–65% of cases.[257 258] This figure is higher in immunocompromised subjects than in immunocompetent subjects.[257] Surgical biopsy should ideally be performed before initiating immunomodulating therapy, including corticosteroids. However, biopsy can still yield a histological diagnosis even if treatment has been started. Of 100 patients undergoing surgical biopsy, the diagnostic yield from 27 patients taking steroid or immunosuppressive therapy was identical to that of untreated patients.[258]

10.2 Open lung biopsy versus VATS biopsy

Surgical lung biopsies may be obtained through conventional limited thoracotomy (open lung biopsy, OLB) or a video-assisted thoracoscopic (VATS) approach. The latter has become

an increasingly common procedure since the early 1990s and is now performed in around 40 centres in the UK and Ireland.[259] Both OLB and VATS require general anaesthesia.

There have been two randomised controlled trials comparing OLB with VATS biopsy in diffuse lung disease. In both studies (total enrolment of n = 103 patients) there was no reported difference in surgery time, complications or diagnostic rate. Ayed and Raghunathan reported a significant reduction in hospital stay and analgesic requirement while in hospital in patients undergoing the VATS procedure.[260] The mean age of randomised patients in this study was 38 years. In contrast, Miller reported no difference in postoperative pain at any time point up to 3 months after the procedure and no difference in inpatient stay.[261] A third randomised study compared VATS biopsy with OLB in patients with indeterminate solitary pulmonary nodule and found significantly reduced hospital stay and pain scores in the VATS group.[262] This observation is confirmed in a systematic review of all randomised trials involving VATS, the majority of which, however, relate to interventions for pneumothorax or VATS lobectomy rather than small resections in patients with ILD.[259]

Retrospective and prospective cost analyses of VATS versus open lung biopsy have yielded conflicting results and are difficult to interpret in the light of differences in analysis and health care delivery.[261 263–266]

10.3 Site of biopsy and number of biopsies performed

There is ongoing controversy over the most suitable site for biopsy in ILD. The lingula and middle lobe are considered technically to be the easiest to access and staple. It has been suggested that these sites be avoided because biopsy samples often show non-specific vascular or fibrotic changes not seen elsewhere in the lung.[148 251 267 268] In contrast, several more recent studies have found that lingula and middle lobe biopsies provide a histological diagnosis equivalent to tissue obtained from other sites.[269–272]

Multiple (multisite and multilobe) surgical lung biopsies increase time, cost and potentially complications. However, the lungs of patients with IIP display marked heterogeneity in histological pattern both between and within lobes.[273] Two recent retrospective observational studies have reported on variation in histological pattern in patients with suspected IPF in whom multiple biopsies were obtained.[274 275] A discordant pattern—namely, UIP reported in one biopsy sample and NSIP reported in a separate sample from the same patient—was observed in 36 (21%) of 171 cases. Both studies show that, in these discordant cases, the clinical course and prognosis followed that of patients in whom multiple biopsies were all concordant for UIP (n = 76) rather than those concordant for NSIP (n = 59). Thus, a specific aim when subjecting patients to biopsy is the reliable identification of UIP, if present. In this regard, the HRCT provides valuable information that should be used to guide biopsy sites. Areas of ''honeycombing'' are best avoided as they will very likely reveal established but non-specific fibrosis. Areas of entirely normal-looking lung should similarly be avoided. In patients with suspected IIP, areas of intermediate abnormality or comparatively normal lung adjacent to honeycomb lung should be targeted.

10.4 Handling of lung biopsy samples

Surgical lung biopsy specimens should be at least 4 cm in maximum diameter when inflated and include a depth (distance from pleural surface) of 3–5 cm. The biopsy sample should be handled with minimal trauma and sent fresh to the laboratory without delay so that it can be gently inflated with formalin using a syringe and a small gauge needle inserted through the pleura.[276] This should ideally be performed by trained personnel in theatre or the tissue sent fresh to the pathology laboratory with minimal delay. In ILD, frozen sections are only of value in suspected malignancy. It may be appropriate to freeze a small portion of unfixed specimen for immunofluorescence, but not at the expense of tissue needed for histological examination. Small pieces of fresh tissue can be taken for microbiology/virology as required. Immunohistochemical techniques, in situ hybridisation and PCR can all be applied to maximise the diagnostic yields.[277 278]

10.5 Diagnostic value and limitations of histology in ILD

The multidisciplinary model for diagnosis in ILD requires an iterative approach in which all available data are integrated in reaching a final diagnosis. One group has tested the effects of such a diagnostic approach and has confirmed that, as more data are added and interaction among diagnosticians is encouraged, there is improved interobserver agreement among expert clinicians, radiologists and pathologists.[6] Importantly, the greatest change in intraobserver agreement between clinicians and radiologists occurs when histological information becomes available. There are, however, few interobserver studies on the pathological diagnosis of ILD. A study carried out by members of the UK ILD Pathology Panel assessed the diagnostic confidence of specialist lung pathologists using the ATS/ERS consensus classification for IIP.[21] The overall kappa coefficient of agreement for the first choice diagnosis was 0.38 (n = 133 biopsies), increasing to 0.43 for patients with multiple biopsies (n = 83). Weighted kappa coefficients of agreement, quantifying the level of probability of individual diagnoses, were moderate to good (average 0.58, range 0.40–0.75). However, in 18% of biopsies, diagnostic confidence was low. Over 50% of interobserver variation related to the diagnosis of NSIP and, in particular, its distinction from UIP. It should be noted, however, that this study was carried out by pathologists in reporting cases in isolation without access to clinical or radiological data. Overall, these data support the value of surgical lung biopsy in achieving a final confident diagnosis in many IIPs if doubt remains regarding the diagnosis after the radiologist and clinician have had the chance to confer. Ideally, surgical lung biopsies should be reported by a pathologist with a stated interest in lung pathology.

A common and particularly vexing scenario is if the diagnostic uncertainty, based on clinical, HRCT and BAL/TBLB data, effectively lies between distinguishing UIP from fibrotic NSIP with an IPF-like profile. Only a surgical lung biopsy can facilitate the distinction between these two conditions. Overall, individuals with histological fibrotic NSIP have a better prognosis than those with definite IPF, but in both conditions declining lung function, particularly a 10% fall in FVC at 6–12 months, is a powerful indicator of poor prognosis. Furthermore, the recommended treatment options for IPF and for fibrotic NSIP with an IPF-like profile are very similar (table 3). Thus, the value of a surgical lung biopsy to the patient and to the clinician may be to guide prognosis at the time of diagnosis, as opposed to estimating prognosis based on serial lung function. Given the clear uncertainties described, together with the risks of surgery, the final decision regarding surgical lung biopsy in such cases should be based on a full and frank discussion with an appropriately informed patient. In this

regard, the approach is identical to that described for considering treatment options in IPF (see Section 13.4).

10.6 When is a surgical biopsy not indicated?

A surgical lung biopsy is not required in cases of ILD if integration of clinical, radiological and, where appropriate, BAL/TBLB data lead to a confident diagnosis. In suspected IPF, a highly suggestive clinical presentation together with typical HRCT scan findings (Section 7.3) obviates the requirement for a surgical lung biopsy.

Summary of recommendations for surgical lung biopsy in ILD

- **Surgical lung biopsy, when required, should be performed before the initiation of treatment. [D]**
- **A confident pathological diagnosis of IPF or the other interstitial pneumonias can only be made if a surgical lung biopsy is obtained. [C]**
- **A confident clinical diagnosis of IPF can be reliably made in the presence of characteristic HRCT and clinical findings. [C]**
- **If a surgical biopsy is performed in cases of suspected interstitial pneumonia, more than one biopsy specimen must be taken from more than one site, preferably from different lobes. [C]**
- **Multiple multilobe lung biopsies are technically easier by VATS procedure than by open lung biopsy [D]. VATS is also associated with less early postoperative pain than open lung biopsy. [B]**
- **It is recommended that the precise biopsy sites are based on HRCT appearances [D]. In patients with suspected IIP, areas of intermediate abnormality or comparatively normal lung adjacent to areas of established honeycombing should be targeted with the specific aim of identifying UIP if present. [D]**

11. THE CARE PATHWAY IN ILD

The pivotal role of a multidisciplinary diagnostic approach in ILD has been emphasised in several sections of this document. The constitution of regional ILD clinics, tertiary ILD centres and a national ILD network together with the rationale for their development are discussed in detail in the Introduction (Section 1.8).

However, it is clear that the routine referral of all patients with ILD to specialist ILD clinics is not currently practicable. Furthermore, the Committee believes that continued involvement by local physicians is highly desirable, even in patients followed in specialist clinics. Without a "shared care" approach, local physicians are often required to deal with acute issues without knowledge of the patient and a grasp of case complexities. Studies are required to evaluate the true benefit of this model of care but, in the interim, it is recommended that patients with ILD be referred to a specialist clinic when:

- there are obvious difficulties in diagnosis, including the question of whether a diagnostic surgical biopsy should be performed;
- there are difficult management decisions (often compounded by diagnostic uncertainty);
- there is a perceived need to access lung transplantation or trials of novel therapies;
- routine therapies are not readily available in local practice (as when intravenous cyclophosphamide therapy is warranted, but local infrastructure falls short);
- a local physician considers that he/she lacks sufficient experience to manage ILD;
- patients request access to subspecialist expertise.

It is emphasised that, following initial assessment in a specialist clinic, decisions on the need for and frequency of clinic follow-up must be individualised to the patient. In many cases a single assessment may suffice, with subsequent local follow-up and re-referral if warranted. Often, occasional strategic review (eg, annually) is thought worthwhile by the patient and referring physician. Less frequently, the complexities of a case demand more frequent follow-up, and this especially applies to cases in which the diagnosis is uncertain and is likely to be modified according to the therapeutic response. Thus, the timing of follow-up in a regional and tertiary clinic should be negotiated carefully without losing sight of the importance of ongoing involvement by the local physician.

12. GENERAL MANAGEMENT STRATEGIES IN ILD

A number of management issues are applicable to the broad range of ILDs. These include providing the patient with disease-specific information and advice on smoking cessation. Several other aspects of ILD management such as palliation of breathlessness and cough, treatment of complications of ILD such as pneumothorax and applying best supportive care are also relevant across a range of ILDs but, for most clinicians, will most commonly arise in the context of IPF and are hence discussed in detail specifically in the section on IPF management. Finally, PH is also relevant to a number of ILDs but is often under-recognised.

12.1 Communicating the diagnosis

Patients should be offered tailored but clear and accurate information regarding the diagnosis, treatment options and prognosis. An abundance of information related to IPF, sarcoidosis and other ILDs is easily accessible to patients and their relatives, for example through the world wide web. Only a small proportion of this might be considered to be of sufficient quality, suitability and usability for the majority of patients. The onus is therefore on the clinician supported by a specialist respiratory nurse to provide this information both verbally and in writing. Patient information sheets for IPF, sarcoidosis and HP are provided in Appendices 6–8 of this guideline available in the online data supplement.

12.2 Smoking cessation

All patients with ILD should be advised to stop smoking. Patients with IPF have an up to 10-fold increased risk of developing lung cancer whether they smoke or not.[60 279] This increase in cancer risk is multiplicative with that from smoking, so patients with IPF who smoke 20 cigarettes a day may have a 200-fold increase in the risk of lung cancer compared with non-smokers without IPF. Patients with IPF who smoke should therefore be a priority for smoking cessation services. Details of smoking cessation services are given in the BTS smoking cessation guidelines[280] but, briefly, every patient with IPF who smokes should receive regular opportunist advice to stop smoking and should be offered specialist support and prescriptions for nicotine replacement therapy or bupropion. There are reports in the literature that patients with IPF who smoke have a better prognosis than those who do not smoke.[107 112] This may be because the coexistence of COPD leads to an earlier

presentation of IPF,[105] and these reports should not discourage the use of smoking cessation services.

There are data suggesting that current smoking may decrease the risk of developing sarcoidosis and/or HP.[64 281–287] It is not clear whether this reduced risk results directly from smoking or from other socioeconomic and/or environmental factors related to smoking. One study has suggested that smoking may lead to a worse outcome in patients with HP who smoke[288] and, given the widespread adverse impact of smoking on health, it is recommended that all patients with ILD are advised to stop smoking.

12.3 Pulmonary rehabilitation

There are no randomised controlled trials of pulmonary rehabilitation in ILD. There are only a few observational studies of pulmonary rehabilitation and these have demonstrated improvement in exercise tolerance and quality of life measures over 6–8 weeks of pulmonary rehabilitation in patients with ILD.[289 290] Pulmonary rehabilitation has an established role in the management of COPD and, based on a substantial body of evidence, is associated with reduced breathlessness, improved health-related quality of life and fewer hospital admissions.[291] Deconditioning, disabling breathlessness, impaired quality of life, nutritional deficit, fatigue and social isolation are common both in patients with COPD and ILD. While further studies are required to determine the optimum form of pulmonary rehabilitation in patients with ILD, it is recommended that patients with ILD be considered for pulmonary rehabilitation based on the same criteria as for COPD.

Summary of recommendations for the care pathway and general management strategies for ILD

- **All patients with ILD should have access to a multidisciplinary team based in a regional centre with expertise in ILD. [C]**
- **Referral to a regional ILD clinic should be made if there are perceived difficulties in diagnosis and/or management, but a tailored shared care model is advocated. [D]**
- **Patients with ILD who are current smokers should receive opportunistic smoking cessation advice from healthcare professionals and this advice should be recorded in the clinical notes. Current smokers should be offered specialist support and nicotine replacement therapy or bupropion on NHS prescription. [B]**
- **Patients with ILD should have access to a local pulmonary rehabilitation programme. [C]**

MANAGEMENT OF SPECIFIC ILDS

This section of the guideline provides guidance and recommendations on the management and specific therapy for patients with IPF, NSIP and other IIPs, ILD associated with rheumatoid arthritis, SSc and PM/DM, HP and sarcoidosis. PH is a complication of ILDs and is discussed in detail in Section 23.

13. IDIOPATHIC PULMONARY FIBROSIS (IPF)

Current epidemiological data report a mean life expectancy for newly diagnosed cases of between 2.9 and 5 years.[13] While it is hoped that an increasing number of patients with IPF will be recruited to clinical trials, benefit from the emergence of novel efficacious drugs or undergo lung transplantation, the current reality for the majority is that the disease will progress over a period of months and years towards a terminal phase. At the time of diagnosis, patients often show relief that they are not suffering from lung cancer. Clinicians may then fail to emphasise that the long-term prognosis could be little different from that of many malignancies. Any reluctance to confront this prognosis, together with the paucity of palliative care services for non-malignant diseases, has led to many patients with advanced IPF receiving suboptimal care. In patients with IPF it would seem reasonable then to adopt a general management approach not dissimilar to that accepted when a diagnosis of inoperable lung cancer is made. This includes providing patient information and support and best supportive care, including palliative treatment of symptoms and complications of the disease.

13.1 Best supportive care and treatment of symptoms and complications of IPF

The natural history of IPF is characterised by periods of relative stability which may be interspersed with episodes of stepwise deterioration in symptoms of breathlessness and cough and declining lung function. Acute exacerbation or "accelerated phase" of IPF is dealt with in a separate section of the guideline.

Although there is no clear definition of "best supportive care" (BSC), the term permeates many national and international guidelines, invariably in the context of cancer. BSC is proactive and incorporates all aspects of palliative care, defined by the World Health Organization (WHO) as "*an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual*". It should be stressed that BSC applies to all patients with IPF, be they young patients on lung transplant lists, those recruited to clinical trials or treated with potential disease-modifying drugs or elderly patients with advanced disease. BSC includes the avoidance, dose reduction or withdrawal of therapy that does significant harm without perceivable benefit. This is particularly pertinent in patients with advanced disease in whom there are few or no data to support the chronic use of corticosteroids or other immunosuppressive therapies with potentially toxic side effects.

BSC should therefore be acknowledged as a specific and important treatment strategy in patients with IPF to be delivered with appropriate input from palliative care medical and nursing specialists. Smoking cessation and pulmonary rehabilitation are important components of BSC and have been discussed under "General management strategies".

Supplemental oxygen therapy and treatment of breathlessness

Subjective dyspnoea is important in terms of perceived quality of life and may contribute to symptoms of depression.[292] However, there is no evidence that oxygen therapy influences quality of life or long-term survival in patients with IPF or other ILD.[293] The provision of oxygen in cardiopulmonary disease has been addressed by a BTS Working Group (http://www.brit-thoracic.org.uk/page294.html). In the absence of suitable controlled studies of long-term, short burst or ambulatory oxygen therapy in ILD, recommendations are made such that they are consistent with those published by the BTS Working Group. It is recommended that patients with persistent resting hypoxaemia Pa_{O_2} at or below 7.3 kPa (55 mm Hg) or below 8 kPa with clinical evidence of PH and who are breathless should be considered for palliative oxygen at home delivered by oxygen

concentrator. These individuals may also benefit form ambulatory oxygen if they remain active outside the home.

Patients who are not chronically hypoxic but who are breathless, mobile and exhibit desaturation on exercise (<90%) should be considered for ambulatory oxygen if improvement in exercise capacity and/or less breathlessness can be demonstrated by formal ambulatory oxygen assessment. Intermittent supplemental oxygen for periods of 10–20 min at a time and delivered by oxygen cylinder (short burst oxygen therapy) may relieve breathlessness associated with hypoxaemia in patients with ILD who do not require oxygen concentrator or ambulatory oxygen. When prescribing oxygen for palliation in ILD, it is reasonable to individually titrate oxygen therapy according to oxygen saturations measured during normal activity.

Nocturnal hypoxaemia is common in patients with IPF and may be associated with daytime impairment of quality of life,[294] but there is no evidence that supplemental oxygen is useful in this setting. Clinical trials are required to determine the role of oxygen on survival and quality of life in patients with ILD.

Oral opiates may be effective in relieving distress from breathlessness in patients with IPF, although nebulised morphine had no effect on dyspnoea or exercise tolerance in six poorly characterised patients with advanced disease.[295] If available, liaison with palliative care services is encouraged and may lead to a more holistic approach to symptom relief.

Cough

Cough is a frequent and troublesome symptom for patients with IPF. In current or ex-smokers, productive cough may arise from coexistent chronic bronchitis. The pathogenesis of the typical irritating dry cough in IPF is, however, poorly understood. In some cases it is associated with gastro-oesophageal reflux disease (see below). An enhanced cough reflex sensitivity to inhaled capsaicin, suggesting upregulation of sensory receptors, has been demonstrated in IPF.[296 297] In one uncontrolled study high-dose steroids apparently reduced capsaicin sensitivity,[297] but the routine use of steroids to treat cough in IPF is not recommended given the potential side effects. Conventional antitussive agents such as oral codeine are widely used but there is no evidence of efficacy. Oral opiates may be used for intractable cough, particularly in end-stage disease.[298]

Gastro-oesophageal reflux disease (GORD)

A pilot study using ambulatory oesophageal pH monitoring has reported a very high incidence of acid reflux in patients with IPF compared with controls.[299] This observation has been confirmed in an extended prospective study of 65 patients with IPF in which 24 h pH monitoring and oesophageal manometry revealed abnormal acid reflux in 87% with only half the subjects reporting classic gastro-oesophageal reflux symptoms.[300] Gastro-oesophageal reflux may play a role in the pathogenesis and progression of IPF[301] and requires further study. It is recommended that all symptomatic patients with IPF should be treated with a proton pump inhibitor.

Pneumothorax

Spontaneous pneumothorax or pneumomediastinum is a recognised complication of IPF and should be suspected when a patient complains of a sudden increase in breathlessness.[302] Sometimes a CT scan may detect a pneumothorax that is not apparent on plain radiography. Pneumothorax usually requires insertion of an intercostal drain and pleurodesis is recommended. Pleurodesis is not a contraindication to future lung transplantation. Pneumothorax can be a late complication of IPF and cause severe breathlessness. In such cases the lung may fail to re-expand after insertion of an intercostal drain because of altered lung compliance and palliative care may be more appropriate.

Lung cancer

IPF predisposes to non-small cell and small cell lung cancer. Diagnosis and staging should be undertaken as for any other patient, although poor lung function from coexisting pulmonary fibrosis makes the possibility of curative treatment less likely. One study suggests that patients with pulmonary fibrosis undergoing pulmonary resection for non-small cell lung cancer have increased postoperative morbidity and mortality.[303] There is insufficient published data to indicate if treatment for lung cancer (eg, with radiotherapy) exacerbates pulmonary fibrosis.[304]

13.2 Potentially disease-modifying therapy for IPF

The reclassification of IPF/CFA by histological subgroup (UIP and other patterns) is discussed in the Introduction. It is now possible to make a confident diagnosis of IPF using a multidisciplinary approach integrating clinical and HRCT criteria and, when available, biopsy data. In clinical practice, however, a confident diagnosis of IPF cannot always be made. Patients commonly present with clinical and HRCT features compatible with, but not diagnostic of, IPF and a surgical biopsy may not be performed for reasons of co-morbidity or patient wishes. In this setting, a clinical diagnosis of ''probable IPF'' would be reasonable, accepting that an unknown proportion of such cases will not actually have IPF, with idiopathic fibrotic NSIP being the most likely alternative. Finally, and less commonly, there will be patients who have a clinical and radiological profile overlapping with IPF but who exhibit a fibrotic NSIP histological pattern at lung biopsy. These patients therefore have ''definite'' fibrotic NSIP but with an IPF-like profile. This distinction between these three patient groups—definite IPF, probable IPF (with a most likely differential diagnosis of fibrotic NSIP) and definite fibrotic NSIP (with an IPF-like profile)—is important since they appear to have different outcomes.[4 5 38] However, provision of evidence-based recommendations for treatment in these three common clinical scenarios is hampered either because of a complete absence of controlled clinical trials addressing the specific disease, as is the case for fibrotic NSIP, or because many older ''pre-reclassification'' studies of IPF/CFA are likely to have recruited a heterogeneous patient population that will have included an unknown mixture of patients with definite IPF, probable IPF, fibrotic NSIP and perhaps other ILDs. In contrast, the recent large multicentre clinical trials in IPF have used selection criteria such that the vast majority of recruited patients will have had a confident diagnosis of IPF based on ATS/ERS consensus criteria.[2]

Thus, there is now an increasing amount of data from clinical trials that applies to patients with ''definite'' IPF. Despite the extreme paucity of data on treatment of ''probable IPF'' or fibrotic NSIP, the Guideline Committee felt compelled to offer some form of guidance on their management since they will commonly arise in clinical practice. The treatment options and recommendations are summarised in table 3. The rationale and evidence base for making the recommendation is discussed below and further addressed in Section 14.

Table 3 Treatment options for IPF and NSIP/IPF

Options for therapy	Diagnosis of definite IPF	Diagnosis of probable IPF	Diagnosis of fibrotic NSIP with IPF profile
	Requires: 1. Clinical features consistent with IPF 2. Diagnostic HRCT scan *or* UIP on biopsy and HRCT scan consistent with IPF	Requires: 1. Clinical features consistent with IPF 2. HRCT scan consistent with but not diagnostic of IPF 3. Absence of lung biopsy	Requires: 1. Clinical features consistent with IPF 2. HRCT scan consistent with but not diagnostic of IPF 3. Histological pattern of fibrotic NSIP
No specific drug therapy: patient co-morbidity, concerns of side effects, patient wishes, mild disease without evidence of progression, etc may preclude specific drug therapy	No specific therapy may be appropriate for some patients [D]	No specific therapy may be appropriate for some patients [D]	No specific therapy may be appropriate for some patients [D]
Trial of high-dose steroid monotherapy (eg, 0.5–1 mg/kg for up to 3 months followed by dose reduction). Maintenance dose and length of treatment dependent on objective response (improvement or lack of progression) in lung function and/or radiology	No – strong recommendation [C]	No – strong recommendation [D]	No –weak recommendation [D]
Prednisolone and azathioprine as per ATS/ERS guidelines (prednisolone 0.5 mg/kg/day tapering over 3 months to 0.125 mg/kg/day and azathioprine 2–3 mg/kg/day to a a maximum of 150 mg/day)	Not recommended without N-acetylcysteine (NAC) pending further evidence		
Prednisolone and azathioprine as per ATS guidelines + NAC 600 mg three times daily*	Yes – weak recommendation [C]	Yes – weak recommendation [D]	Yes – weak recommendation [D]
Interferon-γ-1b	Not recommended pending further evidence		
Pirfenidone			
Bosentan			
Other therapeutic options	There are insufficient data to make evidence-based recommendations on therapeutic regimes other than those described above. Combination or single drug regimes that include low dose prednisolone (20 mg/day or less) and/or azathioprine and/or NAC may be better tolerated than the suggested alternatives but are without evidence base.		
When to start drug therapy if decision to treat is made:	There are no data on which to make evidence-based recommendations for when to start treatment. It is therefore suggested that treatment, if started, could equally reasonably be initiated at diagnosis *or* following objective evidence of disease progression *or* in moderate/severe disease [D]		

*Currently unlicensed for this indication in the UK.

Patients should be carefully evaluated before commencement of treatment. All patients should have a dyspnoea score, full pulmonary function tests, chest radiograph and HRCT scan of the thorax. Submaximal exercise testing such as a 6MWT may also be considered if available.

Corticosteroids as monotherapy for IPF

The use of corticosteroids, either alone or in combination with immunosuppressive drugs, has been standard therapy for patients with IPF over many years. This is largely because numerous previous observational studies, some of which were in CFA, reported that 42–57% of patients had a subjective improvement following steroid therapy, although only 12–25% exhibit an objective response often (variably) defined as an improvement in lung function or chest radiograph.[89 305 306] There is no evidence that such a response is matched by sustained improvements in other clinical outcomes such as mortality or quality of life. While such trials lack the power to exclude minor effects, the ongoing use of corticosteroids is often driven by the compulsion to "do something" in a condition which proves difficult to treat rather than the application of evidence-based medicine.[307 308]

More recent studies do not support the use of corticosteroids in IPF. A UK population-based cohort study of 244 patients with a "physician diagnosis" of CFA reported higher mortality rates in patients treated with either steroids or cyclophosphamide.[52] While these findings may represent selection bias as treated patients may have had more severe disease, two other retrospective studies also failed to demonstrate a sustained beneficial effect of corticosteroids. In a study of 234 patients in Japan there was no difference in mortality between patients treated with corticosteroids and untreated patients.[309] Investigators from the Mayo Clinic reported a restropsective intent-to-treat analysis of survival in 157 patients with IPF on no therapy, 54 patients on maintenance prednisolone only, 167 patients treated with colchicine alone and 71 patients on colchicine and prednisolone. When adjustment was made for age, sex and lung function, there was no significant difference in survival between patients treated with prednisolone and those on no therapy.[310] In keeping with these observations, a thorough evaluation of the role of corticosteroids in the treatment of IPF found no suitable data available for meta-analysis and concluded that there was no evidence that steroids prolonged survival or improved quality of life in IPF.[311] Increasingly, opinion advises against the use of "high-dose" corticosteroids (prednisolone 0.5–1 mg/kg) in patients with IPF who have histologically proven UIP or evidence of extensive honeycombing on HRCT scan.[45 307 312 313] High-dose steroids are therefore not recommended in definite IPF. Although the evidence is substantially weaker, those with "probable" IPF based on clinical and radiological grounds alone are also highly unlikely to derive overall benefit and high-dose steroids are not recommended for these patients. Finally, patients with fibrotic NSIP but with an IPF-type clinical/radiological profile are also unlikely to benefit from high-dose steroids. However, there are data from uncontrolled case series to support a role for steroids in some cases, and thus the recommendation to avoid high-dose steroids in this group is a relatively weak one.

Corticosteroids as adjunct therapy and other drugs for IPF

Although there is no evidence to support a role for steroids as monotherapy in IPF, a number of important studies undertaken before the new classification have incorporated prednisolone into one or more therapeutic arms. Of these, trials combining corticosteroids with azathioprine have had the greatest impact on clinical practice to date. However, it is worth stressing that there have been no randomised controlled trials demonstrating benefit of steroid/immunosuppressive combinations over placebo.

Selection criteria in more recent (post-reclassification) trials have led to the recruitment of a virtually homogeneous population of patients with definite IPF, albeit at varying stages in the natural history of the disease, and the last 2 years have heralded the first large multicentre studies: one examining the effect of adding IFNγ-1b to corticosteroids and the other N-acetylcysteine (NAC), the latter as an adjunct to prednisolone and azathioprine.

Azathioprine

Azathioprine is a purine analogue which inhibits DNA synthesis and has widespread immunosuppressive effects. No study has looked at azathioprine as single agent treatment for IPF compared with placebo or any other treatment. There have been occasional reports of a few patients who appear to have responded to azathioprine, with or without corticosteroids, but it is difficult to interpret such observations objectively.

There have been two prospective studies evaluating the effects of azathioprine with concomitant steroids in IPF. Winterbauer *et al* treated 20 patients with oral prednisolone for 3 months and then added azathioprine 3 mg/kg daily.[314] Improvement was reported in 12 patients (60%). However, in the absence of a control arm, the effects of azathioprine alone cannot be evaluated. The second study was a randomised controlled trial which compared the addition of azathioprine (3 mg/kg) to high-dose steroids alone (biweekly tapering from 1.5 mg/kg/day to 20 mg/day maintenance) in 27 patients with well characterised IPF, the majority of whom would probably now be classified as definite IPF.[315] There was no difference in lung function with treatment at 1 year, the stated primary end point. There was a statistically significant improvement in survival in the azathioprine/prednisolone group (n = 14) when adjusted for age (57% vs 23%), but only after 9 years follow-up and the survival curves did not diverge until 4 years. Side effects were reported to be similar in both groups and appeared to be related to steroid therapy. Azathioprine was reportedly well tolerated in this study but recognised side effects include idiosyncratic reactions, hepatitis, bone marrow suppression and gastrointestinal symptoms. This well conducted trial on few patients is frequently quoted as justification for treating patients with an azathioprine/corticosteroid combination. However, quality of life was not assessed, changes in lung function were not significant between the groups and a significant ($p<0.05$) survival difference at 9 years should be viewed in the context of a median survival for incident cases of just 2.9 years, albeit for "physician diagnosed CFA".[52]

The 1999 ATS/ERS consensus statement suggests prednisolone and azathioprine as a therapeutic option for IPF but with a lower starting dose of prednisolone (0.5 mg/kg/day tapering over 3 months to 0.125 mg/kg/day). Patients treated with azathioprine should be assessed regularly for adverse effects including nausea, vomiting, diarrhoea, hepatic and renal toxicity and bone marrow suppression.

N-acetylcysteine (NAC)

A number of in vitro and animal model experiments led to the suggestion that a redox imbalance may contribute to the development of IPF. The subsequent clinical observation that lung epithelial lining fluid from subjects with IPF was depleted of reduced glutathione laid the foundation for clinical trials of NAC.[316] One short-term (12-week) study in 18 patients with IPF demonstrated a small but significant improvement in lung function and more than 50% of patients also reported a subjective improvement in dyspnoea. Levels of total and reduced glutathione were increased in BAL fluid and epithelial lining fluid after treatment, but there was no change in BAL cell counts. Interestingly, the observed benefits of this treatment were only observed in patients on concomitant immunosuppressive therapy.[317]

This has led to an international randomised double-blind study to assess the effects of NAC in patients in whom a confident or probable diagnosis of IPF was made either on clinicoradiological criteria (82 patients) or clinicoradiological criteria and a lung biopsy (73 patients).[9] All 155 patients analysed in the study received prednisolone (tapering from 0.5 mg/kg/day) and azathioprine (2 mg/kg/day) as per ATS/ERS consensus statements. Of these, 80 patients received NAC (600 mg three times daily) and 75 patients received placebo. Over the study period of 12 months, lung function fell in both groups but was significantly better preserved in those receiving NAC (VC was 180 ml (9%) and T_{LCO} 0.75 mmol/min/kPa (24%) higher in the NAC group than in the placebo group). Survival was similar in both groups over the period observed, although the study was not powered to detect a difference in mortality. Compliance was comparable in both groups suggesting a good side effect profile. However, patients in whom the standard regimen with prednisolone and azathioprine was contraindicated or "not justified" were excluded from the study and 40% of participants were recruited within 6 months of diagnosis. These results are encouraging but can be interpreted in a number of ways: that NAC has a synergistic effect with the other two drugs; that NAC counters possible deleterious effects of the other two drugs; or that NAC has a beneficial effect and the other two drugs are ineffective. Placebo and NAC alone trials are urgently needed.

Interferon-γ-1b (IFNγ-1b)

IFNγ is a Th1 cytokine which has been shown in several in vitro studies to downregulate collagen gene expression and suppress products/effects of profibrotic growth factors.[318–320] Further supporting evidence for its potential role in UIP comes from animal models.[321] This led to the hypothesis that it might prevent progression of pulmonary fibrosis initially tested by Ziesche *et al*.[322] Patients with IPF who had failed to respond to previous immunosuppressive therapy were randomised in a phase 2 open label randomised study. Nine were treated with steroids alone and nine received steroids together with IFNγ-1b. At the end of 12 months the group treated with IFNγ-1b showed stabilised or improved lung function, whereas those on steroids alone all showed a decline. However, there was significant controversy over the diagnosis of IPF in these patients. Subsequently, Kalra *et al* treated 21 patients with advanced IPF with IFNγ-1b for a mean period of 8 months and found only one patient with symptomatic and functional improvement.[323] Furthermore, 11 patients died after a mean of 6 months of treatment.

These studies led to a phase 3 randomised prospective double-blind placebo controlled trial of IFNγ-1b in 330 patients with

IPF.[10] Over 80% of the patients recruited had a radiological diagnosis of definite IPF and over 60% of patients were biopsied to confirm UIP. Hence, the vast majority of participants were confidently diagnosed with IPF. No significant effect on lung function was observed at any time point. There were more deaths in the placebo group (17%) than those treated with IFNγ 1b (10%), but this trend did not reach statistical significance ($p = 0.08$). Survival was found to be significantly better in a subgroup (not predefined) of patients treated with IFNγ-1b who had better lung function (FVC >55% and TLCO >35%) on entry.

A meta-analysis of pooled survival data from three applicable studies[10 324 325] has demonstrated that IFNγ-1b may confer a significant survival advantage in IPF (pooled hazards ratio 0.418; 95% confidence interval 0.253 to 0.69; $p = 0.0003$; $n = 390$).[326] However, the data are not conclusive. The specific hypothesis that IFNγ-1b improves survival in patients with mild and moderately severe IPF has been refuted in a further large multicentre trial (INSPIRE), which has been reported verbally but is not yet published.

It is noteworthy that rapidly progressive respiratory failure in patients with end-stage pulmonary fibrosis treated with IFNγ-1b has been described,[327] indicating that such therapies should always be used with caution.

Cyclophosphamide

Cyclophosphamide is an alkylating agent with powerful immunosuppressive properties. One early prospective randomised controlled study compared high-dose prednisolone (60 mg daily with taper) in 22 patients with combination cyclophosphamide and low-dose prednisolone (20 mg alternate days) in 21 patients, including a significant proportion with collagen vascular disease.[328] If patients showed a lack of response to their randomised treatment they were switched to the alternative regime. After 3 years follow-up, mortality was higher in the steroid cohort (10 of 22 died) than in the cyclophosphamide group (3 of 21 died), but there was no statistical difference in survival between the groups. If death and treatment failure of the first regime were examined as a single outcome, the combined regime was associated with a more favourable clinical course. However, in the cyclophosphamide group, pulmonary function improved in only 1 patient, was stable in 7 and deteriorated in 14. Interpretation of these findings is difficult as a greater proportion of patients with poor lung function (TLC <60%) were randomised to the steroid arm of the trial. A more recent prospective study examined the role of oral cyclophosphamide (2 mg/kg) alone in 19 patients with biopsy-proven UIP who were unresponsive to, or intolerant of, high-dose steroids.[329] Patient evaluation was not consistent; in some, clinical, radiographic and physiological scores were undertaken while, in others, physiological criteria alone were used. Only 1 patient improved, 7 remained stable and 11 deteriorated after 6 months of treatment. A recent retrospective study of IPF compared survival (on an intention-to-treat basis) in 82 untreated patients with 82 patients treated with combination low-dose steroids and cyclophosphamide.[330] Patient groups were matched for age and FVC at initial clinic visit. No survival difference was observed between the groups and this lack of treatment effect persisted when only those diagnosed by surgical biopsy were analysed.

Pulsed intravenous cyclophosphamide has been used to treat patients with IPF who have not responded to steroids in three non-randomised studies and no survival effect has been reported.[331–333]

Cyclophosphamide therapy is associated with significant side effects including bone marrow suppression, haemorrhagic cystitis, infertility, stomatitis and opportunistic infections.[334] These ultimately require most patients to discontinue treatment. There is thus no evidence that cyclophosphamide is of any long-term benefit in terms of survival or quality of life for patients with IPF.

Pirfenidone

Pirfenidone is a pyridone which inhibits fibroblast proliferation and collagen synthesis in vitro[335] and ameliorates bleomycin-induced pulmonary fibrosis in animals.[336] In a study of pulmonary fibrosis in Hermansky-Pudlak syndrome, pirfenidone treatment was associated with a slower decline in lung function compared with placebo.[337] A prospective open label phase 2 study was undertaken to assess the effects of pirfenidone in 54 patients who were terminally ill with end-stage IPF with a demonstrable progressive decline in their condition prior to entry.[338] Forty-six had refused, not tolerated or failed conventional immunosuppressive therapy and eight were untreated at the start of the study. Although 11% died in the first 6 months, the authors reported that lung function stabilised or improved in some patients. Furthermore, 38 of the 46 patients were able to discontinue immunosuppressive therapy. Adverse effects were common but not severe, and pirfenidone was considered generally well tolerated. The authors recommended that further trials should be undertaken in less severely affected patients. Nagai *et al* followed 10 patients with advanced pulmonary fibrosis (8 with IPF and 2 with SSc) treated with pirfenidone for 1 year and reported no definite effect on overall survival although there were minimal adverse events.[339]

A placebo (2:1) controlled double-blind phase 2 study of pirfenidone therapy in 107 Japanese patients with moderate IPF has recently been reported.[8] Planned for 1 year, the study was prematurely stopped by 9 months following an interim analysis that revealed significantly greater acute exacerbations in the placebo group than in the pirfenidone group. Patients receiving pirfenidone also had a significantly smaller decline in VC and a small but significant improvement in degree of desaturation following a 6 min walk at 9 months. Further randomised trials of pirfenidone in IPF are ongoing.

Endothelin-1 antagonists

Endothelin-1 (ET-1) vasoconstrictor promotes fibrosis and cell proliferation, stimulates collagen synthesis in vitro, and in vivo ET-1 levels have been found to be increased in cardiovascular and connective tissue diseases leading to the hypothesis that ET-1 blockade would be of potential benefit in IPF.[340–345] Bosentan is a dual ET receptor antagonist that competes with binding of ET to receptors. It has been used in a 12-month phase 2/3 study of 158 subjects with IPF, the Bosentan Use in Interstitial Lung Disease (BUILD 2) trial, and the results are expected in 2008.

Tumour necrosis factor α (TNFα) modulation

Tumour necrosis factor α (TNFα) is a pleotrophic cytokine which has in vitro potential to upregulate both pro-inflammatory mediators and growth factors implicated in the pathogenesis of IPF. TNF blockade is protective in animal models of bleomycin-induced pulmonary fibrosis.[346–348] In patients with IPF, a number of investigators have demonstrated increased TNFα production by a variety of cells and tissues.[349 350] These

Table 4 Summary of other drugs used in the treatment of IPF

Therapeutic agent	Trial design	Drug combination	Conclusion	Reference
Colchicine Proposed effect: inhibits fibroblast collagen production and may reduce degradation[354–356]	(1) Uncontrolled, randomised, prospective	Colchicine vs high-dose prednisolone	No survival advantage between groups	Douglas *et al*[357]
	(2) Uncontrolled, non-randomised, prospective	Colchicine + prednisolone vs prednisolone only vs colchicine, penicillamine + prednisolone	Does not alter the course of steroid-treated IPF	Selman *et al*[358]
Penicillamine Proposed effect: inhibits collagen synthesis and cross linkage[359 360]	(1) Uncontrolled, non-randomised, prospective	Penicillamine + prednisolone vs prednisolone only vs colchicine, penicillamine + prednisolone	Does not alter the course of steroid-treated IPF	Selman *et al*[358]
	(2) Uncontrolled, non-randomised	Penicillamine + prednisolone vs azathioprine + prednisolone	No difference between groups	Meier-Sydow *et al*[361]
Cyclosporin Proposed effect: suppresses T helper cells and TGFβ signalling[362 363]	(1) Prospective, open, controlled	Cyclosporin	Numbers too few to analyse	Alton *et al*[364]
	(2) Short-term, open label	Prednisolone + cyclosporine	Might permit reduction of steroids before transplantation	Venuta *et al*[365]

IPF, idiopathic pulmonary fibrosis; TGFβ, transforming growth factor β.

observations have led to the trial of etanercept, a fusion protein consisting of the extracellular ligand-binding portion of the high-affinity human 75 K TNFα receptor linked to the Fc portion of human IgG1. Etanercept inhibits both the binding of TNFα and TNFβ to cell-associated TNFα receptors, thereby rendering extracellular TNF biologically inactive. One hundred patients with a confident diagnosis of IPF have been randomised to a double-blind randomised controlled trial in which the primary outcome measure is lung function with 6 min walking distance as a secondary end point and the outcome is awaited. However, sporadic reports of acute pneumonitis, reactivation of tuberculosis and risk of opportunistic infection in patients treated for rheumatoid arthritis with etanercept serve to emphasise the complexity of modulating the immune response.

Warfarin

There is a body of evidence that suggests that microvascular thrombosis and injury is an important process in the pathogenesis of IPF.[311 351–353] Furthermore, pulmonary embolism has been reported as an important cause of death in IPF, although its true incidence is unclear.[97] In a multicentre randomised control trial of anticoagulation in 56 patients with IPF there were significantly fewer deaths in those treated with warfarin and prednisolone compared with controls treated with prednisolone only. However, a large number of subjects treated with warfarin dropped out of the study and the analysis was not performed on an intention-to-treat basis. Hospital admissions for "exacerbation of IPF" were equally frequent between groups, but in-hospital mortality was far lower in the anticoagulated group that received low molecular weight (LMW) heparin than in the control group receiving high-dose steroids. It is possible that the survival effect observed in this study may be attributable to LMW heparin during an acute exacerbation of IPF rather than long-term anticoagulation with warfarin. Despite significant flaws in study design and analysis, the demonstration of a significant survival difference with such a small number of patients may potentially indicate a large effect. Further studies of anticoagulation in IPF are required.

Other treatments

Several other drugs have been studied in IPF and the relevant data are summarised in table 4.

13.3 Lung transplantation for IPF

IPF represents the largest proportion of patients with ILD referred for transplantation. Almost 20% of patients listed for lung transplantation in North America have IPF, double the proportion a decade ago.[366] The actuarial survival following lung transplantation for IPF is 74–79% at 1 year and 40–54% at 5 years, with no significant difference in survival between single and bilateral lung transplants.[367] The annual death rate following transplantation is higher in patients with IPF than in those with COPD.[366] The optimal timing for lung transplantation in IPF is uncertain. A retrospective study of all adult patients (n = 1208) registered for lung transplantation on the Eurotransplant waiting list confirmed that patients with IPF experienced the highest overall mortality (54%) and benefited from earlier transplantation.[368] A single centre study of 653 patients accepted for lung transplantation (100 for pulmonary fibrosis) confirmed that the "time of crossover" at which the risk of death after transplantation fell below that of continued waiting for pulmonary fibrosis was 104 days.[369] A multivariate analysis from a single centre study of 46 patients with IPF accepted for transplantation (28 successfully transplanted, 16 died awaiting transplantation) suggested that lung transplantation reduced the risk of death by 75%.[370]

The measurement of TLCO has proved a dependable measure for predicting survival in patients with IIPs and hence a useful guide to timing of referral for transplantation. Mogulkoc *et al* demonstrated that a TLCO <39% of predicted was strongly predictive of death within 2 years.[109] Latsi and colleagues examined a group of 104 patients (63 with UIP, 41 with NSIP) and found survival was impaired, independent of histological diagnosis,[7] in those with a TLCO <35% of predicted. In general, a TLCO <39% predicted identifies patients with IPF or fibrotic NSIP who should be considered for transplantation.

There are widely disseminated international guidelines for the selection of candidates for lung transplantation[371 372] and, while most transplant centres recruit physically and psychologically robust patients aged 65 or under, relative contraindications vary between centres. It is recommended that clinicians develop a reliable channel of communication with their regional transplant centre so that all appropriate patients may be assessed.

13.4 If and when to start treatment in IPF

The absence of a proven effective treatment for IPF clearly emphasises the urgent need to recruit patients with IPF to high

quality clinical trials and to appropriately select those for lung transplantation. Of the specific treatment options available and discussed in Section 13.2, none can be considered "best current treatment" until further data are available. In this light, communicating the recognised uncertainties of treatment to the patient is an often neglected but crucial aspect of management. An appropriately tailored but frank discussion with the patient greatly enhances the decision-making process. As in many other medical scenarios in which the choice between management strategies is a very close call, treatment decisions should be heavily influenced by—if not entirely dependent on—the wishes of the informed patient. For many patients, BSC without specific treatment for IPF may be the most appropriate strategy. For others, a specific therapeutic intervention outside a clinical trial may be deemed appropriate. If such an approach is taken, appropriate counselling is recommended so that the patient retains some hope of improved outcome based largely on biological plausibility and extrapolation of limited data, while accepting that the treatment regimen is unproven.

There are no studies that have specifically addressed timing of potential treatment in IPF. Broadly, patients with definite IPF exhibiting characteristic HRCT findings and/or a histological pattern of UIP have a poorer prognosis than those with probable IPF or "fibrotic NSIP with an IPF profile". Individuals with T_{LCO} <40% predicted ("advanced disease") have a poorer prognosis than those with better preserved lung function. Intuitively it would seem reasonable to initiate treatment at the earliest possible stage to prevent disease progression. However, there are no data to support this concept. Furthermore, the variability in the natural history of IPF suggests that, in individual patients, serial measurement of lung function over 6–12 months may identify those with progressive disease, defined as a ⩾10% decline in FVC or ⩾15% decline in T_{LCO} from baseline. In addition to the patient's own informed wishes, other factors that will influence the decision to introduce a specific treatment beyond BSC include significant co-morbidity, advanced age and severity of symptoms.

Thus, it is it is uncertain whether it is beneficial to initiate treatment at the time of diagnosis rather than when there is clear evidence of disease progression or when the disease is advanced.

13.5 Use of the "steroid trial" in cases of genuine diagnostic uncertainty

A trial of corticosteroids, initially at high dose (0.5–1 mg/kg prednisolone) and tapering over a period of weeks and months, is often used in the management of patients with ILD. A steroid trial is not recommended in patients with definite or probable IPF as described. There are no suitable controlled studies that address the value of a steroid trial strategy in patients with ILD but in whom there is genuine uncertainty as to the specific diagnosis. A steroid trial should be considered if there are sound clinical and/or radiological grounds for believing the patient may have a steroid-responsive condition such as COP (see Section 15) or HP (see Section 19), but it should be borne in mind that a proportion of such patients are still likely to have IPF, albeit with atypical features. Given that steroid therapy is associated with serious side effects in a significant proportion of patients, the risk-benefit of steroid therapy should be weighed carefully on an individual basis. A dose of 0.5–1 mg/kg prednisolone is recommended with re-evaluation after 8–12 weeks. Maintenance steroids at much lower doses should be considered either if there is objective improvement (eg, 10% improvement in FVC or 15% improvement in T_{LCO}) or if there is apparent stabilisation in a patient in whom lung function was previously declining. Steroid-induced side effects should be assessed and prophylaxis against osteoporosis instigated according to widely accepted guidelines.

An information sheet suitable for patients being considered for corticosteroid therapy is provided as online Appendix 9.

13.6 Conclusions on the management of IPF

All patients with IPF should receive BSC. Patients with IPF who may be eligible for a lung transplant should be identified and referred for assessment. There are sufficient data to conclude that high-dose (0.5–1 mg/kg) corticosteroids as monotherapy are ineffective and toxic and should not be used to treat IPF. Of the current available medical therapies, none are of proven efficacy in the treatment of IPF. Recruitment of patients to high quality trials should therefore be considered a major goal in managing IPF. It is recognised, however, that most patients will not be eligible for a transplant or recruitment to a trial. A pragmatic approach would be to discuss the relative merits and risks for the possible treatment options with the patient and reach an agreement for "best current treatment" on an individual basis. Based on current data, the most widely available treatment for which there is evidence of efficacy is prednisolone (tapering over 3 months from 0.5 mg/kg/day to 10 mg/day maintenance) with azathioprine (2 mg/kg/day) and NAC (600 mg three times daily). *Any* variation from this regime—such as omitting or withdrawing azathioprine or starting with a low dose of prednisolone (20 mg or less)—is wholly without evidence base but such regimens may be attractive and compelling to both patient and clinician. Specific treatment, if given, could equally reasonably be initiated at diagnosis or following objective evidence of disease progression or in advanced disease.

An information sheet suitable for patients being considered for azathioprine therapy is supplied in online Appendix 11.

Summary of recommendations for the management and treatment of IPF

- **Best supportive care should be considered a specific and important treatment strategy in all patients with IPF. It is a proactive approach to symptomatic treatment and may include oxygen therapy, pulmonary rehabilitation, opiates, antireflux therapy, withdrawal of steroids and other immunosuppressants, early recognition of terminal decline and liaison with palliative care specialists. [D]**
- **To date there is no therapy proven to improve survival or otherwise significantly modify the clinical course of IPF. As such, it is recommended that all patients be considered for recruitment to high quality clinical trials of therapy and/or for lung transplantation if appropriate. [C]**
- **High-dose steroid monotherapy (0.5–1 mg/kg) does not improve survival or otherwise modify the clinical course of the disease and is associated with significant morbidity. It is therefore strongly recommended that high-dose steroids not be used to treat patients with IPF. [C]**
- **Prednisolone (tapering from 0.5 mg/day to 10–20 mg/day) with azathioprine (2 mg/kg, maximum 150 mg/day) and NAC (600 mg three times daily) has been shown to have a significantly better treatment effect than prednisolone and azathioprine alone. However, further studies are required and this regime currently**

carries a weak recommendation [C]. Prednisolone and azathioprine without NAC are not recommended.

- **Variations from the above regimens, such as lower dose steroids (20 mg or less) or omission of azathioprine are very likely to be better tolerated but are entirely without evidence base. Appropriate counselling should be given to all patients started on specific regimes.**
- **Treatment, if started, could be equally reasonably initiated at presentation or following objective evidence of disease progression or in moderate/severe disease.**

Recommendations for referral for lung transplant in patients with IPF

The following apply only to patients who fulfil established selection criteria for transplant, thus generally excluding those over the age 65 and/or those with significant co-morbidity.

- **Referral to a transplant centre should be made if the disease is advanced (T_{LCO} <40% predicted) or progressive (≥10% decline in FVC or ≥15% decline in FVC during 6 months of follow-up). [C]**

14. NON-SPECIFIC INTERSTITIAL PNEUMONIA (NSIP)

14.1 Classification of NSIP

A histological diagnosis of NSIP requires that interstitial abnormalities are homogeneous in severity and apparent duration (as distinct from the characteristic heterogeneity in activity, severity and age of fibrosis seen in UIP). Initially, NSIP was subclassified by Katzenstein and Forelli as cellular (type I), mixed (type II) and fibrotic (type III) disease.[3] Cellular NSIP is characterised by an interstitial chronic inflammatory infiltrate with little or no fibrosis. Fibrosing NSIP consists of interstitial thickening by uniform fibrosis of a uniform age, usually with preservation of the alveolar architecture, with little or no interstitial inflammation. In mixed disease, cellular and fibrosing elements of roughly equal severity are admixed.

It is not established that NSIP is, in reality, a single disorder. Patients with cellular NSIP have an almost uniformly good prognosis (see table 5), with only one death in 54 reported cases from six studies.[3 4 14 16 18 373] There is, to date, no evidence that cellular NSIP precedes and leads to fibrotic NSIP. By contrast, there is significant mortality associated with both mixed and fibrotic NSIP, with no clear clinical, radiological or outcome distinctions between the latter two NSIP subgroups. Thus, a broad distinction between "cellular NSIP" (type I) and "fibrotic NSIP" (types II and III) is now widely used in clinical practice.

Even within the fibrotic NSIP subgroup there is no single stereotypical clinicoradiological profile. The spectrum of NSIP is currently being considered in an ATS/ERS workshop and, as yet, the optimal classification of NSIP on clinical grounds has not been finalised. However, based on clinical series, an NSIP pattern at biopsy can be associated with clinical profiles of idiopathic pulmonary fibrosis (NSIP/IPF), organising pneumonia (NSIP/OP) or hypersensitivity pneumonitis (NSIP/HP). In a large HRCT series with patients selected from biopsy features in isolation, the spectrum of findings included abnormalities suggestive of all three disorders.[165]

NSIP/IPF overlap is probably the most prevalent form of NSIP in most European countries and in the USA.[4 5 7 13 15 18 32] The clinical presentation tends to be indistinguishable from IPF with restrictive pulmonary function tests and bilateral basal crackles. The distribution of disease on HRCT scanning is similar to that in IPF but ground glass attenuation tends to be more extensive than in IPF and honeycombing is rarely present. Except in rare cases with predominantly inflammatory abnormalities at biopsy, the outcome is worst in this variant of NSIP although significantly better than in IPF.

By contrast, NSIP/OP overlap is the predominant form of NSIP in series from South Korea and Japan.[16 33 34] Consolidation on HRCT, which is uncommon in NSIP/IPF, is prominent in NSIP/OP, often admixed variably with fibrotic abnormalities. Indeed, the distinction between COP and NSIP is based upon the judgement as to whether the contribution made by organising pneumonia exceeds 10% of the total abnormality. BAL findings are similar to COP but unlike NSIP/IPF overlap, with a predominant lymphocytosis. Although not all patients have a significant response to corticosteroid therapy, progression of disease despite ongoing treatment is relatively unusual. The NSIP/OP overlap is probably best viewed as a fibrosing form of OP and may account for the observation that occasional patients with a histological diagnosis of OP develop clinical and radiological evidence of pulmonary fibrosis.

The HP/NSIP overlap predominates in series from France and Mexico.[14 30] Clinical, BAL and HRCT features closely resemble those in HP, as does the profile observed on genetic fingerprinting of inflammatory cytokines, but characteristic biopsy appearances of HP are lacking. Exposure to antigens known to cause HP is frequent and this may have led to the exclusion of patients in the NSIP/HP variant group in most idiopathic NSIP series.

Thus, it is likely that some patients with a histological pattern of NSIP have fibrosing variants of COP and HP. These subgroups must be distinguished from the largest patient subset with clinical features suggestive of IPF but variable HRCT features. The amalgamation of these heterogeneous clinical and radiological profiles as "fibrotic NSIP" is fundamentally unsatisfactory. However, pending the conclusions of the current ATS/ERS committee, the existence of a "core" NSIP patient group with a true NSIP continues to be debated. Thus, the treatment recommendations made below are primarily tailored to clinical and radiological profiles.

14.2 Diagnosis of idiopathic NSIP

A confident diagnosis of NSIP can be made only at surgical biopsy because a characteristic histopathological pattern is required. The diagnosis of NSIP should not be made from HRCT features in isolation. In patients presenting with the clinical features of IPF, a histological diagnosis of NSIP is seldom associated with honeycombing on HRCT and ground glass attenuation is generally more extensive in NSIP than in IPF.[32] However, these findings are occasionally misleading. A significant minority of patients with UIP at biopsy have HRCT appearances suggestive of NSIP, although survival tends to be better in this IPF subset than in patients with IPF with typical HRCT features.[5]

When NSIP has been identified at biopsy, multidisciplinary evaluation is required. Patterns of NSIP and UIP can occur at different sites in the same patient, usually in association with a poor IPF-like outcome,[274 275] and evaluation of CT scans and the clinical evolution of disease may establish that a histological pattern seen at biopsy is not representative of the disease process ("sampling error"). However, even when biopsies taken from multiple sites show NSIP, the integration of clinical and CT features is essential. The multidisciplinary diagnosis of NSIP can probably best be summarised as an attempt to determine, based on clinical and CT features, which other interstitial lung

disease (usually HP, COP or IPF) most resembles the clinicoradiological profile in question, with a view to rationalising treatment.

14.3 Disease course in relation to clinical features of NSIP

Prior to recognition of the clinical heterogeneity of NSIP, the prognosis of fibrotic NSIP was thought to be good in most patients. In the original series of Katzenstein and Forelli, 35% of patients with type II (mixed) disease had an apparent complete remission and a further 35% were still alive at the end of follow-up.[3] However, in a subsequent large series of patients with mixed or fibrotic disease, the 10-year survival was only 35%.[18] This finding contrasted with the good outcome reported in smaller cohorts,[13 15] but CT features were not well characterised in early work although, in the study of Daniil *et al*,[15] outcome was worse when HRCT appearances more closely resembled IPF.

The link between clinical features and outcome became clearer as series from different parts of the world were compared. In patients from Japan and South Korea, consolidation was often a prominent feature on HRCT and an element of OP was often present at biopsy. In early reports containing BAL information, a striking lymphocytosis was frequent.[14 16 34 374] Clinical and functional improvement occurred in all seven patients treated with corticosteroids in one study[34] and, in a larger series, Nagai needed to treat only 19 of 31 patients (61%) with corticosteroids alone (n = 11) or corticosteroids with immunosuppressive agents (n = 8).[16] Although a complete remission was seen in only 16%, a further 58% partially improved with or without treatment. Deterioration (n = 3) or death (n = 2) was seen in just 15%, underlining the good outcome in most patients.

In striking contrast, when patients with NSIP have the clinical features of IPF with predominantly basal crackles and no evidence of OP on imaging, the outcome appears to be substantially worse. A 5-year survival of only 45% was reported by Nicholson *et al*[4] in patients with NSIP with clinical features typical of IPF, and this outcome improved little with the addition of a further patient subset in a study of serial changes in pulmonary function tests.[7] Thus, a significant proportion of patients with NSIP with the clinical features of IPF appear to have a disease course similar to IPF,[5 7] but there is no means of distinguishing these patients at presentation from the remaining patients with NSIP with more insidious progression or long-term stability. BAL data are not useful in predicting outcome in this patient subset: in contrast to patients with NSIP with an OP element, the cellular profile is seldom lymphocytic but is identical to that of IPF.[229] However, survival remains clearly better than in IPF after adjustment for baseline disease severity.[7]

There is less accumulated experience in patients with NSIP with clinical and radiological features resembling HP, but the outcome appears to be relatively good with no deaths in a combined total of 15 patients in two series and stability or improvement in over 80%.[14 30]

14.4 Treatment of NSIP

Because the entity of NSIP has not been fully worked out and formally subcategorised, it is impossible to gauge the overall impact of treatment given the striking clinical heterogeneity of disease. The relatively good outcome of NSIP compared with IPF seen in all series is largely an observation of treated patient cohorts. Corticosteroids, with or without immunosuppressive agents, have been the mainstay of treatment in most series. Azathioprine,[5 7 14 15 375] cyclophosphamide[5 7 14 15 375] and colchicine[14 376] have been most widely used, with cyclosporin, methotrexate, chlorambucil also tried in isolated cases.

However, because all patient cohorts are wholly or largely treated, the natural history of NSIP is unknown. This is likely to remain the case. Given the fact that average outcome in association with treatment is better than in IPF, most clinicians will decline to observe patients with NSIP without treatment when fibrotic progression is observed. Even the absence of a clear response in patients with predominant fibrosis is inconclusive because the prevention of further progression is a valid therapeutic goal. Therefore, no validated recommendations exist on indications for treatment, duration of therapy or treatment regimens.

In the complete absence of data, the Committee argues in favour of basing therapeutic approaches on the clinicoradiological profiles of disease. Patients should be categorised as most closely resembling IPF, COP or HP and the treatment stratagem selected accordingly.

1. Management in patients with the clinical features of IPF and a distribution of disease on HRCT is broadly similar to that of IPF but is grounded in a far poorer evidence base than for those with IPF. This group of patients has a better overall prognosis than those with biopsy-proven UIP, but a higher mortality than other NSIP patient subsets. Treatment, as with IPF, is based on the hope of slowing or preventing disease progression in most cases rather than achieving regression of disease. The options for treatment are summarised in table 5. Prolonged high doses of corticosteroids should be avoided unless there is clear evidence of a response. Of the other options, as for IPF, none can be strongly recommended.
2. When histological, CT and clinical features overlap with COP, striking or partial therapeutic responses are seen in most patients[16] and an initial high-dose steroid regimen similar to that recommended in COP can be justified. However, when attempts are made to withdraw corticosteroid therapy, the risk of progressive fibrosis should be kept in mind. In contrast to usual treatment approaches in typical COP, long-term treatment may be required to prevent progression of fibrotic disease.
3. In the relatively small patient subset with features of HP, a good outcome is usual and a general approach similar to that adopted in definite HP, with the introduction and continuation of treatment calibrated against disease behaviour, is justifiable.

15. CRYPTOGENIC ORGANISING PNEUMONIA (COP)

Cryptogenic organising pneumonia (COP) is a clinicopathological entity of unknown cause originally described by Davidson in 1983[377] and subsequently reported by Epler as ''bronchiolitis obliterans organising pneumonia'' (BOOP) in 1985.[378] COP is the preferred term because it better captures the clinical and radiological profile which is that of an acinar rather than an airway disease. Furthermore, the term BOOP is often confused with ''obliterative bronchiolitis'', a completely separate entity.

15.1 Clinical features[377–389]

The mean age at presentation is 55–60 years (range 20–80) with no gender predilection. The incidence of COP is unknown. Patients typically present with systemic symptoms of malaise, fever or chills, weight loss and myalgia. Respiratory symptoms are breathlessness and cough which may be dry or productive of clear or discoloured sputum. Symptoms usually develop over

Table 5 Treatment in non-specific interstitial pneumonia (NSIP)

Study	No of cases	No treated (%)	Outcome in those followed up				
			Remission n (%)	Improved n (%)	No change n (%)	Deteriorated n (%)	Deaths n (%)
Katzenstein and Fiorelli[3]*	64§	48 (75%)	21 (44%)	18 (38%)			5 (10%)
Park[34]†	7	7 (100%)	3 (43%)	4 (57%)			0
Cottin[14]*	12	12 (100%)	7 (58%)	3 (25%)		2 (17%)	0
Nagai[16]†	31	19 (61%)	5 (16%)	18 (58%)	3 (10%)	3 (10%)	2 (6%)
Fujita[375]*	24	24 (100%)	20** (83%)				4 (17%)
Daniil[15]	15¶	12 (80%)	3 (21%)	4 (29%)	2 (14%)	3 (21%)	2 (14%))
Nicholson[4]†	28	21 (75%)	6**			2	17 (61%)
Flaherty[373]‡	10	10 (100%)	4 (40%)	5 (50%)			1 (10%)
	191	151 (79%)	43 (23%)	73 (38%)			29 (15%)

*Idiopathic and connective tissue disease-associated NSIP
†Idiopathic NSIP only.
‡Prospective study.
§Outcome known in 48 individuals.
¶Outcome known in 14 individuals.
**Graded as responders or non-responders/decliners.

several months and may be preceded by a suspected respiratory tract infection. On examination, focal or more widespread crackles are usually audible. Blood tests typically reveal a markedly raised ESR, raised CRP and peripheral blood neutrophilia. Lung function tests usually show mild to moderate restriction with reduced TLCO levels and no coexisting airflow obstruction; disproportionate hypoxia may denote shunting within consolidated lung.[390] The BAL cell profile is most often lymphocytic.

15.2 Radiology

The chest radiograph typically shows patchy bilateral peripheral consolidation which is often migratory.[377 378 381] CT scans most often show focal subpleural consolidation with or without air bronchograms. Ground glass shadowing is variably present and other occasional abnormalities include small (<10 mm) nodules along the bronchovascular bundles, larger nodules and peripheral reticulation.[391–395]

15.3 Pathology[396 397]

Patchy cellular airspace fibrosis involving alveoli, alveolar ducts and, less commonly, distal bronchioles are the typical histological features. Fibroblasts are embedded in a myxoid matrix containing a variable infiltrate of inflammatory cells forming characteristic polypoid masses known as Masson bodies or Bourgeons conjunctifs. A mild interstitial infiltrate and foamy alveolar macrophages may also be present.

15.4 Diagnosis

In cases presenting with typical clinical and radiological features, a TBLB specimen showing compatible histology is sufficient to make the diagnosis.[398 399] However, in atypical cases a surgical biopsy may be required. COP should never be diagnosed by histology alone. OP is sometimes due to infection and can also be present in malignant disease or fibrosing interstitial lung disease as a reparative reaction which may be over-represented at a single biopsy site (''sampling error''). Moreover, histological appearances in isolation do not distinguish between COP and secondary OP. Thus, COP is essentially a multidisciplinary diagnosis.

The clinical, radiological and histological features of secondary OP are usually similar to COP. Secondary OP is most frequent in connective tissue and other autoimmune diseases (especially rheumatoid arthritis and PM/DM),[400–405] following lung radiotherapy,[406] and in drug induced lung disease[407] but also occurs in malignant haematological disorders[408 409] and immunodeficiency syndromes.[410] The distinction between COP and secondary OP is important because the prognosis regarding treatment responsiveness and survival is, on average, much worse in secondary OP.[378 385 387 411]

15.5 Natural history and treated course: typical COP and unusual variants

Typical COP

Typical COP is associated with a good overall prognosis. In untreated patients reported in six series,[378 381 383 384 388 412] spontaneous remission occurred in approximately 50% with partial remission in almost all other cases. In treated patients the long-term outcome is good in most cases. The response to treatment is often rapid, with symptomatic improvement frequently reported within days but slower chest radiographic and pulmonary function responses which sometimes require up to 3 months of treatment.[382] Complete remission is more likely when the chest radiograph shows alveolar or airspace opacification as opposed to those with reticulonodular appearances.[381 385 388] Relapse is common but unpredictable as corticosteroid dosages are reduced, with a 58% relapse rate observed in a recent European cohort and multiple relapses for 2 years or longer in a small subgroup.[413] Relapse most often occurs on low-dose corticosteroid treatment and seldom when the maintenance dose of prednisolone exceeds 20 mg daily.

Acute fulminant COP

Acute fulminant COP without pulmonary fibrosis presents as the adult respiratory distress syndrome but with typical OP at biopsy or autopsy.[414–416] This rare presentation is occasionally rapidly fatal and mechanical ventilation is often required. In survivors, a rapid response to corticosteroid therapy is usual. Acute fulminant COP is discussed in further detail in Section 24.

Fibrosing COP

Fibrosing COP has a variable outcome. An element of interstitial fibrosis is often suggested on CT scanning and in most cases this does not progress. However, in a small subset of patients more extensive fibrosis is evident and this can progress to a fatal outcome despite treatment. Cohen and colleagues described 10

patients with rapidly progressive pulmonary infiltration in whom initial clinical, radiological and histological appearances were compatible with OP.[411] Despite vigorous treatment, fatal progression was shown at autopsy to be associated with widespread honeycomb lung. In non-fatal cases the severe respiratory impairment was not reversed by prolonged treatment. This small subgroup may account for the poor outcome seen in a small minority of patients with COP in large series. In one series the 5-year mortality was 23% in 37 patients with COP and death was usually due to progression of respiratory disease.[387] Some cases of fibrotic NSIP may represent fibrosing COP.

Unifocal COP

Unifocal COP accounts for approximately 10% of cases.[12] Patients present with a solitary pulmonary nodule which tends to be resected because of concerns about underlying malignancy. Recurrences have not been reported.

15.6 Treatment of COP

The management of COP has not been studied in a prospective randomised trial and therefore treatment decisions can only be based on general clinical considerations including disease severity and the rapidity of disease progression. Corticosteroid therapy has been the rule, with the occasional addition of azathioprine,[412] cyclophosphamide[411] or cyclosporin[377] in refractory cases. In 12 studies in which presentation details are complete, containing 160 patients, a complete response was seen in 59.4% with partial response in 26.9%, non-responsiveness in 13.7% and a fatal outcome in 6%.[377 378 381–385 388 412 414 417 418] The disappointing outcome in 20% underlines the fact that an atypical disease course will be encountered from time to time and this is likely to require treatment modification, especially when there is coexistent pulmonary fibrosis.

Recommended corticosteroid regimens include initial dosages of 1–1.5 mg/kg prednisolone for 3 months with gradual reduction thereafter,[378] and methyl prednisolone 500–1000 mg intravenously for the first 3 days followed by prednisolone at 20 mg daily with further reductions tailored according to the clinical course.[419] No single recommendation covers all patients and it is appropriate for clinicians to adjust regimens according to initial disease severity and the rapidity and degree of responsiveness. Lazor *et al* demonstrated good response rates with a lower overall steroid usage in 14 patients treated with a standardised protocol (prednisolone 0.75 mg/kg for 4 weeks; 0.5 mg/kg for 4 weeks; 20 mg daily for 4 weeks; 10 mg daily for 6 weeks; 5 mg daily for 6 weeks) compared with 34 other patients treated in a more random fashion. Clinical and radiological improvement was the same in both groups and similar relapse rates were observed (8/14 vs 20/34).[413] The long-term outcome was not adversely affected by rapid withdrawal of prednisolone prior to relapse. These data suggest that rigorous adherence to previously published regimens in patients with a good initial response may lead to overtreatment with steroids in some cases.

Summary of recommendations for COP

- **COP usually responds to corticosteroid therapy but the optimum dose and length of treatment is not known. Initial doses of 0.75–1 mg/kg, weaning over 6–12 months, are reasonable. [C]**
- **Relapses of COP are common but are only rarely associated with poor outcome. The risk versus benefit of prolonged corticosteroid therapy should be carefully considered in patients with relapsing COP. [D]**

16. RESPIRATORY BRONCHIOLITIS INTERSTITIAL LUNG DISEASE (RBILD)

Respiratory bronchiolitis interstitial lung disease (RBILD) is a clinicopathological syndrome which invariably affects current or ex-smokers. Respiratory bronchiolitis per se is thought to be a physiological response to smoking, being evident histologically in most, if not all, current smokers and commonly present in ex-smokers for up to 3 years after quitting.[420] As such, respiratory bronchiolitis is generally a mild condition with no symptoms and only minimal evidence of small airways obstruction. RBILD appears to represent a more severe pulmonary reaction to cigarette smoke in a small minority of smokers, resulting in radiological evidence of ILD associated with symptoms and lung function impairment that may range from mild to severe.[421–423]

Essentially, histological findings in RBILD cannot be distinguished from respiratory bronchiolitis in healthy smokers.[420] In both disorders alveolar macrophages accumulate in respiratory bronchioles, sometimes extending into neighbouring alveoli, with a variable chronic inflammatory cell infiltrate in bronchiolar and surrounding alveolar walls and occasional peribronchial alveolar septal fibrosis.[25 420] The pulmonary parenchyma is otherwise normal except for the frequent presence of smoking-related emphysema.[424]

16.1 Diagnosis of RBILD

A confident diagnosis of RBILD in the clinical setting of ILD can often be based on typical HRCT findings in a current smoker or a smoker who has recently quit.[25 425 426] However, the HRCT abnormalities seen in RBILD may be similar to findings in subacute HP and consist of a variable combination of centrilobular micronodules, ground glass attenuation, bronchial wall thickening and emphysema.[427] When present to a limited extent in healthy smokers, these HRCT abnormalities are likely to represent respiratory bronchiolitis.[162]

Invasive investigations should be performed if other processes need to be excluded, and the threshold for doing so is lower if the presentation is atypical or the disease is extensive or progressive. Patients with RBILD have the same BAL cell profile as healthy smokers with increased macrophage numbers and significant lower percentages of other cellular components; neutrophilia or eosinophilia is rare in RBILD. Hence, BAL may help to distinguish RBILD from HP, in which a BAL lymphocytosis is expected,[224] and from other IIPs in which neutrophil and eosinophil excess is more commonly seen.[229] Similarly, a surgical biopsy will also help to rule out other conditions, but the histological findings in RBILD cannot be distinguished from respiratory bronchiolitis in healthy smokers.[420]

The diagnosis of RBILD can therefore usually be made confidently with history and HRCT findings alone, with BAL and/or lung biopsy used to provide corroborative evidence and to help exclude other conditions. The distinction between RBILD and respiratory bronchiolitis is based on the severity of disease as judged by symptoms, pulmonary function tests and the extent of disease on HRCT.[25]

16.2 Treatment of RBILD

Current smokers should be advised to quit and this measure will often result in disease regression. ''Spontaneous'' improvement (probably largely reflecting smoking reduction or cessation) was

observed in 17 out of 22 patients (in four studies) who went untreated. The remaining 5 patients had stable disease.[383 421 422 428]

No deaths have been reported to date and improvement or stability have been observed in the majority of treated patients, although total patient numbers are small.[383 421–423 428] However, it is not known whether any intervention other than smoking cessation is effective. There is no clear evidence that oral corticosteroid therapy is beneficial, nor are there any long-term follow-up studies. There are reports of patients deteriorating while on treatment with steroids and other immunosuppressive drugs.[421 423] There is also a report of two patients with RBILD presenting with respiratory failure who did not respond to steroids but subsequently improved following smoking cessation.[423]

It is increasingly recognised that various forms of smoking-related damage may occur concurrently and, thus, no overall conclusion can yet be drawn from the observation of a small patient subset with a poor outcome.

17. DESQUAMATIVE INTERSTITIAL PNEUMONIA (DIP)

Desquamative interstitial pneumonia (DIP) is a rare condition which usually affects smokers in their fourth or fifth decades. It is twice as common in men as in women. The term DIP was originally used to describe a diffuse parenchymal lung disease that was believed to occur as a result of desquamation of alveolar epithelial cells.[429] However, it is now known that this pathological abnormality represents accumulation of macrophages which usually contain pigment related to tobacco smoke. This observation has prompted the theory that DIP and RBILD may be related conditions representing two ends of a spectrum of smoking-related ILD.[428]

17.1 Clinical features[430–434]

Patients usually complain of insidiously progressive breathlessness and a cough which develop over weeks or months. Finger clubbing is present in 50% of patients. DIP can occasionally present with severe respiratory failure.

17.2 Radiological features[435–437]

The chest radiograph may be normal but more commonly shows widespread ground glass opacification, most marked in the lower zones. The CT scan typically shows ground glass opacification which is more marked in the lower zones, although it may be uniform, peripheral or sometimes patchy.

17.3 Pathological features[429 431]

The pathology of DIP is characterised by a diffuse and uniform accumulation of macrophages in the alveolar spaces. The macrophages contain golden, brown or black pigment of tobacco smoke. There may be mild thickening of the alveolar walls by fibrosis and scanty inflammatory cell infiltration. Mild emphysema may be an additional finding.

17.4 Diagnosis

The HRCT findings of extensive ground glass shadowing are non-specific and, similarly, BAL cannot reliably distinguish DIP from other conditions such as RBILD, HP or sarcoidosis. A surgical lung biopsy is therefore required to make a confident diagnosis.

17.5 Treatment

Current smokers should be advised to quit and additional treatment is not always necessary. The largest prospective series followed up 32 patients who were not treated at presentation.[305] Over a 22-year follow-up period, 22% improved spontaneously (15% with complete remission), 15% remained unchanged and 62.5% deteriorated and required treatment.

Patients with significant functional impairment or progressive disease usually require treatment with oral corticosteroids. Initial doses have ranged between 20 mg and 60 mg daily and patients usually show a good response. Table 6 summarises the combined findings of 12 studies totalling 158 patients of whom 134 were treated with steroids. The overall response rate was 71.2% and a further 10.6% remained stable. Occasional patients have been given additional immunosuppressive agents including azathioprine and cyclophosphamide.[430 438 439]

While, in general, a good response to treatment has been attributed to the absence of fibrosis on biopsy,[430 438] good responses to steroid therapy have also been described in patients with established fibrosis on biopsy[438] and in a patient with respiratory failure. The suggestion of fibrosis on the CT scan or its presence on lung biopsy should not therefore preclude the

Table 6 Desquamative interstitial pneumonia: summary of studies

				Outcome in those treated				
Study	No of cases	Idiopathic cases	No treated†	Remission n (%)	Improved n (%)	No change n (%)	Deteriorated n (%)	Deaths n (%)
Liebow[429]	18	18	18		15 (83%)	0	2 (11%)	1 (6%)‡
Gaensler[432]	12	12	12	0	9 (75%)	0	2 (17%)	1 (8%)§
Scadding[442]	8	8	7	0	5 (71%)	2 (29%)	0	0
Stack[443]	9	9	9	0	6 (67%)	3 (33%)	0	0
Patchefsky[444]	13	9	11	3 (27%)	3 (27%)	1 (9%)	1 (9%)	3 (27%)
Tubbs[438]	26	24	22	3 (14%)	7 (32%)	0	7 (32%)	5 (22%)*
Carrington[305]	40	34	26	13 (50%)	3 (12%)	3 (12%)	0	7 (27%)
Hartman[305 439]	11	11	11	0	6 (55%)	3 (27%)	2 (18%)	0
Akira[435]	8	8	8	0	7 (88%)	0	1 (12%)	0
Nicholson[4]††	13	13	10	0	8 (80%)**	2 (20%)	0	0
Total	158	146	134	19 (14%)	69 (51%)	14 (10%)	15 (11%)	17 (12%)

*Two deaths unrelated to pulmonary disease.
†Untreated patients invariably improved or underwent remission.
‡Postoperative death.
§Death 10 years after onset.
**Three cases of disease relapse but 100% survival at 10 years.
††Classified as desquamative interstitial pneumonia/respiratory bronchiolitis interstitial lung disease (DIP/RBILD) in this study.

use of steroid therapy as the prognosis of DIP is significantly better than that of UIP.

Relapse of DIP after withdrawal of long-term low-dose steroid therapy has been described in one patient after 7 years,[441] another after 10 years[432] and two further patients after 12 years.[440 441] Relapses appear to respond well to further steroid treatment.

Summary of recommendations for RBILD and DIP

- **Patients with RBILD or DIP should receive appropriate smoking cessation advice and treatment. [C]**

18. LYMPHOID INTERSTITIAL PNEUMONIA (LIP)

Lymphoid interstitial pneumonitis (LIP) was the term originally used by Liebow and Carrington to describe a diffuse lymphocytic interstitial infiltration which distinguished it from other interstitial pneumonias.[445] Subsequent re-evaluation has indicated that some cases thought to be LIP were probably non-Hodgkin's low-grade B cell MALT (mucosa-associated lymphoid tissue) lymphomas. Modern immunohistological and molecular techniques make it possible to distinguish most cases of idiopathic LIP from lymphoma, although a small number of cases appear to undergo malignant transformation.[446–448] LIP is now considered by most authorities to be a distinct histological variant of diffuse pulmonary lymphoid hyperplasia.[2 449] The incidence of idiopathic LIP is low and its pathogenesis is unknown.

There is an association between LIP and hypogammaglogulinaemia, particularly common variable immune deficiency[450] can also occur in association with collagen vascular diseases most commonly Sjogren's syndrome but also SLE and rheumatoid disease.[451–454] It has been described in autoimmune disorders such as pernicious anaemia,[455] autoimmune haemolytic anaemia,[456] Hashimoto's thyroiditis,[452] chronic active hepatitis[457] and primary biliary cirrhosis.[458] LIP can also occur in patients with HIV and it is an AIDS-defining illness in children.[459 460] It has also been reported as a complication of phenytoin therapy[461] and in association with Castlemain's disease.[462]

18.1 Clinical features

Idiopathic LIP is most common in middle-aged women although it can present at any age.[458 463 464] Symptoms are of insidious but often progressive breathlessness over several months associated with dry cough. Fatigue, malaise, weight loss and low-grade fever may also occur. Typical symptoms of associated collagen vascular and autoimmune disorders may be present. Inspiratory crackles are usually audible at the lung bases and finger clubbing may occur with advanced fibrotic disease. Patients often have a mild anaemia, high ESR and dysproteinaemia.[450 465–467] There is a lymphocytosis on BAL.

18.2 Radiological features

The chest radiograph most commonly shows bilateral reticulonodular shadowing with or without septal lines, but there may be more patchy consolidations which can be transient.[452] These changes are usually most marked in the lower zones but may be uniform or affect the upper zones. Lymphadenopathy is not a feature but, if present, should suggest the development of lymphoma. On the CT scan there is ground glass shadowing with perivascular cystic spaces but honeycombing is uncommon.[468 469]

18.3 Pathological features[446–448]

Histological examination of the lung shows diffuse interstitial thickening with small benign-looking lymphocytes, plasma cells and macrophages. This infiltration predominantly affects the alveolar septa. Lymphoid follicles are often present with germinal centres in the distribution of the lymphatics. There is associated type II cell hyperplasia and an increase in alveolar macrophages. The airways are normal and there is no vasculitis.

A surgical lung biopsy is required to confidently distinguish LIP from pulmonary lymphoma, diffuse or nodular lymphoid hyperplasia and other interstitial diseases such as HP and NSIP.

18.4 Treatment

The number of reported cases of LIP is small and no formal controlled trials of treatment have been published; occasional spontaneous improvement occurs. Corticosteroids are the most commonly used treatment although the optimum dose and duration of treatment has varied. In two observational studies of 26 patients, all were treated with corticosteroids and some received additional cyclophosphamide or chlorambucil.[458 463] Combining the results of these reports, 25% showed a dramatic improvement or complete radiological resolution, 15% showed mild improvement and 25% remained stable. However, there was a 38% overall mortality with death resulting from disease progression to fibrosis, infection complicating immunosuppression and transformation to malignant lymphoma. These results are similar to 5-year survival rates in other reports.[470]

There are anecdotal reports of a response to methotrexate, azathioprine and cyclosporin.[463 470 471] Antiretroviral therapy has been shown to be effective in cases of LIP secondary to HIV infection.[472]

19. HYPERSENSTIVITY PNEUMONITIS (HP)

Hypersenstivity pneumonitis (HP, also known as extrinsic allergic alveolitis) is a complex clinicopathological syndrome caused by repeated exposure to a sensitisng antigen. Inhalation of organic particles is the commonest cause, but it can occur following inhalation of inorganic chemicals and, occasionally, ingestion of drugs.[473 474]

19.1 Clinical features[70 475–477]

Traditionally, HP is categorised as acute, subacute or chronic. While this simple classification belies the dynamic nature of this immune-mediated process which affects the lung paranchyma and small airways, the majority of patients present with a clinical and radiological pattern that conforms to one of these categories. Acute HP presents 4–8 h after often heavy exposure with fever, malaise, cough, dyspnoea and chest tightness. The symptoms remit over 24–48 h in the absence of further exposure. The subacute and chronic forms usually occur with ongoing lower-level exposure. Dyspnoea, cough and fatigue develop insidiously and weight loss is a common feature. Patients with chronic HP typically do not give a history of acute symptoms but present with diffuse pulmonary fibrosis which must be distinguished from other conditions including IPF and fibrotic NSIP.

19.2 Radiological features

In acute and subacute HP the chest radiograph characteristically shows diffuse small pulmonary nodules which often give a subtle ground glass appearance. The characteristic HRCT patterns include diffuse or patchy ground glass attenuation typically in mid-zone distribution, poorly defined micronodules

(<5 mm in diameter) and air trapping manifest as a mosaic pattern best seen on expiration.[478 479] Chronic HP may have some of the radiological features of acute and subacute disease but, in addition, there is a scarring process with loss of lung volume. On the chest radiograph the typical changes are of reticular or reticulonodular shadowing predominantly in the upper lobes. The HRCT features are of irregular linear opacities which may be diffuse or mid-zonal, often with honeycombing and traction bronchiectasis.[480 481]

19.3 Pathological features

The usefulness of BAL in ILD is discussed in Section 9. Typically, patients with HP and ongoing antigen exposure have a lymphocytosis (>30% for non-smokers and >20% for current smokers.[213] Transbronchial biopsy does not usually yield sufficient tissue with which to make a confident pathological diagnosis of HP, particularly in atypical cases or those that cause diagnostic difficulty. Surgical lung biopsies are sometimes necessary in patients with subacute and chronic HP. The classic pathological description is of peribronchiolar mixed inflammatory infiltrate which is usually lymphocyte-dominant. Variable numbers of poorly formed granulomas are characteristic but their presence is not necessary to make the diagnosis. Fibrosis is variable depending on the chronicity of the case. Occasionally the clinical syndrome of subacute and chronic HP may histologically resemble fibrotic NSIP or UIP[14 27] with only subtle features—such as a possible bronchocentric accentuation to the inflammation, isolated giant cells or occasional granulomas—to hint at underlying HP.

19.4 Diagnosis

Integration of clinical, radiological and pathological findings is essential to make a confident diagnosis. A high index of suspicion is required when taking a history of environmental and occupational exposures and sampling the workplace and home environment may yield novel causes.[482–484] HP should be considered in any patient with a histological diagnosis of fibrotic NSIP or, indeed, in cases of UIP in whom the distribution of disease is not typical of IPF. It is noteworthy that the presence of precipitating antibodies and sometimes BAL lymphocytosis indicates exposure, not disease.

A particularly challenging clinical problem is when clinical, radiological and/or histological assessment indicates that HP is the most likely diagnosis but a causative agent cannot be identified, even after carefully revisiting the exposure history. In a recent study of 85 patients with HP based on clinicoradiological or pathological grounds, a causative antigen could not be identified in 25%.[485] In recognition of this uncommon but important scenario, a recent National Heart, Lung, and Blood Institute and the Office of Rare Diseases (NHLBI/ORD) workshop indicated that HP can be a valid clinical diagnosis even in the absence of a proven causative agent.[194]

19.5 Management

Avoidance of the triggering environmental agent is the most effective treatment of HP. In the acute and subacute forms, allergen avoidance should result in clinical resolution of the disease. In contrast, continued exposure usually (but not invariably[486]) leads to disease progression and lung fibrosis. If the exposure is work-related, liaison between the employer and occupational health professionals may generate strategies for effective avoidance without threatening the patient's livelihood. Respiratory protection masks have been shown to reduce the level of circulating antibodies and improve symptoms,[487] but continued monitoring of symptoms and lung function is critical since most masks will not exclude particles <1 μm in size and can be bypassed even if correctly fitted.

The potential benefit of corticosteroids is difficult to determine in the context of allergen avoidance. A randomised double-blind placebo controlled study of corticosteroids in acute farmer's lung reported more rapid improvement in lung function in the steroid-treated patients at 1 month without any effect on long-term outcome.[488] Persisting symptoms despite antigen withdrawal are an indication to introduce oral corticosteroids (0.5 mg/kg/day) until symptoms and radiographic changes have resolved. Even in patients with chronic HP, antigen withdrawal and corticosteroid therapy may lead to a limited but clinically beneficial response.

Summary of recommendations for HP

- **The diagnosis of HP requires a high index of suspicion and in difficult cases an integrated multidisciplinary approach is essential. [D]**
- **Avoidance of the causative antigen, when identified, is the most important and effective aspect of management. [C]**
- **Corticosteroids may have a role in treating severe or progressive disease. [C]**

20. DIAGNOSTIC UNCERTAINTY AND USE OF THE "CORTICOSTEROID TRIAL"

A trial of corticosteroids, initially at high dose (0.5–1 mg/kg prednisolone) and tapering over a period of weeks and months, is often used in the management of patients with ILD. There are no suitable controlled studies that address the value of this strategy in patients with ILD but in whom there is genuine uncertainty as to the specific diagnosis. A corticosteroid trial is not recommended in patients with definite or probable IPF as described. A corticosteroid trial should be considered if there is sound clinical and/or radiological ground for believing the patient may have a steroid-responsive condition such as COP or HP, but it should be borne in mind that a proportion of such patients are still likely to have IPF, albeit with atypical features. Given that corticosteroid therapy is associated with serious side effects in a significant proportion of patients,[489] the risk-benefit of treatment should be weighed carefully on an individual basis. A dose of 0.5–1 mg/kg prednisolone is recommended with re-evaluation after 8–12 weeks. Maintenance steroids at much lower doses should be considered either if there is objective improvement (eg, 10% improvement in FVC or 15% improvement in TLCO) or if there is apparent stabilisation in a patient in whom lung function was previously declining. Corticosteroid-induced side effects should be assessed and prophylaxis against osteoporosis instigated according to widely accepted guidelines.

21. ILD ASSOCIATED WITH CONNECTIVE TISSUE DISEASES (CTDs)

21.1 An overview of management

Many of the principles described previously for the general management of the ILDs also apply to the ILDs in connective tissue disease (CTD). Rheumatoid arthritis (RA) is the most common of the CTDs to be associated with ILDs, but data on treatment are limited. Systemic sclerosis (SSc) is much less prevalent than RA but is more commonly complicated by ILD and the evidence base is much more extensive. It should be stressed that not all the recent advances in our understanding of

the natural history of the IIPs can be extrapolated to their CTD-associated counterparts.

21.2 HRCT and histological findings in CTD-associated ILD and prognostic significance

The histological entities of the ATS/ERS classification for IIP can all be associated with the CTDs.[490] As in IIP, fibrotic disease predominates. However, the prevalence of individual histological patterns differs strikingly between CTD and IIP.

In the only large study of lung histology in SSc there was a high prevalence of NSIP (62/80, 75%) and a very low prevalence of UIP (6/80, 8%),[28] a finding that is broadly consistent with other smaller series.[491 492] The HRCT features of lung disease in SSc can range from predominant ground glass attenuation to a predominant reticular pattern and are broadly similar to the range seen in idiopathic NSIP. Coarse reticulation and honeycombing are less common and, in this regard, biopsy and HRCT data are remarkably concordant in SSc.[493] Patients with SSc with UIP tend to have marginally poorer lung function than SSc patients with NSIP,[28 491 492] probably accounting for a slightly reduced survival.[494] Overall, however, outcome differs little between UIP and NSIP in SSc, even after adjustment for baseline disease severity.[28] Thus, the range of HRCT appearances in SSc from ground glass to reticular does not translate into corresponding differences in outcome.[495] In part this may reflect the observation that the ground glass changes seen in SSc are often associated with traction bronchiectasis or an admixed reticular pattern that almost always denotes fine fibrosis.[168 496] Furthermore, UIP in SSc has a better outcome than IPF, perhaps reflecting a lower profusion of fibroblastic foci in UIP in CTD in general[497] or earlier diagnosis of the lung disease.

In comparison to SSc, lung disease in RA is less well characterised. Recent data suggest that NSIP and UIP subgroups make up similar proportions of patients with rheumatoid lung.[29] The spectrum of HRCT changes also suggests that NSIP and UIP-type patterns occur with similar frequency,[498 499] but there are insufficient data to draw firm conclusions regarding the correlation between HRCT findings and histological pattern in RA. Indeed, the picture is confused by the recent finding that a UIP-like picture on HRCT may be associated with NSIP histology in RA,[500] a particular discordance that is exceedingly rare in idiopathic disease.[22 23] Comparisons between outcome in UIP and NSIP in RA have not been sufficiently powered to provide robust conclusions. As with SSc, however, UIP associated with RA appears to have a better outcome than the idiopathic form of the disease.

In polymyositis/dermatomyositis (PM/DM), NSIP predominates over UIP, OP or other patterns of interstitial pneumonia.[178] The HRCT appearances tend to reflect this, being broadly those of idiopathic NSIP although airspace consolidation is a common coexisting feature.[501 502] In Sjogren's syndrome, despite the traditional view that LIP is the characteristic lung histological finding,[451] fibrotic NSIP was almost always diagnosed at biopsy in a recent large analysis in which the HRCT pattern also tended to reflect the histological diagnosis.[503]

Hence, with the possible exception of RA, NSIP is the predominant histological diagnosis in CTDs. HRCT findings reflect this to some degree, but there tend to be particular HRCT profiles associated with specific CTDs. Other than for SSc, data on treated outcomes in relation to the HRCT pattern have yet to emerge in suitably large series. There is little evidence that the classification of fibrotic patterns on biopsy or HRCT usefully informs therapeutic decisions and, at present, the selection of treatment for CTD-associated ILD should not depend upon differential HRCT patterns of lung disease. An exception is the uncommon but important potentially reversible presentations of DIP or OP presenting with pure ground glass or predominant airspace consolidation, respectively, on HRCT scanning (seen most often in RA and PM/DM).

21.3 Which patients with CTD-associated ILD should be treated?

No formal placebo controlled trial has been performed in lung disease in CTD and, thus, current management is based on anecdotal and inconclusive retrospective data. The decision to treat must be largely based on the likelihood, in individual patients, that the risk of treatment (drug toxicity) will be outweighed by the benefit (protection against progression of disease). Apart from a minority of patients with predominantly HRCT inflammatory appearances, treatment is usually aimed at slowing or preventing progression rather than in the hope of a striking short-term response. Early lung involvement in PM/DM is an important exception to this rule, as discussed in the PM/DM section below.

Treatment issues, including the question of which patients to treat and the selection of therapeutic agent, have been most widely explored in SSc, perhaps because ILD is most prevalent in that disease. In SSc the threshold for introducing treatment is reduced when:

- The duration of systemic disease is short (<4 years), indicating a higher risk of progression of lung disease.[504 505]
- The disease is severe, as judged by pulmonary function tests and the extent of fibrosis on HRCT scanning. TLCO provides a stronger prediction of mortality[28 506 507] and correlates better with the extent of disease on HRCT scans than other lung function variables.[508]
- There is evidence of recent deterioration, as judged by symptomatic worsening and/or, a decline in serial pulmonary function tests. Ongoing deterioration in treated patients is more predictive of mortality than any clinical feature at presentation.[28]
- HRCT appearances are strongly suggestive of predominantly inflammatory disease (seen in a minority of cases).[495]
- BAL is more contentious, with opposing views that a BAL neutrophilia identifies greater risk of progression[509] or merely greater disease severity at the time of sampling.[494]

In the absence of a strong evidence base, these broad considerations are equally applicable to other CTDs. In summary, decisions on which patients to treat are far more dependent on disease severity and likely progressiveness (based on observed change and the duration of systemic disease) than on histological and HRCT observations.

21.4 Treatment of ILD in SSc

Although corticosteroid therapy was used historically in the ILD of SSc, there are no convincing data showing that high dosages are efficacious. Furthermore, it is now clear that the risk of renal crisis rises substantially with corticosteroids. In an index case-control study, renal crisis was associated with a minimum daily prednisolone dose of 20 mg.[510] In a more recent but larger study, corticosteroid therapy in general (including prednisolone doses as low as 10 mg daily) was associated with renal crisis.[511] It is possible that more severe systemic disease may be associated with both renal crisis and a higher likelihood of steroid therapy, with linkage between the two associations.[494] However, based on frequent anecdotal accounts of a striking temporal relationship, the link between high-dose corticosteroids and renal crisis is largely accepted.

The most widely used initial treatment regimen is low-dose corticosteroid therapy (eg, prednisolone 10 mg daily) and an immunosuppressive agent, usually oral cyclophosphamide. The widespread use of oral cyclophosphamide, generally at a dose of 1.0–1.5 mg/kg, is largely based on open observational data and retrospective comparisons of serial clinical data between treated and untreated groups.[234 512–515] However, in a recent large multicentre study in SSc-associated ILD in which the majority of patients had milder disease than in many previous studies, oral cyclophosphamide resulted in a mean FVC that was 2.53% higher than the placebo group after 1 year of treatment.[516] Corticosteroid use was at the discretion of the attending physician, although patients taking >10 mg prednisolone per day were excluded from the study as were subjects with clinically significant PH. The difference in lung function, while statistically significant, is clinically modest and, given the long-term toxicity associated with the drug, does not yet justify the routine use of oral cyclosphamide in unselected patients with SSc.

More recently, pulsed intravenous cyclophosphamide has been evaluated in three trials.[517–519] In all three studies, open therapy was associated with evidence of partial regression of ILD based on serial pulmonary function tests[517 519] or serial HRCT scans[518 519] and treatment was well tolerated. Regimens vary between studies with dosages of 500–1000 mg and dose intervals of 2–4 weeks, with monthly treatment most frequent. In all these studies corticosteroid therapy was also used in varying doses, and it is not entirely clear whether the apparent benefit of treatment was due to combination treatment or to a specific cyclophosphamide effect.

Other immunosuppressive agents have been used in the ILD of SSc but data are limited. A beneficial response to oral azathioprine in association with low-dose prednisolone has been reported in an uncontrolled retrospective analysis.[520] Because the apparent benefits in this study are similar to apparent benefits reported with oral cyclophopsphamide in other studies but the toxicity of azathioprine is lower, many physicians introduce oral azathioprine in combination with low-dose prednisolone as initial therapy, except in very severe or progressive disease. However, no randomised controlled trial exists comparing the efficacy of immunosuppressive agents. Placebo controlled trials comparing oral with intravenous cyclophosphamide are to be reported in the near future.

The outcome in the ILD of SSc is substantially better than in IPF after adjustment for baseline disease severity, and this difference is robust when examined in treated patients.[76] However, in keeping with the largely fibrotic nature of the disease, complete remission as judged by serial HRCT scans is rare. Even with aggressive therapy, severe interstitial fibrosis remains a major malignant prognostic parameter.

Short notes on cyclophosphamide therapy and a patient information sheet are supplied in online Appendices 5 and 10, respectively.

21.5 Treatment of ILD in RA

There is an extreme paucity of data for the management of ILD in RA. ILD in RA may result from the disease itself or as a consequence of its treatment (eg, methotrexate-induced pneumonitis), the two sometimes being indistinguishable. A smoking history of >25 pack-years substantially increases the risk of developing ILD.[175]

Initial treatment of rheumatoid ILD, if required, is typically with oral corticosteroids (eg, oral prednisolone 0.5 mg/kg/day) which should be tried for 1–3 months. If there is improvement as judged by physiological and/or radiological criteria, this could be reduced to 10 mg/day or 20 mg/alternate days. A failure to respond or deterioration during this steroid trial should prompt an evaluation of immunosuppressant treatment such as cyclophosphamide,[521] azathioprine,[522] D-penicillamine[522] or methotrexate, although there are only limited supportive data for any of these regimes. Cyclosporin A has been useful as a steroid-sparing agent when other agents have failed or disease has progressed despite corticosteroids and immunosuppressants.[522 523] The potential benefit of anti-TNFα therapy[524] should be viewed in the context of several cases of rapid occasionally fatal progression of lung disease in patients with RA-associated ILD treated with anti-TNF therapy.[525 526]

Cyclophosphamide can also be useful for the treatment of methotrexate-induced pneumonitis which has not responded to the usual management of methotrexate withdrawal, oxygen therapy and/or corticosteroids.[527] COP in RA is highly likely to respond to corticosteroids.[528]

21.6 Treatment of ILD in PM/DM

A lack of randomised controlled trials makes the optimal treatment for PM-associated ILD unclear. The most widely used initial treatment is corticosteroids,[404 529–536] usually with oral prednisolone 0.75–1.0 mg/kg/day (or equivalent) with gradual tapering. Fulminant disease may require high-dose intravenous methylprednisolone (1.0 g/day for 3 days).[535 537–539]

In patients with a suboptimal response or adverse effects from corticosteroids, consideration should be given to second-line therapies with either immunosuppressant or cytotoxic agents.[178 536 540 541] Although data are limited to small series and case reports, responses have been noted with cyclophosphamide (intravenous or oral),[541–551] azathioprine,[537 541 545 551–554] methotrexate,[533 554] cyclosporin A[501 535 537 555–560] and tacrolimus.[561]

Prognosis is good with early treatment.[501 535 536 561] Short-term improvement is seen in more than 90% of treated cases.[501 561] Patients with raised creatine kinase (CK) levels have a threefold better response to corticosteroids than those with normal CK levels.[535] In the longer term, response rates are variable but in one study where all patients received corticosteroids, with 50% additionally having cyclophosphamide or azathioprine, ILD resolved in 75% (partial in 56%; complete in 19%) with deterioration seen in the remaining 25%.[541]

Survival rates at 3 and 5 years vary from 74% to 90%[178 541] and from 50% to 87%,[178 536 541] respectively. Importantly, the outcome of the muscle disease is not always concordant with the pulmonary process.[541]

Recommendations for the treatment of CTF-associated ILD

- **In general, the threshold for starting treatment in the hope of preventing progression of pulmonary fibrosis in CTD-associated ILD is reduced when disease is severe (as judged by HRCT or pulmonary function tests), recently progressive, or there is a short duration of systemic disease. [C] In many patients the potential benefits of therapy will be outweighed by the risks.**
- **For the majority of CTDs, with the exception of SSc, recommended initial treatment for ILD is oral prednisolone at an initial dose of 0.5–1 mg/kg with the aim of tapering to a maintenance dose of 10 mg/day or less, often in association with an immunosuppressive agent (usually oral or intravenous cyclophosphamide or oral azathioprine). [C]**
- **ILD associated with PM/DM often warrants early treatment with oral prednisolone (0.75–1 mg/kg) and**

cyclophosphamide or other immunosuppressive therapy to prevent disease progression. [C]

- **In SSc-associated ILD, recommended treatment, if required, is with low-dose oral steroids (10 mg/day) and/or cyclophosphamide (oral or intravenous) [C] High-dose corticosteroid therapy (daily prednisolone dose >10 mg) should be avoided if at all possible because of the risk of renal crisis. [C]**

22. SARCOIDOSIS

A number of factors need to be taken into account before treatment is considered;

- Spontaneous remission occurs in 55–90% of patients with stage I radiological disease, 40–70% with stage II disease and 10–20% with stage III disease.[115 182 562–565]
- Most remission occurs within the first 6 months.
- The natural history is variable and predicting the course and prognosis are difficult.
- There are significant racial differences in the severity of disease and organs involved.
- The long-term effects of treatment on the natural history of the disease are unknown.

22.1 Corticosteroid treatment: an overview

Corticosteroids have been used as the main form of treatment since the 1960s for treatment of symptoms and resolution of disease with controlled[566 567] and uncontrolled studies.[568 569] Their role is clear when there is critical organ involvement, with ocular involvement not responding to topical treatment, neurological or myocardial disease, hypercalcaemia or other significant organ involvement. These situations are not addressed in these guidelines. In pulmonary disease, which is usually less severe or non-progressive and often spontaneously remits, the role of steroids is more difficult to ascertain. There are many reports of the short-term benefits of steroids reducing symptoms and inflammation. Issues that need to be clarified are the medium-term benefit (years) and whether, in the long term, therapy changes the natural history of the disorder.

In a systematic review, Paramothayan and Jones[570] found eight randomised placebo controlled trials of oral or inhaled corticosteroids where outcomes were measured. No further randomised controlled trials have been published since then. In aggregated results from 407 patients from four of the five randomised controlled trials with oral corticosteroids[566 571–573] there was an improvement in chest radiographs at 6 and 24 months (Peto odds ratio 2.54; 95% CI 1.69 to 3.81, $p<0.001$), with subgroup analysis showing the improvement was in patients with stage II–III but not stage I radiographic changes. Lung function could not be aggregated and, in most studies, there was no significant effect of treatment on lung function.[573] In two studies there was a small improvement in FVC and TLCO after 3–7 months treatment.[571 572] Results on change in symptoms, such as cough, were not available. In one study a global score (aggregating chest radiograph, lung function and symptoms) showed an improvement after 3 months of treatment. Adverse effects were not reported in all studies in the systematic review but only a small number of patients withdrew because of side effects. Overall, the findings suggest that chest radiographs may improve in those with stage II–II disease up to a period of 2 years, with little consistent effect on lung function.

The regime of treatment used in these studies varied from between 15–40 mg prednisolone/prednisone [566 567 572 573] and 4–32 mg methylprednisolone[571] given for 3–24 months. There is no consensus on dose or regime. Alternate day therapy is as effective as daily therapy, but there is no evidence it is better.[574] Side effects are significant.[575] Bisphosphonates have been shown to prevent and treat steroid-induced osteoporosis.[576] Alendronate has been shown in a non-blinded randomised controlled trial of 43 patients to prevent bone loss in steroid-treated patients.[577]

22.2 Effect of steroid therapy on the natural history of sarcoidosis

The long-term effect of treatment with corticosteroids on the natural history of the disease is not clear. A BTS open label study of long-term corticosteroid therapy alternately allocated 58 patients with stable disease not requiring treatment observed over 6 months to long-term corticosteroid treatment (30 mg for 1 month, reducing by 5 mg every month to maintenance of 10 mg, adjusted based on radiographic findings, and 10 mg continued over time) or use of steroid treatment only for symptoms or deteriorating lung function.[118] At 5 years there was a marginally better VC (9%) in those on long-term treatment, with mild side effects requiring withdrawal of 2/27 patients. In addition, a randomised, double-blind, placebo controlled trial of treatment at presentation with oral prednisolone for 3 months followed by inhaled budesonide for 15 months (198 patients) with open follow-up for 5 years found that 26% of the prednisolone group and 38% of the placebo group still had radiographic changes at 5 years, and the placebo-treated patients more frequently required steroid therapy because of relapse in the follow-up period (2/74 vs 16/75 patients, $p<0.05$). Patients with stage II–III disease but not stage I disease treated with steroids had significantly greater improvements in FVC and TLCO than those in the placebo arm.[578] These findings may support the use of steroids in all patients with stage II–II disease. However, it was noteworthy that 24/39 patients in the placebo group had spontaneously improved from stage II–III disease to stage 0 ($n = 22$) or stage 1 ($n = 2$) at 5 years. Furthermore, the improvement in lung function was relatively small.

A potential deleterious effect of steroids on the outcome of sarcoidosis has also been raised. In an observational study from one centre of 337 patients, a relapse rate of 74% was noted in patients who had a remission induced by steroid therapy compared with 8% of those who had a spontaneous clinical remission ($p<0.01$).[579] Many patients were African-Americans, a population recognised to have more aggressive disease and a poorer prognosis, and many were treated initially for non-pulmonary organ involvement; 50% of relapses occurred within 2–4 months of discontinuing steroid therapy and 20% more than 12 months later. In an observational study of patients with intrathoracic sarcoidosis comparing mortality in referral and population-based settings, the mortality was 4.8% and 0.5%, respectively, and the number of patients with stage III disease was 17% and 11%, respectively. Steroid use was sevenfold higher in the referred setting.[67] Clearly, the results in both studies could be explained by major confounding factors, particularly severity of disease. It thus remains unproven if steroid treatment has a negative impact and is associated with a poorer prognosis.

22.3 Inhaled steroid treatment for sarcoidosis

Inhaled therapy as first-line treatment

Uncontrolled[580 581] and controlled[582–584] studies of inhaled steroids suggest a possible effect in selected patients. Two randomised

controlled trials which assessed the effect of inhaled corticosteroids alone were included in a systematic review of steroids in sarcoidosis.[570] The results could not be aggregated. In one study of 47 patients there was no improvement in VC, FEV_1 or TLCO after 6 months of treatment with budesonide, although a combined score of symptoms (dyspnoea, cough, malaise and fatigue) improved ($p<0.03$).[582] In the other study of 19 patients treated for 8–10 weeks there was no improvement in the chest radiograph or TLCO, but TLCO reported in terms of improvement or deterioration (+15%) showed a significant benefit in the treated group ($p<0.04$).[583] A third randomised controlled trial was not included as the data could not be extracted,[585] but it demonstrated no effect of high-dose inhaled steroids. The results are inconclusive and do not demonstrate a benefit, but suggest that inhaled corticosteriods may help symptoms in selected patients.

Inhaled treatment in maintenance phase following oral steroids

Two randomised controlled trials reported the use of inhaled corticosteroids after patients had received oral corticosteroids either as part of the study protocol or before entering the study[572 586] and were reviewed in a systematic review.[570] The results could not be aggregated as the level of steroids used differed significantly. In a study of 77 patients with stable sarcoidosis, Du Bois *et al* used inhaled fluticasone propionate or placebo for 6 months. Forty-four of these patients were on oral steroids at the start of the study. There was no difference in symptoms, peak expiratory flow rate, FEV_1, FVC, TLCO, TLC or rescue bronchodilator therapy.[586] Pietinalho *et al* gave 3 months of oral corticosteroids followed by 15 months of inhaled budesonide or oral followed by inhaled placebo to 189 adults. In the actively treated group there was a significantly greater effect on the chest radiograph in those with initial stage II disease but not in those with stage I disease at 3 and 6 months but not at 18 months. Neither the FVC nor TLCO changed over the study period in patients with stage I disease in either the treatment or placebo groups. In those with initial stage II disease, TLCO was significantly higher at 18 months but not earlier, the largest changes being seen in those with lower initial lung function.[572] A further study with 21 patients showed no significant benefit with inhaled steroids.[587] Overall, the data for using inhaled corticosteroids during the maintenance phase of treatment in sarcoidosis are inconclusive.

In summary, the studies of the long-term benefits of steroids in pulmonary sarcoidosis are inconclusive. In view of the significant rate of spontaneous remission and significant side effects, treatment is not indicated for:

- asymptomatic stage I disease;
- asymptomatic stage II disease with mildly abnormal lung function and stable disease (measured 3–6-monthly);
- asymptomatic stage III disease with mildly abnormal lung function and stable disease (measured 3–6-monthly).

Treatment should be considered for patients with:

- deteriorating lung function over 3–6 month intervals;
- deteriorating radiological changes;
- significant pulmonary symptoms of cough, shortness of breath, chest pain or haemoptysis.

22.4 Alternatives to corticosteroids

The significant toxic effects of long-term and or high-dose steroids are well recognised and, in some patients, the side effects of steroids are intolerable. Furthermore, a small number of patients have progressive pulmonary disease despite corticosteroid therapy, do not respond to initial treatment with steroids, or have severe non-pulmonary disease such as that involving the skin or central nervous system. Alternative immunosuppressive drugs have been tried, both as treatment and as steroid-sparing agents, with particular interest in treatments specifically targeting the underlying mechanism that promotes inflammation. These include methotrexate, cyclosporin A, hydroxychloroquine, azathioprine, chlorambucil, cyclophosphamide, lenflunamide, pentoxifylline, thalidomide, infliximab and entanercept. Most studies are small case series with significant potential for bias. In a systematic review updated to April 2004, only four randomised controlled trials were found using alternative drugs to corticosteroids, looking at methotrexate, cyclosporin A and two studies of chloroquine, all in addition to corticosteroids.

For methotrexate, a folic acid antagonist, case series of 14 patients,[588] 50 patients[589] and 91 patients[590] showed some benefit with the addition of methotrexate. The only randomised controlled trial was of 24 patients and compared methotrexate (16 patients) or placebo (8 patients) in addition to oral prednisolone with 2:1 allocation over 1 year.[591] Prednisolone 40 mg was given during the run-in period of 4 weeks, after which the dose varied depending on the response. Methotrexate was given in a dose of 10 mg per week and these patients used significantly less prednisolone in the second 6 months (median 8.3 mg/day (0.83–21.7) vs 16 mg/day (11–22) ($p<0.001$)). However, only 15 patients remained in the study beyond 6 months and, on an intention-to-treat basis, methotrexate was no different from placebo. Lung function, radiography and symptoms were similar in both the methotrexate and placebo arms.

The use of cyclosporin A, a T cell suppressor, has been reported to improve neurosarcoidosis in two retrospective studies[592 593] but was not beneficial in other studies.[594 595] Wyser performed a randomised controlled study of the efficacy of cyclosporin A as a steroid-sparing agent in 37 patients with pulmonary sarcoidosis treated over 18 months.[594 595] No benefit in terms of lung function or dyspnoea could be shown and there were significantly more side effects in the treatment group.

Chloroquine and hydroxychloroquine are antimalarial agents which have been reported in case series for cutaneous and renal sarcoidosis, neurosarcoidosis and hypercalcaemia.[565 596–599] Two randomised controlled studies examined the effects of chloroquine versus placebo in patients with pulmonary sarcoidosis. In a randomised placebo controlled multicentre trial, 52 patients who had not received steroids but had either lung infiltrates for 6 months and dyspnoea, progressing lung infiltrates for 6 months or infiltrates for a year, were studied; 24 received chloroquine (600 mg/day for 8 weeks, 400 mg for 8 weeks) and 28 received placebo.[600] No benefits were found and side effects were greater in the treatment group. Baltzan *et al*[601] performed a double-blind randomised placebo controlled study in patients with sarcoidosis who received tapered doses of chloroquine during a run-in period over 6 months followed by chloroquine 250 mg/day for a follow-up period of 6–48 months (median 19.7). Chloroquine reduced the rate of decline in FEV_1 and TLCO over 20 months. Overall, the results with chloroquine are not consistent.

Azathioprine, a purine analogue, has been shown in case series to improve chest radiography and dyspnoea in patients with sarcoidosis.[602] A study of azathioprine and steroids combined suggested an effect of azathioprine,[603] while another retrospective case review suggested a benefit in only 2/10 patients.[604] There are no randomised controlled trials of azathioprine in sarcoidosis.

A case series in lung disease[605] showed that 8/10 patients probably improved due to chlorambucil. Another case series showed that 15/31 patients refractory to steroids had significant improvement with the addition of chlorambucil and 13 had a moderate improvement. The side effects were significant. There are no randomised controlled trials of chlorambucil in sarcoidosis.

Cyclophosphamide, an alkylating agent, has been used in neurosarcoidosis and some case reports show an improvement with reduction of steroid dose.[606]

Lenflunomide is a cytotoxic drug used in the treatment of RA. A retrospective case series of its use in chronic sarcoidosis has been reported[607] with 32 patients treated, 15 with concurrent methotrexate. There appeared to be a response in the majority of patients. However, there are no randomised controlled trials of leflunomide treatment in sarcoidosis.

Pentoxifylline, a xanthine, has been studied in a case series of 23 patients with sarcoidosis given the drug for 6 months, with reported improvement in symptoms and lung function.[608] Thalidomide has been reported to improve cutaneous sarcoidosis in case series.[609 610]

TNF has been shown to play a role in the inflammatory process and various inhibitors have been studied. Etanercept is a p75 TNF receptor fusion protein that binds TNF. A phase 2 trial in patients with progressive stage II and II disease was stopped after recruitment of 17 patients because of treatment failure in 11.[611] Infliximab is a chimeric monoclonal antibody which blocks TNF. Case reports of benefit in neurosarcoidosis have been reported.[612–617] In one report three patients with corticosteroid-refractory disease improved in terms of lupus pernio (two patients) and lung function (one patient)[618] and, in another series, five patients with refractory sarcoidosis, two of whom had pulmonary disease, improved following infliximab therapy.[619] Trials of anti-TNF therapy in sarcoidosis are ongoing (http://www.clinicaltrials.gov/ct).

Overall, there are insufficient studies of high quality to clarify the role of immunosuppressive agents in sarcoidosis. There is some evidence that supports the use of methotrexate as a steroid-sparing agent. As side effects of these drugs are significant, they should be used with caution in a setting when disease is progressing and there are no alternatives.

22.5 Lung transplantation for sarcoidosis

End-stage respiratory disease with pulmonary fibrosis and stage IV radiological changes occurs in a small number of patients. Overall mortality in sarcoidosis is 1–5% due to pulmonary or myocardial or CNS involvement. Lung transplantation has been used in patients with sarcoidosis, and such patients represent 2.8% of all lung transplant recipients in the USA.[620] Short-term outcome showed a higher degree of graft failure with 83% survival in sarcoidosis compared with 91% survival in transplantation for other causes, infection being significantly more important in other transplants.[620] Survival estimates from studies with small numbers give a 1-year survival of 62–72% and a 4–5-year survival of 46–56%.[621–623] Short-term survival is influenced by race, being lower when the donor or recipient is African-American.[620] Outcomes show the occurrence of obliterative bronchiolitis is similar to transplantation in other inflammatory diseases.[622] There is no consensus on whether single or double lung transplantation should be performed.

Sarcoidosis is the most common underlying disease to recur in the transplanted lung in 35–62.5% of cases,[622 624] however the recurrence is usually asymptomatic and frequently resolves during follow-up.

Before surgery it is important to define involvement of other organs with sarcoidosis, particularly the heart. A relative contraindication to transplantation is mycetomas,[625 626] and complicating bronchiectasis should be defined. Markers of mortality on the transplantation waiting list include PH, American-African race and amount of supplemental oxygen used.[126]

Recommendations for the management of sarcoidosis

- **Because of the high rate of spontaneous remission, treatment is not indicated for asymptomatic stage I disease. [B]**
- **Because of high rates of remission, treatment is not indicated in asymptomatic stage II or III disease with mildly abnormal lung function and stable disease. [D]**
- **Oral corticosteroids are the first line of therapy in patients with progressive disease determined by radiology or on lung function, significant symptoms or extrapulmonary disease requiring treatment. [B]**
- **Treatment with prednisolone (or equivalent) 0.5 mg/kg/day for 4 weeks, then reduced to a maintenance dose which will control symptoms and disease progression, should be used for a period of 6–24 months. [D]**
- **Bisphosphonates should be used to minimise steroid-induced osteoporosis. [D]**
- **Inhaled corticosteroids, either as initial treatment or maintenance therapy, are not of significant benefit. [B] Inhaled corticosteroids may be considered for symptom control (cough) in a subgroup of patients. [D]**
- **Other immunosuppressive or anti-inflammatory treatments only have a limited role in sarcoidosis, but should be considered in patients when corticosteroids are not controlling the disease or side effects are intolerable. At present, methotrexate is the treatment of choice. [C]**
- **Lung transplantation should be considered in end stage pulmonary sarcoidosis. [D]**

23. PULMONARY HYPERTENSION (PH) IN ILD AND CTD

There are a number of authoritative guidelines on the assessment and management of pulmonary hypertension (PH).[627 628] In the UK, the diagnosis and treatment of PH is often undertaken in conjunction with one of several regional specialist centres that provide local guidance for referral (http://www.pha-uk.com/specialist.asp). The guidelines and recommendations in this document focus on PH associated with interstitial lung disease and connective tissue diseases and should be used in conjunction with advice from the regional PH centres.

23.1 Definitions and nomenclature

PH is defined as a resting mean pulmonary artery pressure (PAP) >25 mm Hg with normal left atrial pressure. It can be a consequence of underlying chronic cardiorespiratory disease causing systemic and/or regional hypoxia, pulmonary thromboembolic disease or an intrinsic disorder of the pulmonary microcirculation, and the latter is specifically termed pulmonary artery hypertension (PAH). In a recent internationally adopted classification system, PH associated with CTD (including SSc) is classified as a subset of PAH. PH associated with ILD is categorised with "other" hypoxic causes of PH.[628] This classification serves as a reminder that the pathophysiology of

idiopathic PAH, for example, differs from other causes of PH, and this should be considered when interpreting clinical trials that include a heterogeneous sample of subjects with PAH and PH. The classification, however, belies the complex nature of PH associated with conditions such as IPF or sarcoidosis in which hypoxia, microthromboembolic disease and an intrinsic vasculopathy may all play a role in the development of raised PAP.

23.2 Diagnosis of PH in ILD

The clinical symptoms and signs of PH characteristically appear late in the course of ILD and the symptoms will often be masked by the underlying pulmonary disorder.

The "gold standard" for measuring PAP and thereby diagnosing PH is right heart catheter. This invasive test carries with it a small but inherent risk to the patient. There is therefore a need for simple and reliable non-invasive indicators of PH.

Lung function testing

A reduced TLCO is of only limited value in predicting PH in the presence of ILD. In IPF the prevalence of PH has been shown to be significantly higher in subjects with TLCO <40% predicted and resting oxygen saturation <88%.[629] In patients with SSc without evidence of concomitant lung disease, TLCO <50% predicted or a declining TLCO on serial testing does predict for the presence of PAH.[630 631] The role of submaximal exercise testing in detecting PH in ILD is unknown.

Transthoracic Doppler echocardiography

Transthoracic Doppler echocardiography (TTE) is commonly used to estimate the right ventricular systolic pressure (RVSP) which, in the absence of pulmonary outflow obstruction, is equivalent to the systolic PAP. The estimated RVSP can only be determined in the presence of a systolic tricuspid regurgitant (TR) jet. Even in skilled hands, a TR jet can only be detected in 70–80% of cases. In one study of 347 patients with advanced lung disease including ILD, PAP could only be assessed by TTE in 44% of individuals.[632] The absence of a detectable TR jet does not rule out significant PH.[633] TTE has been reported to correlate reasonably well with systolic PAP measured at right heart catheter and has a high sensitivity (>85%) for detecting PH.[632 634] However, significant discordance (>10 mm Hg) between TTE and right heart catheter measurement of systolic PAP is not uncommon.[632] The specificity and positive predictive value of TTE can be increased if a higher threshold of systolic PAP measurement is adopted; in patients with SSc, including those with lung fibrosis, the specificity and positive predictive values for correctly identifying PH have been reported to be 97% and 98%, respectively, using a TTE-determined systolic PAP threshold of ⩾45 mm Hg.[635] In another large study of advanced ILD, however, this same threshold has been shown to perform poorly with a positive predictive value of just 60%.[632]

In summary, TTE is a non-invasive, cost-effective and widely available investigation which is suitable for screening patients for PH. The ideal threshold for PAP determined by TTE above which one should proceed to right heart catheterisation is uncertain, and if PH is clinically suspected, right heart catheter should always be considered.

Brain natriuretic peptide (BNP)

Brain natriuretic peptide (BNP) is predominantly secreted by cardiac ventricles under stress[636] and has been shown to be raised in patients with chronic lung disease and PH.[637 638] In a prospective study of 176 patients with lung disease of whom half had ILD, raised plasma BNP levels were found to have a sensitivity, specificity, positive predictive value and negative predictive value of 0.85, 0.88, 0.73 and 0.92, respectively, for the presence of PH as determined at right heart catheterisation.[639] Routine assay for BNP is not widely available and further studies of this promising test are needed.

23.3 PH in IPF

Epidemiology

A longitudinal study of 70 unselected patients with IPF and who had right heart catheter measurements at initial presentation reported that PH (mean PAP >25 mm Hg) was present in 8.1% of subjects.[640] Retrospective studies have reported a higher prevalence of PH. In a study of 136 selected patients with IPF who had undergone TTE, raised systolic PAP (>35 mm Hg) was observed in 84% of subjects.[641] In a study of 118 patients with IPF aged 65 years or under being considered for lung transplantation, 41% were found to have resting PH at cardiac catheterisation.[629] It is therefore likely that the prevalence of PH is higher in patients with advanced IPF than in those with mild disease.

Impact of PH on prognosis in IPF

Patients with IPF and pulmonary artery enlargement on plain chest radiography have a poorer prognosis than those with normal PA appearances.[112] Several recent retrospective studies have provided further evidence that PH may represent a poor prognostic indicator in IPF. In a study of 88 patients with IPF in whom systolic PAP at presentation could be assessed by TTE, those with systolic PAP >50 mm Hg had 1-year and 3-year mortalities of 56% and 68%, respectively, compared 0% and 36% in those with systolic PAP ⩽35 mm Hg.[642] The 1-year mortality of 48 patients with mean PAP ⩾25 mm Hg was 28% compared with 5.5% in 70 patients with normal PAP.[629 643] The presence of PH at transplant assessment may be associated with an early mortality after transplantation.[644]

In summary, it is likely that PH—particularly if severe (mean PAP >40 mm Hg or systolic PAP >50 mm Hg)—is associated with a high early mortality in IPF. It is speculated that detection of raised PAP captures an aspect of the natural history of the disease not apparent from lung function testing alone, but further studies are required to establish the true prevalence and prognostic implication of PH in IPF.

23.4 PH in sarcoidosis

Epidemiology

PH is an uncommon complication of sarcoidosis. It is, however, well recognised in subjects with severe lung disease and a review of the United Network of Organ Sharing (UNOS) Registry has reported that 75% of the 363 patients with sarcoidosis listed for lung transplantation had PH (mean PAP >25 mm Hg) and one-third exhibited severe PH (mean PAP ⩾40 mm Hg).[645] In a prospective observational study of unselected patients with stage 0–IV sarcoidosis, TTE identified resting PH (defined as systolic PAP⩾40 mm Hg) in 5.7% of subjects,[646] a figure consistent with previous studies using right heart catheter measurements.[647] Although PH is more likely to occur with stage III and IV sarcoidosis, PH with stage 0 and I disease is well described in case series[646 648] and may arise from unsuspected cardiac involvement, granulomatous infiltration of pulmonary vessel walls including capillaries and veins (resulting in an

occlusive venopathy) or heightened sensitivity to vasoactive factors and pulmonary artery compression by mediastinal/hilar adenopathy.[649]

Impact of PH on prognosis in sarcoidosis

There are no substantial data that address the impact of PH on the natural history of sarcoidosis, but individual case reports indicate it may not respond to corticosteroid therapy and PH is associated with an increased risk of death in subjects with sarcoidosis listed for lung transplantation.[126 621]

23.5 PH in SSc

Epidemiology

Most studies have indicated that 10–20% of patients with SSc exhibit PH, and this frequently occurs in the absence of significant ILD (ie, isolated PAH).[650–653] In a large prospective study designed to "screen" for PAH in patients with SSc without significant ILD, only 6% of 570 subjects were found to have PAH based on TTE and only half of these were confirmed at cardiac catheterisation.[654] Most (but not all) studies report that PAH occurs far more frequently in limited cutaneous SSc (associated with anti-centromere antibodies) than with the diffuse form of the disease.[631 651 655 656]

Impact of PH on prognosis in SSc

Pulmonary complications, specifically PAH, are a major cause of mortality in SSc. The median survival of untreated SSc-associated PAH has been reported to be only 12 months, poorer than for idiopathic PAH.[657 658]

PH associated with other CTDs

The true incidence of PH in most CTDs is not known. The available data are largely retrospective in nature and the methods used to measure PAP and to define PH vary. However, PH is a well recognised complication of SLE and may be present in 6–14% of patients.[659 660] In a large study of PH in patients with CTD, 8% of 83 subjects with mixed connective tissue disease (MCTD) had PH based on TTE.[661] PH in association with Sjogren's syndrome, PM/DM and RA has only been reported rarely.

23.6 Treatment of PH in ILD and CTD

It is important to distinguish that both the evidence base and rationale for treating PAH, including PAH associated with SSc, differs from that of PH associated with ILD. The major clinical trials of therapy in PH have predominantly enrolled patients with idiopathic PAH. Individuals with SSc-associated disease have been represented to a lesser extent and subjects with ILD-associated PH have been in a minority. Furthermore, these trials have employed short-term end points, typically improvement in exercise capacity at 3–4 months. It is not established that exercise capacity is a valid surrogate for mortality in PH. There are no randomised controlled trials that have specifically addressed the impact on mortality of treating PH associated with ILD or CTD, including PAH associated with SSc.

The principal therapeutic options for treating PH are conventional therapy with supplemental oxygen and anticoagulation, and specific therapy with calcium channel blockade, prostanoids, endothelin antagonists and phosphodiesterase-5 inhibitors.

Conventional therapy

Supplemental oxygen

The use of supplemental oxygen is discussed in detail in Section 13.1. There is no evidence that oxygen therapy is beneficial in the treatment of IPF or other ILDs. It is reasonable to prescribe oxygen, titrated to achieve an oxygen saturation of >90% via an oxygen concentrator, in patients with ILD, chronic hypoxia (arterial oxygen tension <8.0 kPa) and cor pulmonale. In contrast to COPD, there is no evidence that long-term oxygen therapy (>15 h/day) is associated with improved survival in patients with ILD and chronic hypoxia. Controlled studies of oxygen therapy in ILD are required.

Anticoagulation

Prospective cohort studies indicate that long-term warfarin therapy is associated with improved survival in idiopathic PAH and patients with PH due to chronic thromboembolic disease.[662–664] There are no data that can inform on the risks versus benefits of warfarin therapy in PH associated with ILD. A randomised controlled trial of warfarin in IPF, discussed in detail in Section 13.2, reported improved survival in the anticoagulated group, but there is no evidence that this was a consequence of treating underlying PH.[42] Warfarin therapy should therefore only be prescribed in IPF or other ILD if there is strong clinical, radiological or histological evidence of thromboembolic disease. Further studies of anticoagulation in IPF are required. Although there is also no evidence, extrapolating the data from observational studies in idiopathic PAH would suggest that warfarin therapy should be considered in subjects with CTD and isolated PAH.

Specific therapy

Specific therapy for PH should be undertaken in close liaison with a regional specialist PH centre. Calcium channel blockers, prostenoids, endothelin antagonists and phosphodiesterase-5 inhibitors have all been approved for use in patients with advanced (NYHA or WHO grade III or IV) PAH, including PAH associated with SSc.

Calcium channel blockers improve survival in a subgroup of patients with idiopathic PAH who demonstrate a significant response to an acute vasoreactivity test.[663 665–667] The evidence base for calcium channel blockers in PAH with SSc is less robust since these patients represented smaller subgroups within the larger clinical trials. There is no evidence that calcium channel blockers reduce mortality in patients with ILD-associated PH.

The evidence base for the use of prostenoids, endothelin antagonists and phosphodiesterase-5 inhibitors has been summarised in recent international guidelines,[628] a Cochrane analysis[668] and a meta-analysis.[669] All three classes of drugs appear to have similar efficacy in improving exercise capacity in patients with idiopathic PAH and NYHA or WHO class III or IV disease, but the impact on survival is not known. Of the subjects recruited to the large landmark clinical trials of PAH, approximately 30% had CTD (predominantly SSc)-associated PAH and the vast majority of subjects had idiopathic PAH.[669] In general, the subgroup of patients with SSc-associated PAH had a less impressive response to therapy than those with idiopathic PAH.[670–673] The 1- and 3-year survival in SSc-associated PAH has consistently been reported to be poorer than in idiopathic PAH regardless of therapy,[674] emphasising inherent differences in the two conditions. A placebo controlled randomised trial of specific vasomodulatory therapy in patients with grade III or IV SSc-associated PAH would be ethically contentious. Patients with

grade III and IV CTD-associated PAH should be referred to a specialist regional PH centre for assessment and consideration of therapy. Patients with less severe CTD-associated PAH should be referred and considered for controlled clinical trials.

Patients with ILD-associated PH have comprised only a very small proportion of subjects in randomised controlled trials of treatment and thus there are no data to support the use of specific therapy in this context. Several high quality but small studies have shown that treatment with prostanoids (inhaled iloprost) or phosphodiesterase-5 inhibitors (sildanefil) reduce pulmonary vascular resistance in most patients with ILD-associated PAH.[675 676] However, pulmonary artery vasodilatation may be counterproductive by increasing ventilation-perfusion mismatch[677] or increasing shunt fraction[675] and thereby worsening hypoxaemia in subjects with ILD. Randomised controlled trials of specific treatment for PH in ILD are required. Patients with ILD and PH should be considered for treatment, ideally in the context of a high quality clinical trial and following assessment in a specialist regional PH centre if the PH is judged to be contributing to symptoms and is disproportionate to the extent of ILD or is particularly severe (systolic PAP>50 mm Hg).

Recommendations for PH in ILD and CTD

PH in ILD

- **Pulmonary hypertension should be considered in patients with ILD who have either breathlessness or lung dysfunction (reduced TLCO or desaturation on exercise) that seem disproportionate to the extent of parenchymal lung disease. [D]**
- **Transthoracic echocardiography is a suitable screening tool for the detection of PH in patients with ILD. [B]**
- **Long-term oxygen therapy should be prescribed in patients with ILD, chronic hypoxia (<8 kPa) and cor pulmonale. [D]**
- **Patients with ILD and PH that is judged to be contributing to symptoms and is disproportionate to the extent of ILD or is severe (systolic PAP >50 mm Hg) should be considered for referral to a regional specialist PH centre for assessment and recruitment to high quality clinical trials. [D]**

PAH associated with CTD

- **Patients with SSc should have annual lung function testing and TTE should be performed in those with declining TLCO or TLCO <50% predicted. [C]**
- **Long-term warfarin therapy should be prescribed in patients with CTD-associated PAH. [D]**

24. ILD PRESENTING WITH ACUTE RESPIRATORY FAILURE

Presentation with acute respiratory failure and the consideration of admission to an intensive care unit (ICU) or high dependency unit (HDU) is a particular challenge in patients with ILD. The two most common scenarios in which ILD presents with acute respiratory failure are (1) rapid deterioration in a patient with previously diagnosed ILD and (2) an initial presentation with rapidly progressive disease.

Deterioration in previously diagnosed ILD with borderline respiratory failure or need for ventilation

In the most frequent scenario, deterioration occurs in a patient treated for underlying ILD in whom new lung infiltrates are observed. The differential diagnosis always includes deterioration of the underlying disease or infection, including opportunistic infection. The differential diagnosis often includes (1) drug-induced lung disease; (2) cardiac decompensation, especially in multisystem autoimmune disorders in which there may be pre-existing pulmonary vascular or other cardiac involvement; and (3) pulmonary embolism, although this is unlikely in the presence of new radiographic infiltrates.

Apparently de novo presentation of acute diffuse ILD with associated respiratory failure

The most frequent presentation consists of deterioration over weeks in a previously apparently healthy individual, culminating in a clinical picture of increasing respiratory failure associated with diffuse lung infiltration on chest radiography. ILD that presents in this way may represent (1) progression of a longer standing but hitherto unsuspected ILD or (2) de novo acute ILD.

Progression of a longer standing but hitherto unsuspected ILD

The presentation may represent an acute exacerbation of IPF (see Section 24.2). Alternatively, infection may unmask an underlying ILD with an acute presentation resulting from loss of pulmonary reserve. Review of old chest radiographs may be highly revealing.

De novo acute ILD

The two most frequent presentations with rapidly progressive ILD are acute interstitial pneumonia and fulminant OP. The wider possibilities include subacute diffuse alveolar damage in occult connective tissue disease, vasculitis and, rarely, aggressive HP. Occasionally, the differential diagnosis is broadened unexpectedly, based on HRCT appearances.

However, the differential diagnosis always includes processes other than primary ILD, including infection, pulmonary oedema, alveolar haemorrhage syndromes and drug-induced lung disease. Clinical and HRCT features may suggest that primary ILD is highly likely. Investigations including echocardiography and BAL, when HRCT findings raise the possibility of infection or alveolar haemorrhage, are required to exclude other diagnostic possibilities.

24.1 Investigations for ILD presenting with respiratory failure

Although mechanical ventilation is sometimes required at presentation, there is more often a window of opportunity during which investigation can be performed before ventilation is required.

Urgent TTE is a simple means of identifying overt cardiac decompensation or valvular heart disease, but is user-dependent and sometimes insensitive in identifying global ventricular dysfunction, diastolic impairment and stress-induced mitral regurgitation. Thus, pulmonary artery catheterisation is sometimes warranted on clinical grounds despite apparently reassuring echocardiographic findings.

In the presence of radiographic infiltrates, pulmonary embolism is unlikely. If deterioration has occurred without new infiltrates on chest radiography in a patient with known ILD and pulmonary embolism is suspected, CT-pulmonary angiography (CTPA) is a useful investigation since it will effectively exclude thromboembolism and provide high-resolution images that may identify infiltrates not readily apparent on the chest radiograph.

In most patients with known or suspected ILD in an ICU or HDU setting, infection is the dominant differential diagnosis

with opportunistic infection a particular complication in patients with known ILD on immunosuppressive therapy. Reaching an accurate diagnosis is central to confident management. However, there are a number of factors that mean infection can seldom be excluded by non-invasive means, either when there is major progression of disease in a previously stable situation or in de novo presentations of suspected ILD:

1. In autoimmune disease, infection and disease progression are often markedly similar in clinical presentation (fever, cough, increased breathlessness and increased radiographic shadowing).
2. No serological markers in autoimmune disease correlate closely with intrinsic disease activity in ILD.
3. Non-specific laboratory indices of infection (white blood cell count, ESR, CRP) lack sensitivity or specificity as all may be influenced by underlying systemic disease activity.
4. Chest radiography is notoriously unhelpful in distinguishing between infection and progression of ILD in a critical care population.
5. HRCT is occasionally diagnostic of major progression of fibrotic disease in advanced ILD,[678] obviating the need for invasive investigation, and it also provides useful information on the optimal site for bronchoscopic or surgical biopsy evaluation. However, HRCT has not been consistently useful in identifying opportunistic infection in the ventilated patient with ILD. Ground glass opacification on HRCT is non-specific, being present equally in opportunistic infection and rapidly progressive ILD.

For these reasons, invasive investigations are usually required effectively to exclude infection and, in selected cases, to make a confident diagnosis.

BAL and TBB in the HDU and ICU

The value of BAL and TBB should be considered on a case-by-case basis. When pulmonary infiltrates are associated with immunosuppressive therapy, BAL makes a crucial contribution to the detection of opportunistic infection.[679] The identity of likely infective organisms depends upon whether the patient is neutropenic,[680] the nature of the underlying disease process and immunosuppressive therapy,[681 682] the prior administration of antimicrobial therapy,[683] and the timing of the BAL relative to hospital admission and onset of ventilation.[684] Bacterial pathogens are the most prevalent isolates and fungal, mycobacterial and viral infection should be excluded with the appropriate cultures. Clinicians should seek microbiological advice before performing BAL if the use of novel diagnostic procedures is contemplated.

BAL is usually safe in immunosuppressed patients, including those with haematological dysfunction[680] and in critically ill ventilated patients.[685 686] However, in patients with major respiratory compromise who are not yet ventilated, deterioration in respiratory mechanics and gas exchange is a major consideration.[687 688] In high-risk patients, BAL should be performed in the ICU.

The added value of TBB in patients undergoing BAL is contentious. In severely immunosuppressed patients with pulmonary infiltrates (including patients with HIV, haematological malignancy, receiving antirejection therapy), TBB is strikingly more diagnostically sensitive than BAL and serious complications are rare.[689] It is not clear that TBB offers the same diagnostic advantage over BAL in patients with known underlying ILD and acute deterioration. However, the risks of pneumothorax following TBB in mechanically ventilated patients are not unacceptably high. In one series of 71 patients the rate of pneumothorax was 10.4% (as opposed to an expected rate of 5%) and there were no serious complications.[690] However, a pneumothorax in a ventilated individual, especially if receiving positive end expiratory pressure, may lead to a catastrophic deterioration in gas exchange. Thus, TBB is appropriate in selected ventilated patients with underlying diffuse lung disease with a view to targeting new infiltrates, both for histology and culture, in the hope of obviating surgical biopsy.

Surgical lung biopsy in the HDU and ICU

A surgical biopsy is occasionally appropriate in selected ventilated patients with known ILD, despite a higher risk and reduced benefit in critically ill patients. Surgical lung biopsy should be considered when other tests are non-diagnostic. The diagnostic yield of surgical lung biopsy in ventilated patients has varied from 46% to 100%.[691–694] However, it is not always easy to quantify the influence of the additional information on management. In one study of ventilated patients with ILD, the attainment of a diagnosis from surgical lung biopsy led to continuation of the current treatment in 33%, increased immunosuppression in 26%, initiation of immunosuppression in 22% and changes in antimicrobial therapy in 19%.[692] Even when the long-term outcome appears likely to be poor, surgical lung biopsy may provide useful information. The absence of reversible disease at biopsy may allow inappropriate support to be minimised[691 693] and withdrawal of care issues to be discussed definitively with family members.[695 696] The advantages of surgical lung biopsy must be balanced against the risks of the procedure. In ventilated patients it may carry a short-term mortality as high as 10% and postoperative complications in a further 20% have a variable influence on long-term survival which is difficult to quantify.[691–694] Increased mortality in ventilated patients with pulmonary infiltrates undergoing surgical lung biopsy has been linked to an immunocompromised status at the onset of respiratory failure or current immunosuppressive therapy, severe hypoxia, multiorgan failure and older age.[691 693 694]

The threshold for proceeding to a surgical biopsy is lower when the underlying ILD diagnosis is unknown than when a diagnosis of ILD is already secure, prior to deterioration. If it is obvious that a surgical lung biopsy is required with no likely diagnostic yield from BAL or TBB, semi-invasive investigation may be associated with both additional risk and unnecessary delays in diagnosis and effective treatment. Immediate surgical lung biopsy is sometimes warranted. There may be a small window of opportunity for performing crucial investigations prior to mechanical ventilation and it is often appropriate to move high-risk patients to the ICU for BAL or surgical lung biopsy. Occasionally, proactive mechanical ventilation is required in order to allow key investigations to be performed.

24.2 Specific ILD entities that may present with acute respiratory failure

Once infection and other causes of acute respiratory failure are excluded to as great an extent as is feasible, there are three ILD entities that comprise the majority of cases of acute ILD: acute interstitial pneumonia (AIP), acute exacerbations of IPF and fulminant COP.

Acute interstitial pneumonia (AIP)

First described by Hamman and Rich,[697] AIP is characterised by a histological picture of diffuse alveolar damage, as also seen in

the acute respiratory distress syndrome.[698] There is a wide age range but presentation is most often reported in the sixth decade and there is no gender predilection.[699–703] The aetiology is uncertain. It is likely that lung injury from occult infection or other toxic exposures accounts for some cases, but similar histological appearances in some patients with autoimmune disease[703] and in acute exacerbations of IPF[704] suggest that AIP may represent an atypical fulminant presentation of IIPs that more usually manifest as chronic fibrotic disease.

The presentation usually consists of rapidly progressive dyspnoea, evolving over days to weeks, often associated with a viral prodrome. A neutrophilia is usual on BAL.[705] On HRCT, ground glass opacification, distortion and traction bronchiectasis are almost invariable, and consolidation, interlobular septal thickening and nodular opacities are highly prevalent.[699 701 702 706–708] Honeycombing is rare and suggests an acute exacerbation of IPF (see below) rather than AIP. A higher mortality is associated with more extensive ground glass opacification or consolidation, especially when traction bronchiectasis is prominent.[699]

The diagnosis of AIP demands typical clinical and HRCT features but is not wholly secure without histological evidence of diffuse alveolar damage, given the clinical and HRCT overlap with fulminant OP. The survival rate is probably less than 20% but has ranged from 10% to 50% in reported series.[699 701 702 706 707]

Acute exacerbations of IPF

It is known that some patients with IPF have an atypically precipitous course in which acute deterioration follows periods of relative stability.[709 710] Episodes in which the aetiology is uncertain are best termed ''acute exacerbations'' of IPF. Case definitions vary considerably between series[704 711 712] with criteria commonly including (1) previous or concurrent diagnosis of IPF; (2) unexplained worsening or development of dyspnoea within 30 days; (2) HRCT scan showing bilateral ground glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern compatible with the pattern of UIP; (4) no evidence of pulmonary infection by endotracheal aspirate or BAL; (5) exclusion of alternative causes including left heart failure, pulmonary embolism and identifiable causes of lung injury. Gas exchange criteria, usual in historical series, have been discarded in a recent consensus statement.[713] Acute exacerbation is also a very rare feature of idiopathic fibrotic NSIP.[714]

Disease severity in IPF, as judged by pulmonary function impairment, does not predict the risk of an acute exacerbation.[715] Surgical lung biopsy may be a risk factor.[254 716 717] Hypoxia is usual and a presentation with respiratory failure is common. A rapid decision is often required on whether to institute mechanical ventilation. However, invasive ventilation is seldom appropriate when the diagnosis is secure because of the poor outcome associated with IPF (see Section 24.3).

There are no diagnostic laboratory findings in acute exacerbation in IPF and the typical BAL neutrophilia[710 712] is also expected in AIP. Diffuse ground glass abnormalities are usually present on chest radiography[704] and are characteristic on HRCT scans, with or without consolidation, and associated with typical IPF findings (predominantly bibasal subpleural reticular abnormalities or honeycombing).[710–712] A higher mortality is associated with diffuse, as opposed to focal, ground glass opacification, typically present when hypoxia is severe.[711] Diffuse alveolar damage associated with UIP is found at surgical biopsy in most cases,[704 710–712 718–720] although OP without associated diffuse alveolar damage is occasionally seen.[720] In most patients the history of recent deterioration and presence of extensive ground glass on HRCT scanning makes the diagnosis obvious, although heart failure, opportunistic infection and drug-induced lung disease may all give rise to this clinicoradiological profile in a patient with pre-existing IPF.

In patients with extensive ground glass on CT scanning and severe hypoxia, survival seldom exceeds 10% despite treatment. However, in patients presenting with milder forms of disease the outcomes are more variable, probably reflecting major differences in diagnostic criteria.

Fulminant COP

In occasional cases COP is devastatingly severe at presentation and may progress to death without overt pulmonary fibrosis. The entity of fulminant COP was first described in five patients presenting with respiratory failure following rapidly progressive dyspnoea over the preceding 2 weeks.[415] Three required mechanical ventilation; two patients died, with the other three responding well to high-dose corticosteroid therapy. Histological findings consisted of OP in isolation. Fulminant OP has since been described in a number of case reports and has a variable but often good outcome, in contrast to AIP. However, when presenting with a clinical picture of the acute respiratory distress syndrome (ARDS),[721] fulminant OP may be indistinguishable from AIP, clinically and on HRCT scanning, although traction bronchiectasis, interlobular septal thickening and intralobular reticular abnormalities tend to be more prominent on HRCT in AIP.[707]

24.3 Decisions on the admission of ILD patients to the ICU

The likelihood of a successful outcome is the key consideration that should inform a decision to admit patients with ILD to the ICU for invasive ventilation. Often palliation, sometimes after a trial of non-innvasive ventilation, is more appropriate. However, there is only a limited evidence base upon which to make informed decisions and the following guidance should be interpreted in this light and on a case-by-case basis. It is valuable, although not always possible, to reach an early conclusion, usually based on HRCT appearances and clinical judgement that disease is clearly irreversible. Pre-emptive counselling of patients that palliation or non-invasive supportive therapy rather than invasive ventilation is appropriate is an important component of management and clarity on this point may be immensely helpful to medical staff and family members alike.

Patients with previously known ILD

In patients with known pre-existing ILD the underlying diagnosis is crucial. Case series in IPF, the most prevalent fibrosing ILD, have consistently demonstrated a uniformly high hospital mortality in intubated patients with near 100% mortality in the short term even if discharged from the ICU.[722–726] In known ILD that is not IPF, observed longitudinal behaviour prior to an acute deterioration is important. If there has been progression to advanced fibrotic disease despite treatment, a palliative approach as for IPF is usually warranted, even if the diagnosis is known to be fibrotic NSIP or fibrotic HP.[723 727]

In advanced ILD in general, mechanical ventilation may seem an attractive option when a problem is potentially reversible. However, it is sometimes far from clear that weaning from mechanical ventilation will be possible, even with complete reversal of the supervening process. A decision that non-invasive ventilatory support is appropriate but mechanical ventilation

should not be undertaken should be made jointly by a respiratory physician and an intensivist, ideally before an immediate decision on ventilation is required. Mechanical ventilation may also seem attractive in patients with ILD who might be considered for lung transplantation. However, mechanical ventilation is increasingly regarded as an absolute contraindication to lung transplantation: the outcome from transplantation is poor because of a high risk of pneumonia due to airway microbial colonisation and severe muscular deconditioning from immobility and complications such as sepsis and nutritional problems.[371] Current data suggest a threefold increase in 1-year post-transplant mortality in ventilated patients.[728]

Patients with apparently de novo ILD

In general, the threshold for admission to ICU will often be lower in such cases either because the presentation is clearly "primary" or acute ILD on a background of apparently good lung function, or because the presence of underlying ILD has not been previously recognised. It is particularly important to be alert to the latter scenario, either by obtaining previous radiographs and/or on the basis of the HRCT scan. Evidence of extensive fibrotic change or a pattern of disease typical of IPF usually indicates that invasive ventilation is highly unlikely to have a successful outcome.

24.4 Management of specific ILD entities on the ICU

As described, the three most frequent ILD diagnoses are AIP, acute exacerbation of IPF and fulminant COP. Management of coexisting infection and general supportive measures should be guided by local practice and national guidelines in close liaison with microbiological advice. Specific therapies for ILD in this setting have generally consisted of high-dose intravenous corticosteroid therapy and other forms of immunosuppression. However, in the absence of any controlled data on treatment of rapidly progressive ILD, the guidance is largely based on anecdotal experience.

- Early treatment is highly desirable. There is limited indirect evidence that the outcome may be better in AIP with early high-dose corticosteroid therapy[729] and in more frequently reversible processes such as fulminant OP, treatment delays may be life-threatening. Furthermore, delays in instituting corticosteroid or immunosuppressive therapy may squander a short therapeutic window during which the patient is free of infection and vigorous immune modulation is feasible.
- Pulsed intravenous methylprednisolone is first-line therapy in almost all rapidly progressive primary ILDs. A dose of 750 mg or 1 g is usual, given on three consecutive days. Thereafter, pending assessment of the clinical response, maintenance therapy (a dose of 0.5–1 mg/kg/day prednisolone or equivalent) is usual.
- It is usual to assess the response to corticosteroid therapy during the 5–7 days after initial treatment before considering second-line treatment but, in severe disease, an immunosuppressive agent should be added sooner. Of the alternative immunosuppressive agents, intravenous cyclophosphamide offers obvious advantages because of a relatively rapid onset of action (often within 1 week) and because the level of toxicity is acceptable in most cases. Intravenous cyclophosphamide is much less toxic than oral cyclophosphamide.[730] A dose of 600–650 mg/m^2 is usual, as increasingly used in automimmune diseases such as SSc.[494] Mesna protection against bladder toxicity is recommended if the total dose exceeds 1 g. A further dose can be given as early as 7–10 days later, white blood count nadir permitting. In less extreme circumstances, following an initial response, 2-weekly treatment is often warranted.
- The concurrent initial use of intravenous corticosteroids and cyclophosphamide increases the likelihood of infection but may be justifiable when disease is exceedingly severe and time to intervene is short. This is especially important in vasculitic disorders such as Wegener's granulomatosis in which cyclophosphamide is more efficacious than high-dose corticosteroid[730] and should be used as first-line therapy. When progressive severe vasculitis is suspected but cannot be confirmed, early empirical cyclophosphamide treatment is justified.

Finally there are three clinical scenarios that are particularly prone to suboptimal management as a consequence of misdiagnosis:

- Even when clinical and HRCT features suggest AIP or fulminant OP, it is vital to consider drug-induced lung disease which may mimic both disorders. A large database detailing known and suspected drug-induced pulmonopathies, including a large number of drugs that rarely but definitely induce lung disease, can be readily accessed (pneumotox.com). A working knowledge of the drugs that most frequently cause lung disease is not sufficient. Failure to withdraw an offending drug in this scenario is a life-threatening error. Continuation of a possible offending agent should be confined to clinically indispensable treatments.
- Apparently acute ILD, presenting over weeks, may be simulated by diffuse malignant lung disease. This may manifest as classical lymphangitis carcinomatosis on HRCT, but there is a significant patient subgroup with extensive progressive disease and highly variable infiltrative HRCT appearances. Malignancy may be overlooked, especially when those managing the case have reached an early diagnosis of primary ILD. In this clinical scenario, malignancy should always be considered when HRCT appearances are difficult to classify.
- Chronic progressive infection may occasionally simulate a rapidly progressive ILD. Tuberculosis is notorious in this regard, but fungal and other chronic infections may also mimic progressive ILD.

24.5 Summary of management of ILD on the ICU

ILD-associated respiratory failure may represent either rapid deterioration in a patient with previously diagnosed ILD or an initial presentation with rapidly progressive disease. In both cases exclusion of infection is crucial and this will often require invasive investigations. The decision to proceed to BAL or TBB is made on an individual basis, but BAL in particular is safe in ventilated patients. Surgical lung biopsy is appropriate in selected patients despite the potential risks, and the threshold to perform surgical biopsy is lower if the underlying ILD has not previously been identified. Patients with IPF should not generally be admitted to the ICU for respiratory support because of the extremely high associated mortality. There are no controlled trials of treatment in patients with acute ILD presenting with respiratory failure. Treatment with high doses of corticosteroids with or without other immunosuppressive therapy is reasonable based on case series and anecdotal data.

An algorithm for the management of ILD presenting with acute respiratory failure is provided in Appendix 4.

Summary of recommendations for ILD presenting with acute respiratory failure

- **Early accurate and secure diagnosis is critically dependent upon considering a broad differential diagnosis including new-onset ILD and ILD progression, and non-ILD processes such as pulmonary oedema, malignancy, drug-induced lung disease and infection. [D]**
- **Accurate diagnosis in ILD with borderline respiratory failure often requires BAL to exclude infection and is best performed in selected patients on the ICU before ventilation is required, or with ventilatory support immediately available. [D]**
- **Decisions on transbronchial and surgical lung biopsy must be individualised to the clinical scenario. Both procedures are often justifiable, despite increased risk, if there is a realistic possibility that the additional information will influence management. [D]**
- **ICU support for patients with IPF and respiratory failure is usually not appropriate due to the very high associated mortality. [C]**
- **In most rapidly progressive ILDs presenting with respiratory failure, intravenous corticosteroid therapy is the initial treatment of choice. Intravenous cyclophosphamide is the second-line treatment of choice and is usually administered in patients not responding to parenteral corticosteroids. [D]**
- **In cases of known or suspected vasculitis, intravenous cyclophosphamide should be considered as first-line treatment. [C]**

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APPENDICES

Appendix 1: Aide memoire for the first clinic visit in suspected ILD

In addition to routine respiratory history and examination:

- History of acid reflux, symptoms suggestive of connective tissue disease including Raynaud's phenomenon.
- Detailed occupational history.
- Exposure to birds and other potential antigens.
- Current and previous drugs (see Appendix 2 in online data supplement)

Investigations for most (if not all) patients with suspected ILD:

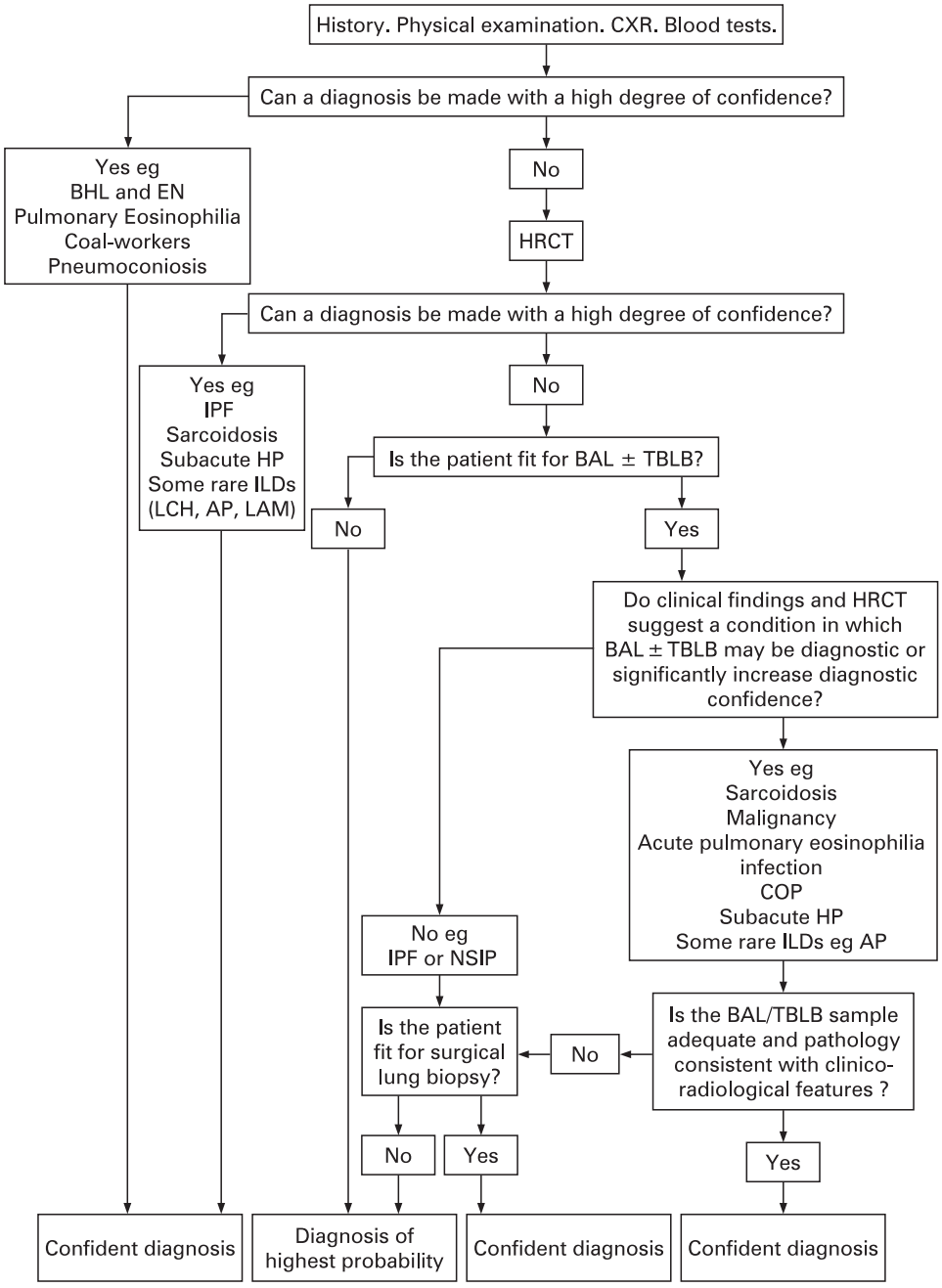
- Full blood count, urea and electrolytes, calcium, lung function tests, ESR, CRP, rheumatoid factor, ANA.
- Oxygen saturation at rest.
- Urinalysis.
- HRCT scan.
- Spirometry, lung volumes and gas transfer.
- ECG.

Additional tests in selected patients:

- Suspected sarcoidosis: serum ACE
- Suspected hypersensitivity pneumonitis: precipitating antibody to suspected antigen
- Suspected vasculitis: ANCA

See algorithm for further diagnostic pathway in ILD (Appendix 3)

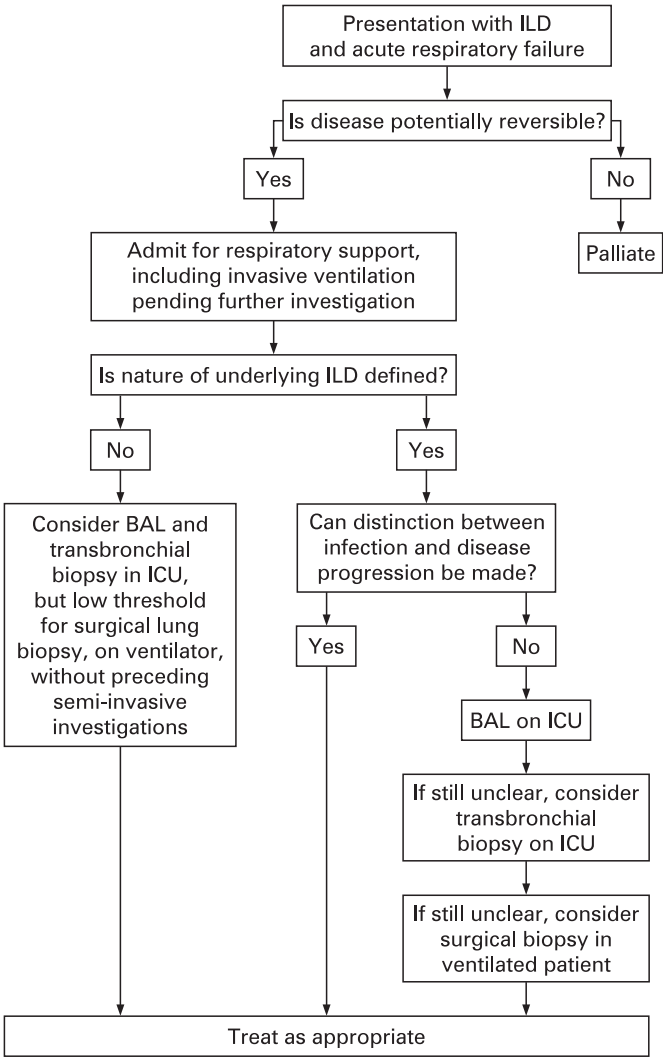
Appendix 3: Diagnostic algorithm for interstitial lung disease (ILD)



It is anticipated that in many cases of ILD, a confident diagnosis, or diagnosis of highest probability will be made locally by the chest physician in conjunction with radiology and pathology colleagues. It is recommended however that regional ILD centres are established in which regular ILD multi-disciplinary meetings are held. These centres should have close links to local hospitals and the diagnosis and management of a significant proportion of ILD should be discussed in this setting. Finally, in diagnostically "difficult" cases of ILD, the national panel of expert ILD pathologists (already established) and radiologists (recommended to be established) may be approached for guidance.

Abbreviations:
BHL – Bilateral Hilar Lymphadenopathy
EN – Erythema Nodosum
LCH – Langerhans Cell Histiocytosis
AP – Alveolar Proteinosis
LAM – Lymphangioleiomyomatosis
COP – Cryptogenic Organsing Pneumonia
HP – Hypersensitivity Pneumonitis

Appendix 4: Management algorithm for interstitial lung disease (ILD) with acute respiratory failure



Abbreviations

ACA: anticentromere antibody
ACE: angiotensin-converting enzyme
ANA: antinuclear antibody
ARDS: acute respiratory distress syndrome
ATS: American Thoracic Society
BAL: bronchoalveolar lavage
BNP: brain natriuretic peptide
BOOP: bronchiolitis obliterans organising pneumonia (synonymous with the preferred term "cryptogenic organising pneumonia")
BSC: best supportive care
BTS: British Thoracic Society
BUILD-2: Bosentan Use in Interstitial Lung Disease-2
CFA: cryptogenic fibrosing alveolitis (no longer to be considered synonymous with IPF. The term "CFA-clinical syndrome" is preferred to CFA to describe the typical clinical and radiographic features seen in idiopathic interstitial pneumonias).
CK: creatine kinase
CNS: central nervous system
COP: cryptogenic organising pneumonia
COPD: chronic obstructive pulmonary disease
CRP: C-reactive protein
CT: computed tomography
CTD: connective tissue disease
DIP: desquamative interstitial pneumonia
DPLD: diffuse parenchymal lung disease (synonymous with the preferred term "interstitial lung disease")
ERS: European Respiratory Society
ESR: erythrocyte sedimentation rate
ET-1: endothelin-1
EAA: extrinsic allergic alveolitis (synonymous with the preferred term "hypersensitivity pneumonitis")
FEV_1: forced expiratory volume in 1 s
FVC: forced vital capacity
GORD: gastro-oesophageal reflux disease
GRADE: grading of recommendations, assessment, development and evaluation
HDU: high dependency unit
HP: hypersensitivity pneumonitis
HRCT: high resolution computed tomography
ICU: intensive care unit
IFNγ: interferon-γ
IIP: idiopathic interstitial pneumonia
ILD: interstitial lung disease
IPF: idiopathic pulmonary fibrosis
ITU: intensive therapy unit
LCH: Langerhans' cell histiocytosis
La: Lane antigen (anti-La is synonymous with anti-SS-B (soluble substance B))
LAM: lymphangioleiomoyomatosis
LIP: lymphocytic interstitial pneumonia
LMW: low molecular weight
MALT: mucosa-associated lymphoid tissue
MCTD: mixed connective tissue disease
six minute walk test
NAC: N-acetylcysteine
NHLBI: National Heart Lung and Blood Institute
NSIP: non-specific interstitial pneumonia
NYHA: New York Heart Association
OLB: open lung biopsy
OP: organising pneumonia
ORD: Office of Rare Diseases
PAH: pulmonary artery hypertension
PAP: pulmonary artery pressure
PCR: polymerase chain reaction
PH: pulmonary hypertension
PM/DM: polymyositis/dermatomyositis
RA: rheumatoid arthritis
RBILD: respiratory bronchiolitis associated interstitial lung disease
RNP: ribonuclear protein
Ro: Robert-antigen (anti-Ro is synonymous with anti-SS-A (soluble substance A))
ROC: receiver operator characteristics
RVSP: right ventricular systolic pressure
Scl-70: scleroderma antigen 70 kDa (anti-Scl-70 is synonymous with anti-DNA topoisomerase 1)
SIGN: Scottish Intercollegiate Guideline Network
SLB: surgical lung biopsy (synonymous with the term "open lung biopsy")
SLE: systemic lupus erythematosus
Sm: Smith-antigen
SSc: systemic sclerosis
TBB: transbronchial biopsy
TBLB: transbronchial lung biopsy
T_{LCO}: transfer factor for carbon monoxide
TNF: tumour necrosis factor
TR: tricuspid regurgitant/regurgitation
tRNA: transfer ribonucleic acid
TTE: transthoracic Doppler-echocardioagrpahy
UIP: usual interstitial pneumonia
UNOS: United Network for Organ Sharing
VATS: video-assisted thoracoscopy
VC: vital capacity
WHO: World Health Organization

had a chest CT scan on referral. They fail, however, to describe a role for chest CT, but do imply that it may be indicated for patients undergoing video-assisted thoracoscopic drainage (VATS). There is no evidence in the current literature supporting the use of CT scans before VATS. The British Thoracic Society guidelines do not recommend routine CT scans in children with empyema.[2]

In our centre all patients with empyema requiring intervention undergo VATS (approximately 40/year). We would suggest that chest CT scanning is not indicated before VATS in nearly all cases. We have found chest CT scans to be helpful, however, in situations where the patient has not responded to appropriate treatment with antibiotics and VATS. In this situation the possibilities are reaccumulation of pleural fluid, abscess formation or more extensive parenchymal involvement, differential diagnoses that are distinguished by CT scanning and information that is critical to the decision to reoperate (or not).

In addition, Jaffe *et al* do not take the opportunity to critically examine the role of chest ultrasound scans in patients with empyema. In our experience, clinical examination and chest radiography can determine the presence of pleural fluid. If the purpose of the ultrasound scan is to determine whether the fluid is simple (a parapneumonic effusion) or organised (empyema), this can be achieved more simply with a lateral decubitus or erect chest radiograph. The decision to undertake definitive management with urokinase or VATS is determined by the presence of unremitting infection and/or fluid volume in the pleural space. It is an outdated paradigm that the distinction between simple and organised pleural fluid makes any difference to subsequent treatment or outcome. The main use for ultrasound scanning should be for those children who are found to have a unilateral whiteout on the chest radiograph at presentation and for whom the distinction between pleural space and parenchymal disease is difficult to make.

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Author's response

We thank Massie *et al* for correctly questioning the clinical need for routine chest CT scanning before performing video-assisted thoracoscopic surgery (VATS). Our study was pragmatically designed to reflect clinical practice in our institute, where thoracic surgeons routinely request a pre-operative CT scan for use as a "road map" when performing minimally invasive endoscopic surgery where direct visual access is limited. This helps to plan and assist in placement of the ports and instruments in order to decrease risk and avoid potential complications such as bronchopleural fistula which would result as a consequence of puncturing the lung parenchyma in close proximity to the pleura. We agree with them that there is no evidence base to support this practice in terms of risk, and our study was not designed to answer this question.

The principle of providing surgical "road maps" (which cross-sectional imaging now provides) is prevalent in many areas of cardiothoracic imaging where CT and MRI are added as an adjunct to echocardiography and ultrasound scans in order to enhance anatomical (and, indeed, sometimes functional) information to enhance quality and provide a safer more informed patient journey.

We are surprised that Massie *et al* advocate the use of a lateral decubitus chest radiograph in place of an ultrasound scan which is not, in fact, a recommendation of the BTS guidelines. Indeed, this would be a retrograde step in terms of the quality of information and the radiation burden, and should only be advocated where there is no access to ultrasound.

As discussed in our paper, ultrasound is an invaluable tool as it is cheap, mobile, easy to use, can differentiate transonic from purulent fluid, solid lung from fluid and enables the radiologist to mark the spot for chest drain insertion. Although it has been used to stage the disease, we agree that it is not useful in predicting the clinical outcome as was evident in our study. Importantly, ultrasound does not carry a radiation burden.

One of the key messages we had hoped to emphasise in our study is the critical need to reduce exposure of children to unnecessary radiation. With this in mind, we disagree with Massie *et al* and continue to advocate the use of ultrasound as the most important imaging modality in managing children with empyema. The BTS guidelines also support this view.

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CORRECTIONS

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A U Wells, N Hirani, and on behalf of the British Thoracic Society Interstitial Lung Disease Guideline Group, a subgroup of the British Thoracic Society Standards of Care Committee, in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Soc. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008;**63**(Suppl V):v1–v58.

The correct list of authors for these guidelines is: B Bradley, H M Branley, J J Egan (Irish Thoracic Society), M S Greaves, D M Hansell, N K Harrison, N Hirani, R Hubbard, F Lake (TSANZ), A B Millar, W A H Wallace, A U Wells, M K Whyte, M L Wilsher (TSANZ), The British Thoracic Society Standards of Care Committee, in collaboration with the Thoracic Society of Australia and New Zealand, and the Irish Thoracic Society.

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