

2008 British guidelines on the management of interstitial lung diseases

What are the key new messages for clinical practice?

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The British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society have recently published new guidelines on the management of interstitial lung disease.¹ We discuss here several of the key new messages.

Approach to patients presenting with acute respiratory failure

The guidelines usefully clarify an approach to patients presenting with acute respiratory failure, when the diagnosis is often unclear and decisions of whether to ventilate without a clear idea of prognosis, or increase immune-suppression in the presence of possible infection, are challenging. A key message are invasive procedures often needed to be performed and the earlier these are done, the more likely the patient will tolerate the procedure and the more helpful they will be. This applies to patients with an acute presentation of an apparently new diffuse interstitial process or patients with a rapid deterioration in previously diagnosed interstitial lung disease (ILD). A differential diagnosis to ILD in both groups includes infection, malignancy, drug reaction and heart failure and the likelihood of each is related to current therapies and severity of underlying disease. Following a meticulous review of the patient's history, medications and old X rays (looking for pre-existing idiopathic pulmonary fibrosis [IPF]), a computer tomography (CT) or CT pulmonary arteries, are often the first step in investigations, where the pattern of changes (such as honeycombing suggesting previously undiagnosed IPF) or exclusion of emboli, can help plan further steps.

Three investigations, namely broncho-alveolar lavage (BAL), trans-bronchial lung biopsy (TBLB) and surgical lung biopsy, in order of increasing risk, need to be considered. BAL is required

to exclude infection, and is safe and simple except in those who are not ventilated and whose respiratory failure may worsen. Even if the procedure results in patients being intubated, in high risk patients an early diagnosis of infection may be lifesaving. A TBLB carries an acceptable risk (10.4% complications in ventilated patients compared with 5% under usual conditions) but only a great increase in yield over a BAL in certain settings such as severely immunosuppressed patients. Despite a high yield, a surgical lung biopsy carries a significant risk in these unwell patients, and less frequently changes therapy. So each case needs to be assessed on individual likelihoods and the increased risk of investigation more likely to be tolerated in the group where there was no pre-existing ILD. It should not be forgotten that information from high risk procedures that could allow a reduction in treatment, such as through diagnosing IPF where the prognosis despite treatment is very poor, may be helpful for family and carers.

Key message Early invasive procedures may be needed to confirm/exclude treatable complications such as opportunistic infection.

Classification of non-specific interstitial pneumonitis

The guidelines reflect the continuing difficulty of classifying (NSIP), with the likelihood that it may represent separate disease entities. From 1994, with the original classification, it has continued to evolve and a new classification is under consideration by an ATS/ERS working group at present. The separation into good prognosis cellular NSIP and fibrotic NSIP is supported by a number of studies of treatment in NSIP. With fibrotic forms however, it appears unlikely they form one disease entity. Description and

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treatment along the lines of the ILDs they appear to overlap with seems the best way to approach the problem at present. The most common type, reported in particular in USA and Europe, are those with clinical features of IPF but variable CT findings, in particular with little honeycombing. Less common are fibrosing organising pneumonitis (OP) and hypersensitivity pneumonitis (HP) profiles, reported from South Korea and Japan, and France and Mexico, respectively. The latter may well be fibrotic variants of OP and HP.

Most difficult is the NSIP/IPF variant. The prognosis is better than IPF but worse than other forms of fibrotic NSIP. Honeycombing is unusual and ground glass changes more extensive on CT than in IPF but in some patients, despite CT changes highly suggestive of NSIP, the pathology may show IPF. Again it points to the need to get a surgical biopsy in patients where clinical features and CT are not 100% concordant with a diagnosis of IPF and a clinico-radiological diagnosis should be made and treatment given accordingly.

Key messages Classification of NSIP continues to evolve and NSIP likely represents a spectrum of disorders.

Surgical lung biopsy is usually required in the presence of clinical-radiological discordance.

Best supportive care and triple drug therapy for idiopathic pulmonary fibrosis The guidelines aim to provide advice on best treatment in IPF when some previous practice has been relatively non-evidenced based. The concept of “best supportive care” (BSC) is acknowledged as an important treatment strategy in IPF. BSC encompasses: palliation of breathlessness with domiciliary oxygen; pulmonary rehabilitation; smoking cessation; anti-reflux therapy; palliation of cough with oral opiates; and withdrawal of unnecessary therapies.

The use of oral corticosteroids, either alone or with immunosuppressive drugs, has been standard therapy in IPF. The usage of oral corticosteroids resulted from studies that reported approximately 50% of patients felt better following corticosteroid therapy, although less than 50% cases had any objective response such as an improvement in lung function or chest X-ray.^{2,3} The previous BTS guidelines on ILD⁴ stated that “there is no direct evidence that steroids improve survival”. So why the ongoing use of corticosteroids in IPF? Mapel et al. concluded that this may be due to the “physician’s ever-present compulsion to ‘do something’”.⁵

Studies from the UK⁶, USA⁷ and Japan⁸ show that corticosteroid monotherapy in IPF offers no survival advantage. The treatment recommendations of the ATS/ERS consensus statement on IPF⁹ have been partially superseded by the publication of the IFIGENIA study¹⁰, which examined the role of adding N-acetylcysteine

(NAC) 600 mg 3 times daily to standard therapy of oral corticosteroids with azathioprine. The addition of NAC/placebo to prednisolone/azathioprine has shown a 12 month relative difference of 9% in vital capacity (VC) and 24% in gas transfer in favour of NAC.

Key messages High dose corticosteroid monotherapy is not recommended in patients with a definite/probable diagnosis of IPF.

Current best therapy is triple therapy with prednisolone, azathioprine and NAC.

Best supportive care is offered to patients with advanced disease in whom triple therapy is not appropriate.

Treatment of ILD in Systemic Sclerosis (SSc) Studies have failed to show any convincing benefit when SSc-ILD patients are treated with corticosteroids.^{11,12} Additionally, high dose corticosteroids (≥ 20 mg/day prednisolone) are associated with renal crisis, independent of blood pressure.¹³ High dose corticosteroids are therefore not recommended unless there is accelerated disease, in which case the kidneys should be “protected” with iloprost, which may ameliorate renal vasospasm.¹⁴

Early studies of cyclophosphamide have shown variable benefits on pulmonary function and survival,¹⁵⁻¹⁹ although the consensus opinion is that cyclophosphamide is the best drug for SSc-ILD.²⁰ Intravenous cyclophosphamide can result in partial regression of SSc-ILD, as judged by serial pulmonary function tests (PFT)^{21,22} or serial high resolution CT (HRCT).^{21,23} More recently 2 randomised controlled trials of cyclophosphamide vs. placebo have shown a trend towards stabilisation of pulmonary function in a subset of patients²⁴ and a small (2.5% predicted) better forced vital capacity (FVC).²⁵

In the Fibrosing Alveolitis in Scleroderma Trial (FAST)²⁴ patients received low dose prednisolone (≤ 10 mg/day) with monthly (for 6 months) intravenous cyclophosphamide followed by oral azathioprine, or placebo. No significant differences were found, although there was a trend to an approximately 4% better FVC in the treated group. In the Scleroderma Lung Study²⁵ patients were treated with 12 months of oral cyclophosphamide (≤ 2 mg/kg body weight) and followed for a further 12 months. Oral cyclophosphamide had a significant but modest beneficial effect on lung function (2.5% better predicted FVC) compared to placebo at 24 months.

Key messages If treatment is required in SSc-ILD, use low-dose oral steroids (10 mg/day) and/or cyclophosphamide (oral or intravenous).

High-dose corticosteroid therapy (daily prednisolone dose >10 mg) should be avoided if possible because of the risk of renal crisis.

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