

Challenges in pulmonary fibrosis: 7 · Novel therapies and lung transplantation

T J Williams, J W Wilson

Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital and Monash University, Commercial Road, Melbourne 3004, Victoria, Australia

Correspondence to: Dr J W Wilson, Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital and Monash University, Commercial Road, Melbourne 3004, Victoria, Australia; john.wilson@med.monash.edu.au

Received 26 April 2005
Accepted 12 December 2005

ABSTRACT

The spectrum of diseases collectively known as pulmonary fibrosis does not have reliable therapeutic options. Many treatment protocols have been the subject of clinical trials, resulting in few significant improvements in outcome. Recently, cellular mechanisms have been the focus of investigations in progenitor cell studies, suggesting an immunomodulatory role for mesenchymal stem cells. The possible role of fibrogenic cytokines and the use of antagonist molecules are promising for future therapies. A range of anti-inflammatory treatments, including macrolide antibiotics, may also hold promise. When medical therapy has been unsuccessful in altering the course of the disease, lung transplantation may offer a significant survival advantage. Improvement in pre-transplant assessment and postoperative care, combined with more effective immunosuppressive regimes, has seen survival rates of 40% after 5 years. New options for therapy will lead to improved survival in coming years.

NOVEL THERAPIES

The basis for the use of anti-inflammatory therapies in idiopathic pulmonary fibrosis (IPF) is the finding of a chronic inflammatory infiltrate associated with progressive matrix and collagen deposition with angiogenesis. The definition of specific pathological entities in the spectrum of IPF has led to the need for precision in diagnosis and specificity in treatment plan.^{1,2} The combination of prednisolone and either azathioprine or cyclophosphamide in current treatment recommendations provides optimal outcomes for usual interstitial pneumonia (UIP) based on available evidence.¹ The limited effectiveness of established approaches has led to a search for novel therapies based on antifibrotic strategies. Parallels have been drawn with other immunologically-driven lung conditions characterised by cell infiltration, fibrosis and increased vascularity, including chronic asthma. Although remodelling changes in asthma have been shown to recede with corticosteroid therapy, there is little objective evidence to support this view in IPF.³ However, potential targets for therapeutic intervention in IPF are (1) cells involved in the inflammatory response, (2) cytokines/growth factors likely to orchestrate cellular events, and (3) chemical mediators of the inflammatory/fibrogenic response. The quest for novel therapies has been limited by a range of factors, including the applicability of animal models⁴ and relative infrequency of IPF in the general population. The diversity of entities called IPF has led to the need for a biopsy-proven disease classification.² Accurate diagnosis may also be difficult because of

mixed forms of the disease.⁵ Despite shortcomings, some promising antifibrotic strategies have emerged that are directly applicable to IPF.

Cellular targets

IPF is characterised by an increase in fibroblast activity, collagen and matrix deposition as well as angiogenesis. Although likely to be associated with an influx of inflammatory cells and structural cell progenitors (fibroblasts, angioblasts), there is evidence to support the use of mesenchymal stem cells for therapy in IPF. Studies in the bleomycin mouse model have shown that gene-labelled stem cells (lacZ) derived from bone marrow migrate to and proliferate within the injured lung.⁶ Furthermore, these cells have apparently caused regression of established fibrosis.⁷ Although the mechanism for regression is not clear, there may be an immunomodulatory function of mesenchymal stem cells operating to suppress inflammation and promote restoration of lung “modelling” rather than scarring with “remodelling”. A recent report indicates that haploidentical mesenchymal stem cells derived from bone marrow have immunosuppressive and healing properties in severe graft versus host disease refractory to prednisolone, infliximab and daclizumab.⁸ This inflammatory response directed at host tissues was abrogated and the integrity of the epithelial surfaces was restored. Although it may be expected that stem cells might home to the prepared field of inflammation in the lung, the response did not generate further tissue deposition. An additional important study indicates the possibility of harvesting mesenchymal stem cells from adult peripheral blood, making the feasibility of a therapeutic option more likely.⁹

The tissue remodelling seen in the asthmatic airway associated with myofibroblast and angiogenic activity is considered to be associated with abnormal T lymphocyte function. CD4 helper lymphocytes may be subject to Th1/Th2 subset imbalance and fibrogenic cytokine generation.¹⁰ Factors include excessive interleukin (IL)-4 and IL-13, with reduced interferon (IFN)- γ ,¹¹⁻¹³ all implicated in fibrogenesis. Direct evidence exists in lung biopsies from subjects with IPF.¹⁴ Potentially, manipulation of the cell-mediated immune response to reduce the Th2 cytokine effect may also carry an antifibrogenic effect.

Fibrogenic cytokines

Targeting fibrogenic factors may be a useful strategy in the treatment of IPF. Transforming growth factor (TGF)- β is a potent fibrogenic agent that has been implicated in the pathogenesis of IPF for some time.^{15,16} Receptors for TGF- β are present

on many relevant cell types and it may be produced by platelets, eosinophils, macrophages, fibroblasts and T cells.^{17–19} It has a number of actions that enhance fibrosis, including fibroblast chemotaxis, proliferation and stimulation of collagen synthesis. It also inhibits collagenase production, reducing breakdown and resorption of matrix components.^{18 20–22} TGF- β may exist in an inactive form which is activated after release. In addition to increased production in IPF, studies have shown the collateral effect of induction of expression of procollagen, fibronectin and TGF- β mRNA in associated macrophages.²³ Also, it is likely that the effect of TGF- β is dependent on Smad expression.²⁴ Mice lacking Smad3 (cytoplasmic transcription factor for the TGF- β type II receptor) are resistant to bleomycin-induced pulmonary fibrosis.²⁵ These mechanisms underscore the potent role of this factor in the fibrotic response. Antagonists to TGF- β_1 are likely to be useful in the therapeutic setting, and a clinical trial of monoclonal antibodies to TGF- β in fibrotic ocular disease is currently underway.²⁶ Induction of naturally occurring matrix components that can antagonise TGF- β , such as decorin, may also be therapeutically useful options.²⁷

Tumour necrosis factor (TNF) α is a pro-inflammatory cytokine with fibrogenic properties.^{28–30} It is produced mainly by monocytes and macrophages and is capable of stimulating collagen synthesis and fibroblast proliferation.^{29 31} It also acts indirectly by inducing TGF- β .³² In TNF α transgenic mice, animals develop a lymphocytic fibrosing alveolitis³³ and TNF α gene knockout mice are resistant to bleomycin-induced pulmonary fibrosis.³⁴ Also, strains more sensitive to bleomycin show more significant TNF α responses.³⁵ In addition to experimental studies, there is a large body of data linking TNF α to human IPF. Macrophages in bronchoalveolar lavage (BAL) fluid from patients with IPF produce more TNF α in supernatant fluid than controls,³⁶ TNF α is more highly expressed in affected areas of lung in fibrotic lung disease,³⁷ and there is early evidence that the use of the soluble TNF α receptor agent etanercept with prednisolone may improve lung function in biopsy-proven UIP. Use of this agent in rheumatoid arthritis and a range of other chronic inflammatory disorders provided significant benefits where corticosteroids have not proved to be useful. Recent evidence should be kept in mind, which indicates that oversupply of TNF α may actually suppress fibrosis.^{38 39}

The Th1 cytokine IFN γ -1b may be antifibrotic through suppression of Th2 fibrogenic functions. Evidence supports an effect suppressing growth and division of fibroblasts⁴⁰ as well as collagen synthesis.⁴¹ There has been speculation regarding the importance of interferons as antifibrotic agents in IPF since growth factors were identified as novel therapeutic options.⁴² An early trial addressed the role of IFN γ -1b over 12 months. This pilot study of 18 subjects with IPF unresponsive to corticosteroids found significant benefit in total lung capacity and arterial oxygen after 1 year of treatment.⁴³ Those on active treatment showed improvement, while those on placebo did not. A larger multi-centre study of 330 patients unresponsive to corticosteroids studied over 58 weeks showed no significant improvement in lung function or survival.⁴⁴ Of the actively treated subjects, 10% died before the end of the study compared with 17% in the placebo group. Pneumonia appeared to be more frequent in the actively treated group, and a subsequent report suggests that a pro-inflammatory state may follow the initiation of treatment in some subjects.⁴⁵ Although encouraging, cytokine therapies in inflammatory states must be assessed carefully, given the potential for a range of responses⁴⁶ that may further depend on receptor subtypes or polymorphisms.

Small molecule agents

The antifibrotic actions of the small molecule drug pirfenidone have been studied in pulmonary fibrosis, based on the ability of this agent to block TGF- β gene expression and stimulated collagen production in the rodent bleomycin model.^{47 48} The rodent models were able to show inhibition of fibrosis⁴⁹ using pirfenidone and clinical trials have since shown some value.⁵⁰ Well tolerated in this open study, this agent is currently under further investigation in rheumatological, hepatic, renal and cardiac diseases.

The prostanoid PGE₂ is produced through metabolism of arachidonic acid via the cyclooxygenase pathway, and specifically by cyclooxygenase-1. It is known to have a bronchodilatory action in asthma, opposing the cysteinyl leucotrienes. Produced by alveolar macrophages in sarcoidosis,⁵¹ an antifibrotic role has been confirmed with the finding of reduced levels in lung fibroblasts from patients with IPF,⁵² as well as enhancement of fibrosis in bleomycin-treated mice derived from cyclooxygenase-2 strains.⁵³ Interestingly, these animals had lost protection against the fibrotic effects of TGF- β . Cyclooxygenase-2 appears to provide some protective effect against some forms of fibrosis and its product PGE₂ may have an anti-inflammatory effect.⁵⁴ Treatments that raise cAMP levels and cyclooxygenase-2 activity may have some benefit in IPF.

The macrolide rapamycin has been known to act in an antifibrotic capacity for some time.⁵⁵ The mechanism of action may relate to direct inhibition of action of fibrogenic factors. Studies in the bleomycin model have been promising, substantially reducing accumulated lung collagen weight.⁵⁶ For use in clinical disease, some consideration may need to be given to the timing of treatment to achieve significant outcomes.⁵⁷

There is currently a range of agents that show significant promise in IPF. Future studies may be based on cell-cell interactions or more directly address factor-dependent fibrogenesis. The difficulty with appraising the evidence in this area is compounded by the need for a precise diagnosis and logistics of clinical trials involving limited numbers of eligible patients over relatively long periods.

LUNG TRANSPLANTATION

The standard therapy for idiopathic interstitial pneumonias (IIP) has generally been corticosteroids in combination with a cytotoxic agent (azathioprine or cyclophosphamide). It has been recognised that there are a number of histological forms of IIP, the most common (UIP) representing what has previously been referred to as IPF.^{2 58} It has been recently shown (confirming opinions) that standard therapy for UIP does not improve outcome.⁵⁹

Thus, lung transplantation is an attractive option in IPF. Interstitial lung disease has been an early target for early evolving techniques with 10 months survival in a single lung transplant (SLTx) recipient with interstitial lung disease (due to silicosis) reported in 1971.⁶⁰ With the Toronto Lung Transplant Group's first long-term survivor receiving SLTx for IPF in 1983,⁶¹ SLTx became the main indication for this procedure for almost a decade, heralding an exciting new era for management of this disease.

Few patients can receive lung transplantation due to extreme organ shortages. Many die on the waiting list^{62 63} and the results—while improving—are a long way short of an enduring solution to severe end-stage lung disease in most patients. New approaches to the treatment of IIP are keenly awaited.

Table 1 Indications for lung transplantation in interstitial lung disease reported to the ISHLT/UNOS Registry⁶⁴

Idiopathic pulmonary fibrosis (IPF)*	68%
Other forms of interstitial lung disease	32%
Sarcoidosis	10%
Pulmonary lymphangiomyomatosis	4%
Connective tissue diseases	2%
Histiocytosis X	1%
Other†	15%

Interstitial lung disease is the diagnosis in 25% of all lung transplantations.

*Recorded in the Registry as IPF, not as histological subtype. However, a large majority will be the usual interstitial pneumonia (UIP) form of idiopathic interstitial pneumonia.

†Not specified but including occupational lung diseases; chemotherapy/radiotherapy related; extrinsic allergic alveolitis.

Lung transplant procedures

Each year approximately 1400–1650 lung transplants are reported to the International Society for Heart and Lung Transplantation Registry,⁶⁴ 53% SLTx and 47% bilateral lung transplants (BLTx). Overall, chronic obstructive pulmonary disease (including α_1 -antitrypsin deficiency) is the commonest indication (48%) for lung transplantation, followed by interstitial lung disease (25%) and cystic fibrosis (18%). The SLTx procedure presently accounts for almost 70% of all lung transplants for interstitial lung disease. IPF represents 68% of the patients with interstitial lung disease who receive transplants, with sarcoidosis the next commonest indication (10%) and other interstitial lung diseases being uncommon transplant indications (table 1). It is interesting that few patients with connective tissue-related pulmonary fibrosis have received lung transplants despite some initial enthusiasm.⁶⁵ Highly selected patients with limited scleroderma and interstitial lung disease have had acceptable outcomes.^{65 66}

Generally, patients are considered for SLTx unless there is an indication otherwise. BLTx may be the preferred procedure if both lungs have persistent infection with fungi (especially *Aspergillus fumigatus*) or bacteria (particularly Gram negative bacilli, methicillin-resistant *Staphylococcus aureus* or atypical mycobacteria). Coexisting severe irreversible heart disease may require combined heart-lung transplantation as the only viable transplant option. Although pulmonary hypertension is almost invariably present in end-stage interstitial lung disease, it rarely mandates BLTx or heart-lung transplantation (HLTx) for this reason alone.

Indications for lung transplantation in interstitial lung disease

Generally, lung transplantation is indicated where there is a survival advantage compared with best available therapy, or with the specific aim to improve very poor quality of life.

The 1-year and 5-year survival rates following lung transplantation for IPF according to the 2004 ISHLT/UNOS

International Registry reporting experience over the last 12 years are 68% and 40%, respectively.⁶⁴ Generally, patients with a clinico-radiological or histological diagnosis of UIP will have a worse prognosis than this at initial referral to the transplant centre. Thus, although a trial of immunosuppression is not unreasonable in UIP, assessment for transplantation should not be delayed while trialling drug therapies. The rate of UIP is, however, variable and detailed assessment of clinical, radiological and physiological parameters will help estimate prognosis.⁶⁷ The rate of change over 6–12 months may give greater precision⁶⁸ and therefore be more helpful in the precise timing for listing.

Many patients with interstitial lung disease are in their seventh and eighth decades, often with a number of medical comorbidities, risk factors (such as ischaemic heart disease⁶⁹ or cancer⁷⁰) or major complications of therapy for interstitial lung disease (especially corticosteroids). Detailed evaluation in this group is therefore mandatory.

Patients with other forms of interstitial lung disease will generally be judged on more general criteria (table 2) as well as assessing the tempo of disease and the impact on quality of life.

Selection criteria

With the present shortage of organs for lung transplantation, selection criteria need to identify not only patients who might benefit but also those with a realistic chance of a prolonged high-quality survival. Organ allocation systems are not all alike. Broadly, organ allocation systems are based on time priority (“first come first served” systems) or systems that are based on clinical urgency (“sickest first”). International guidelines for patient selection and listing have been developed,⁷¹ but these have generally been adapted to suit local circumstances (table 3).

The criteria include general criteria that have been derived from other forms of solid organ transplantation. Historically, solid organ transplantation has been reserved for single organ failure where replacement of the organ will return the recipient to near-normal health status. Serious co-morbid conditions such as progressive neuromuscular disease, liver cirrhosis, active hepatitis, multisystem diseases, HIV infection or recent cancer would generally be regarded as absolute contraindications to transplantation.

Lung transplant-specific criteria additionally include factors such as previous thoracic surgery (especially pleurodesis), severe kyphoscoliosis and obesity that may substantially impact on the risks of a major thoracic operation. The criteria may be absolute (a single criterion would preclude transplantation) or relative (where the presence of multiple factors in combination may preclude transplantation).

The international guidelines set an upper age limit for BLTx at 60 years and SLTx at 65 years, but this is frequently debated.⁷² Co-morbidities are common in subjects aged >65 years, and careful screening is required for coronary artery disease and malignancy in these patients. Despite careful screening, the overall outcome is worse in older patients but transplantation may still improve their chances of survival.⁶⁴

The majority of patients with interstitial lung disease referred for lung transplant assessment have UIP. These patients are often at or above the age of 65 years and have other medical comorbidities, particularly as a result of prolonged treatment with systemic corticosteroids (obesity and osteoporosis). The mortality of lung transplantation in those with a body mass index (BMI) of >30 kg/m² was increased threefold in one small series.⁷³ The ISHLT/UNOS Registry was unable to detect an effect of obesity on 5-year survival, but those transplanted with

Table 2 Indications for listing for lung transplantation in patients with interstitial lung disease

Prognostic factor	Quality of life
VC <60% predicted	Severe dyspnoea
Kco <50% predicted	House-bound
Hypoxia	Oxygen-dependent
Hypercapnia	
Rapid deterioration	

VC, vital capacity; Kco, transfer coefficient.

Table 3 Contraindications to lung transplantation in patients with interstitial lung disease

Absolute	Relative
<i>General</i>	
Body weight <70% or >130% of ideal	Age >65 years
Moribund/bed-ridden	Mechanically ventilated
	Severe kyphoscoliosis
<i>Medical</i>	
Poor renal function (creatinine clearance <50 ml/min)	Osteoporosis
Infection with HIV	Poorly-controlled diabetes
Recent or active malignancy	High-dose corticosteroids (prednisolone >20 mg/day)
HBsAg positive	Colonisation with fungi or atypical mycobacteria
Hepatitis C with biopsy-proven liver disease	
Progressive non-pulmonary disease (eg, neuromuscular disease, liver cirrhosis)	
Pan-resistant organisms	
<i>Psychosocial</i>	
Substance addiction (alcohol, tobacco or narcotics)	Uncommitted/poor compliance
Uncontrolled psychosis	Poor psychosocial support
	Severe psychoaffective disorder

a BMI >30 kg/m² were rare.⁶⁴ Osteoporosis seems to accelerate after solid organ transplantation.^{74 75}

Assessment process

Approaches to assessment of patients for lung transplantation show considerable variation from programme to programme. The essential elements are: (1) an initial screening to identify absolute contraindications; (2) a detailed assessment including relevant investigation by an experienced multidisciplinary team; (3) a team discussion of the case and a final decision on suitability and timing of listing for transplantation. The key objectives are to identify not only whom and when to list for transplantation, but also what factors may impact on surgery and postoperative care.

Patients with IPF are often rapidly deteriorating at the time of referral, so assessment needs to be expedited.⁷⁶ Ideally, patients with UIP are referred at diagnosis. Transplant assessment and listing should not be delayed pending a trial of immunosuppression. Indeed, a prolonged and unsuccessful trial of corticosteroids may render the patient unsuitable for transplantation. The presence of pulmonary hypertension and the impact on right ventricular function need to be carefully assessed to determine the likelihood of needing cardiopulmonary bypass intraoperatively.⁷⁷ Generally, patients will require coronary angiography as the only reliable way of determining the presence and suitability for intervention of co-existing coronary artery disease.^{78 79} Evaluation of the lung and the gastrointestinal tract for malignancy is routinely performed. A high index of suspicion is needed if lesions are to be found among the abnormal lung parenchyma.

Waiting list issues

Regular review on the waiting list is required to detect complications that may impact on suitability for transplantation. The development of increasing breathlessness and hypoxia may reflect disease progression, but the differential diagnosis includes pneumonia and pulmonary embolism which appears prevalent in these patients.⁸⁰ Patients with IPF are often quite

heavily immunosuppressed, predisposing them to opportunistic pathogens including *Aspergillus*, *Pneumocystis carinii* (if not on prophylaxis) and cytomegalovirus.

Donor/recipient matching

Organ donors for lung transplantation are generally so-called “brain dead” donors where careful evaluation, according to established criteria, has determined that the brain has ceased to function and withdrawal of ventilatory support is indicated. Consent is then obtained from the senior next of kin and the appropriate institutional and legal authorities (such as the Coroner). Live donor transplantation, generally as two lobes from two donors, a lobe each into one hemithorax has been performed in some centres for IPF.⁸¹ This procedure was initially restricted to close relative “living-related” donors, but more recently has been extended to non-related donors. Most recently it has been appreciated that the lung is less susceptible to the effects of warm ischaemia than many other organ transplants,⁸² and successful utilisation of non-beating heart donors has now been reported.⁸³

Donor criteria for lung transplantation include general criteria and organ-specific criteria. The general criteria include: no serious systemic infections or risk factors in the donor (such as HIV, hepatitis B, or variant CJD) and no history of malignancy. Lung-specific criteria include: a clear chest radiograph, minimal airway secretions, no known history of respiratory disease, minimal smoking exposure (<20 pack-years) and acceptable gas exchange (typically defined as PaO₂ >300 mm Hg (>40 kPa) on 100% fractional inspired oxygen and 5 cm positive end expiratory pressure). Donor age has been steadily increasing, and most programmes will assess donors up to the age of 65 years. Heart-lung donor organs require additional cardiac evaluation, and potential live donors require detailed medical and psychosocial evaluation. Donor shortages have led to progressive re-evaluation of both the general and organ-specific criteria. The newly described marginal or extended indication donors,⁸⁴ where one or more of the organ-specific criteria are not met, have been used extensively by many programmes. This has resulted in more patients receiving a lung transplant without apparent adverse effects on recipient outcome.⁸⁴⁻⁸⁶

The main considerations in matching the donor to the recipient are compatibility of blood groups and size. A negative lymphocyte cross-match is highly desirable, although survival is reported in the presence of documented pre-sensitisation.⁸⁷ If possible, transplanting an organ from a cytomegalovirus (CMV)-positive donor into a CMV-naïve recipient should be avoided, although the availability of more effective antiviral therapy has substantially reduced the incidence of deaths due to acute CMV illness.^{88 89} Lung transplantation from a donor with past exposure to Epstein-Barr virus (EBV) into an EBV-naïve recipient results in a high risk of post-transplant lymphoproliferative disease. The low (<10%) rate of EBV-negative donors makes it impractical to wait for an EBV-negative donor in most instances.

Perioperative issues

Lung procurement and preservation are technically relatively simple, although the logistics are often complex. Working in cooperation with other organ procurement teams, the lungs and hila are dissected free with placement of catheters for infusion of cardioplegia and pneumoplegia solutions to enable extracorporeal transportation. A pulmonary vasodilator (such as epoprostanol) is often infused before cross-clamping. The

Table 4 Post-lung transplant immunosuppression

Maintenance	Induction/augmentation
Cyclosporin A or tacrolimus	IL-2 receptor antagonists Basiliximab/rituximab
Azathioprine or mycophenolate mofetil or cyclophosphamide or methotrexate	Antilymphocyte globulins OKT3/ATG
Prednisolone or prednisone	Methylprednisolone Total lymphoid irradiation (TLI)

circulation is arrested with cold cardioplegia, the aorta and vena cava are cross-clamped and cold pneumoplegia (typically 3–6 litres) is infused under pressure into the main pulmonary artery. Organs can then be dissected free, placed in transport solutions in sterile containers and stored at 4°C for transport. Ischaemic times of <6 h are regarded as desirable for lung transplantation,⁹⁰ although successful results may occur after much longer periods.⁹¹

Patients with IPF may have asymmetrical lung function as judged by perfusion lung scanning. Generally, the side with the lowest perfusion (and presumably lowest ventilatory function) is chosen for SLTx, although a previous thoracotomy site may affect decision-making if pleural adhesions are suspected. Intraoperative haemodynamic monitoring is required to determine if and when cardiopulmonary bypass is required. If BLTx is performed, the most affected side is generally done first and cardiopulmonary bypass is used as required. The anastomoses performed include pulmonary artery, left atrial and bronchial sites. These need to be carefully checked after the lung is reinflated in the chest as there may be reorientation of the lung as ventilation is resumed, potentially twisting and kinking the anastomoses.

Post-transplant care

ICU

Almost all patients will be sent intubated and ventilated from the operation suite to the intensive care ward. The key objectives of care are to minimise reperfusion pulmonary oedema (RPO); support the respiration and circulation; protect renal function; initiate immunosuppression; control pain; and prevent, detect and treat infections. As any particular management decision may be consistent with some objectives but run contrary to others, experience, judgement and due care are required.

Patients usually require a conventional approach to mechanical ventilation and may be extubated within 24–48 h. The development of RPO will delay extubation significantly. It is difficult to predict which patients will develop RPO, so patients are generally maintained slightly dry and inotropes are used to support their circulation. Severe RPO requires continued ventilatory support with positive end expiratory pressure. Occasionally a period of extracorporeal membrane oxygenation support is needed.

Optimal pain control is extremely important during attempted weaning and extubation. Both in SLTx, but particularly in BLTx, effective epidural analgesia for 5–7 days postoperatively aids early extubation and also aids deep breathing and coughing.

Postoperative pulmonary infections are frequent. Donor-acquired, hospital-acquired, community-acquired and recipient organisms all need to be considered in the diagnosis and treatment strategy. Opportunistic pathogens do not generally need to be considered for the first 4–6 weeks.

Immunosuppression

Although the ultimate objective of immunosuppression is to induce immunological tolerance, the relatively small donor/recipient populations in lung transplantation mean that a high degree of HLA mismatch is almost inevitable. A three-phase approach (induction, maintenance and augmentation) has therefore generally been used. There are very few randomised controlled trials in lung transplantation, so the approach to immunosuppression in lung transplantation has generally been adapted from other organ transplantation.

Induction is generally high-dose methylprednisolone with many programmes also using antilymphocyte preparations (OKT3, ATGAM) or monoclonal antibodies directed against the IL-2 receptor (basiliximab, rituximab). Calcineurin antagonists (cyclosporin A and tacrolimus) are the mainstay of maintenance immunosuppression with dosing according to drug levels. In addition, azathioprine and prednisolone have been used as part of a three-drug maintenance regimen. More recently, mycophenolate mofetil has been used in place of azathioprine. Drug toxicity is common with renal impairment, hypertension, seizures, tremors, hypercholesterolaemia, gastrointestinal upset as well as the plethora of corticosteroid-induced side effects frequently seen. Furthermore, immunosuppression leads to increased infection and cancer risks. Thus, careful monitoring and evaluation of the risk/benefits of the immunosuppression are vital to ongoing recipient wellbeing. Recently, rapamycin (and everolimus) have been used in lung transplantation to reduce calcineurin antagonist side effects with some success.⁹²

Episodes of acute rejection are generally assumed to be due to under-immunosuppression and will be treated with pulse methylprednisolone with augmentation of baseline therapy. Other approaches to augmenting immunosuppression are shown in table 4. Chronic rejection, generally presenting as the bronchiolitis obliterans syndrome, has been the subject of many reports claiming a response to augmentation of immunosuppression, but none has been confirmed in randomised controlled trials.^{93–98} This may be due partly to the effect of increased immunosuppression triggering recurrent infections.

Rehabilitation

Patients are often markedly deconditioned at the time of transplantation, despite pretransplant rehabilitation. The operation, drugs (especially corticosteroids and cyclosporin A), infections and immobilisation in the ICU significantly exacerbate this. Early mobilisation, even in the ICU, is normally undertaken to hasten the improvement in activity and quality of life after transplantation.

Infectious prophylaxis

As with most immunosuppressed patients, community-, recipient- and hospital-acquired organisms are most frequently responsible for post-transplant infections. Infections associated with cellular immune defects need to be the subject of a careful search. Common among these are herpes viruses (CMV, HSV, HZV, EBV), fungal (especially *Aspergillus*) and bacterial agents (especially *Mycobacterium tuberculosis* and atypical mycobacteria). The widespread use of suphamethoxazole/trimethoprim prophylaxis has led to *Pneumocystis carinii* seldom being seen. Prophylaxis for herpes viruses with ganciclovir/valganciclovir or valaciclovir as appropriate is extensively practised and has led to a marked reduction in CMV-related complications. Infection with *Aspergillus* is of great concern, with many programmes

Table 5 Outcome from lung transplantation for interstitial lung disease

	SLTx	BLTx
Spirometry	Mild to moderate restriction	Mild restriction
Tlco	Moderately reduced	Mildly reduced
Resting Sa _o ₂	Normal	Normal
Peak exercise Sa _o ₂	Mild desaturation	No desaturation
SMWT	Improved to 480–670 m	Improved to 600–700 m
Vo ₂ peak	41–58% predicted	40–59% predicted
QOL	Substantially improved	Substantially improved

SLTx, single lung transplantation; BLTx, bilateral lung transplantation; Tlco, carbon monoxide transfer factor; Sa_o₂, arterial oxygen saturation; SMWT, 6 min walking test; Vo₂peak, peak oxygen consumption; QOL, quality of life.

currently using nebulised amphotericin, oral itraconazole or voriconazole as part of prophylactic regimens.⁹⁹

Survival

The most recent ISHLT/UNOS registry report shows 1-year and 5-year survivals of 68% and 40%, respectively, following lung transplantation for IPF. This gives an odds ratio for 1-year mortality of 1.6 compared with the whole lung transplant recipient population. Patients with sarcoidosis have almost identical survival rates following lung transplantation. In contrast, patients with chronic obstructive pulmonary disease have 1-year and 5-year survival rates of 80% and 47%, respectively.

As expected, however, prognosis is improved in patients receiving lung transplantation for IPF, with a recent survival analysis showing a crossover point at 105 days (better future survival) and an equity point (better total survival) at 360 days after lung transplantation.¹⁰⁰ Further analysis of the data¹⁰¹ shows that patients with IPF have a higher early mortality and, even 1 year after surgery, they have a higher yearly mortality rate. Patients with chronic obstructive pulmonary disease also have a higher than normal yearly mortality after the first year, despite their excellent early survival. This may in part be explained by the higher recipient age, poorer physical condition, with the greater use of SLTx (perhaps resulting in more complications in the native lung) in both these groups. Furthermore, in IPF, once bronchiolitis obliterans develops, mortality appears to be high.¹⁰² An age of 65 years has an odds ratio for 1-year mortality of 1.75 and hospitalisation just prior to the time of lung transplantation of 1.33, these factors being highly relevant in patients with IPF.⁶⁴

Intuitively it would seem that BLTx should result in better survival owing to a greater reserve lung function and the absence of infectious complications in the native lung.¹⁰³ There has been only one report of a direct comparison of SLTx with BLTx for IPF in a single institution. This was not a randomised controlled trial but showed, if anything, better survival in SLTx recipients.¹⁰⁴ SLTx is a shorter and generally less technically demanding procedure, the lateral thoracotomy resulting in less postoperative pain and diaphragm dysfunction. There is some anecdotal evidence that prolonged immunosuppression may lead to some recovery of function in the native lung.¹⁰⁵

In the ISHLT/UNOS Registry¹⁰¹ the causes of early deaths (<30 days) include graft failure (30%), infection (24%), cardiovascular (12%), technical (8%) and all other causes combined (25%). Late deaths (>1 year) are attributed to bronchiolitis obliterans (30%), infection (20%), graft failure (15%), malignancy (7%) and all other causes combined (28%). Early survival has generally improved greatly in the last two

decades. Little impact on late deaths has been made with chronic rejection, generally presenting as progressive breathlessness and airflow obstruction (the bronchiolitis obliterans syndrome), remaining a major problem in long-term survivors of lung transplantation.

Lung function

SLTx recipients with IPF usually have a persistent mild restrictive ventilatory defect with mild to moderate reduction in transfer factor (table 5). BLTx recipients generally have very mild restriction with slightly reduced transfer factor.¹⁰⁶ A deterioration of 10% in forced expiratory volume in 1 s is very suggestive of a significant allograft-related complication and warrants further evaluation.¹⁰⁷

Exercise capacity

Before lung transplantation patients with IPF generally walk <400 m on oxygen in a 6-minute walk test (SMWT) with operative mortality increased if <300 m.¹⁰⁸ At 3–6 months after transplantation this has improved to a plateau of approximately 700 m.^{106 109} There appears to be no significant difference in SMWT distance achieved in SLTx compared with BLTx (table 5).

Incremental cardiopulmonary exercise testing shows a similar pattern in SLTx and BLTx recipients. Exercise is terminated prematurely at a low work rate and low peak oxygen consumption (typically 40–60% predicted maximum oxygen consumption).¹⁰⁶ Neither cardiac nor ventilatory limitation is seen, although a very early anaerobic threshold due to poor peripheral muscle oxygen utilisation is generally the limiting factor. Mild desaturation and some encroachment on ventilatory reserve are seen in otherwise well patients with IPF following SLTx but not BLTx.

Quality of life

Quality of life is often extremely poor in IPF before lung transplantation and substantially improves following recovery from surgery.¹¹⁰ The advent of lung transplantation has added hope and expectation to the lives of many suffering from terminal respiratory failure. Once lung transplantation has occurred, the improved quality of life experienced by recipients should be seen in addition to any life extension achieved.

SUMMARY

Our understanding of the mechanisms of fibrosis, together with a recognition of the differential roles of inflammation and remodelling, has led to a better understanding of treatment for the two processes. Suppression of inflammation alone in UIP with currently available agents will not significantly affect clinical outcomes. Investigation of promising new agents ranging from TGF- β antagonists to pirfenidone and stem cell therapies may provide potent novel steroid-independent treatments.

The outcome from IPF has been greatly improved with the advent of lung transplantation. Currently, greatly enhanced survival can be expected if co-morbidities, opportunistic infection and chronic rejection can be controlled. A great therapeutic challenge lies ahead to assess and accurately diagnose IPF, to explore new treatments where available and to then refer suitable candidates early in the course of their disease for lung transplant assessment.

Competing interests: None.

REFERENCES

- American Thoracic Society/European Respiratory Society.** Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 2000;**161**:646–64.
- American Thoracic Society/European Respiratory Society.** International multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002;**165**:277–304.
- Gauldie J.** Proinflammatory mechanisms are a minor component of the pathogenesis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2002;**165**:1205–6.
- Borzone G, Moreno R, Urrea R, et al.** Bleomycin-induced chronic lung damage does not resemble human idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2001;**163**:1648–53.
- Flaherty KR, Travis WD, Colby TV, et al.** Histopathologic variability in usual and nonspecific interstitial pneumonias. *Am J Respir Crit Care Med* 2001;**164**:1722–7.
- Kotton DN, Ma BY, Cardoso WW, et al.** Bone marrow-derived cells as progenitors of lung alveolar epithelium. *Development* 2001;**128**:5181–8.
- Ortiz LA, Gambelli F, McBride C, et al.** Mesenchymal stem cell engraftment in lung is enhanced in response to bleomycin exposure and ameliorates its fibrotic effects. *Proc Natl Acad Sci USA* 2003;**100**:8407–11.
- Le Blanc K, Rasmusson I, Sundberg B, et al.** Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. *Lancet* 2004;**363**:1439–41.
- Abuljadayel IS.** Induction of stem cell-like plasticity in mononuclear cells derived from unmobilised adult human peripheral blood. *Curr Med Res Opin* 2003;**19**:355–75.
- Bousquet J, Jeffery PK, Busse WW, et al.** Asthma. From bronchoconstriction to airways inflammation and remodeling. *Am J Respir Crit Care Med* 2000;**161**:1720–45.
- Tamai K, Ishikawa H, Mauviel A, et al.** Interferon-gamma coordinately upregulates matrix metalloproteinase (MMP)-1 and MMP-3, but not tissue inhibitor of metalloproteinases (TIMP), expression in cultured keratinocytes. *J Invest Dermatol* 1995;**104**:384–90.
- Gillery P, Fertin C, Nicolas JF, et al.** Interleukin-4 stimulates collagen gene expression in human fibroblast monolayer cultures. Potential role in fibrosis. *FEBS Lett* 1992;**302**:231–4.
- Belperio JA, Dy M, Burdick MD, et al.** Interaction of IL-13 and C10 in the pathogenesis of bleomycin-induced pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2002;**27**:419–27.
- Majumdar S, Li D, Ansari T, et al.** Different cytokine profiles in cryptogenic fibrosing alveolitis and fibrosing alveolitis associated with systemic sclerosis: a quantitative study of open lung biopsies. *Eur Respir J* 1999;**14**:251–7.
- Khalil N, Greenberg AH.** The role of TGF-beta in pulmonary fibrosis. *Ciba Found Symp* 1991;**157**:194–211.
- Khalil N, O'Connor RN, Flanders KC, et al.** TGF-beta 1, but not TGF-beta 2 or TGF-beta 3, is differentially present in epithelial cells of advanced pulmonary fibrosis: an immunohistochemical study. *Am J Respir Cell Mol Biol* 1996;**14**:131–8.
- Roberts AB, Sporn MB, Assoian RK, et al.** Transforming growth factor type beta: rapid induction of fibrosis and angiogenesis in vivo and stimulation of collagen formation in vitro. *Proc Natl Acad Sci USA* 1986;**83**:4167–71.
- Roberts AB, Sporn MB.** Transforming growth factor-betas. In: Sporn MB, Roberts AB, eds. *Handbook of experimental pharmacology*. Heidelberg: Springer-Verlag, 1990:419–72.
- Sporn MB, Roberts AB, Wakefield LM, et al.** Some recent advances in the chemistry and biology of transforming growth factor-beta. *J Cell Biol* 1987;**105**:1039–45.
- Coker RK, Laurent GJ, Shahzeidi S, et al.** Transforming growth factors-beta 1, -beta 2, and -beta 3 stimulate fibroblast procollagen production in vitro but are differentially expressed during bleomycin-induced lung fibrosis. *Am J Pathol* 1997;**150**:981–91.
- Overall CM, Wrana JL, Sodek J.** Independent regulation of collagenase, 72-kDa progelatinase, and metalloendoproteinase inhibitor expression in human fibroblasts by transforming growth factor-beta. *J Biol Chem* 1989;**264**:1860–9.
- Eickelberg O, Kohler E, Reichenberger F, et al.** Extracellular matrix deposition by primary human lung fibroblasts in response to TGF-beta1 and TGF-beta3. *Am J Physiol* 1999;**276**:L814–24.
- Broekelmann TJ, Limper AH, Colby TV, et al.** Transforming growth factor beta 1 is present at sites of extracellular matrix gene expression in human pulmonary fibrosis. *Proc Natl Acad Sci USA* 1991;**88**:6642–6.
- Venkatesan N, Pini L, Ludwig MS.** Changes in Smad expression and sub-cellular localization in bleomycin induced pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 2004;**287**:L1342–7.
- Bonniaud P, Kolb M, Galt T, et al.** Smad3 null mice develop airspace enlargement and are resistant to TGF-beta-mediated pulmonary fibrosis. *J Immunol* 2004;**173**:2099–108.
- Crystal RG, Bitterman PB, Mossman B, et al.** Future research directions in idiopathic pulmonary fibrosis: summary of a National Heart, Lung, and Blood Institute working group. *Am J Respir Crit Care Med* 2002;**166**:236–46.
- Zhao J, Sime PJ, Bringas P Jr, et al.** Adenovirus-mediated decorin gene transfer prevents TGF-beta-induced inhibition of lung morphogenesis. *Am J Physiol* 1999;**277**:L412–22.
- Sueoka N, Sueoka E, Miyazaki Y, et al.** Molecular pathogenesis of interstitial pneumonitis with TNF-alpha transgenic mice. *Cytokine* 1998;**10**:124–31.
- Viceek J, Palombella VJ, Henriksen-DeStefano D, et al.** Fibroblast growth enhancing activity of tumor necrosis factor and its relationship to other polypeptide growth factors. *J Exp Med* 1986;**163**:632–43.
- Ortiz LA, Lasky J, Hamilton RF Jr, et al.** Expression of TNF and the necessity of TNF receptors in bleomycin-induced lung injury in mice. *Exp Lung Res* 1998;**24**:721–43.
- Kohase M, May LT, Tamm I, et al.** A cytokine network in human diploid fibroblasts: interactions of beta-interferons, tumor necrosis factor, platelet-derived growth factor, and interleukin-1. *Mol Cell Biol* 1987;**7**:273–80.
- Scharffetter K, Heckmann M, Hatamochi A, et al.** Synergistic effect of tumor necrosis factor-alpha and interferon-gamma on collagen synthesis of human skin fibroblasts in vitro. *Exp Cell Res* 1989;**181**:409–19.
- Miyazaki Y, Araki K, Vesin C, et al.** Expression of a tumor necrosis factor-alpha transgene in murine lung causes lymphocytic and fibrosing alveolitis. A mouse model of progressive pulmonary fibrosis. *J Clin Invest* 1995;**96**:250–9.
- Piguet PF, Kaufman S, Barazzone C, et al.** Resistance of TNF/LT alpha double deficient mice to bleomycin-induced fibrosis. *Int J Exp Pathol* 1997;**78**:43–8.
- Cavarra E, Carraro F, Fineschi S, et al.** Early response to bleomycin is characterized by different cytokine and cytokine receptor profiles in the lungs of fibrosis-prone and fibrosis-resistant mice. *Am J Physiol Lung Cell Mol Physiol* 2004;**287**:L1186–92.
- Zhang Y, Lee TC, Guillemin B, et al.** Enhanced IL-1 beta and tumor necrosis factor-alpha release and messenger RNA expression in macrophages from idiopathic pulmonary fibrosis or after asbestos exposure. *J Immunol* 1993;**150**:4188–96.
- Pan LH, Ohtani H, Yamauchi K, et al.** Co-expression of TNF alpha and IL-1 beta in human acute pulmonary fibrotic diseases: an immunohistochemical analysis. *Pathol Int* 1996;**46**:91–9.
- Kuroki M, Noguchi Y, Shimono M, et al.** Repression of bleomycin-induced neuropathy by TNF. *J Immunol* 2003;**170**:567–74.
- Fujita M, Shannon JM, Morikawa O, et al.** Overexpression of tumor necrosis factor-alpha diminishes pulmonary fibrosis induced by bleomycin or transforming growth factor-beta. *Am J Respir Cell Mol Biol* 2003;**29**:669–76.
- Pfeffer LM, Murphy JS, Tamm I.** Interferon effects on the growth and division of human fibroblasts. *Exp Cell Res* 1979;**121**:111–20.
- Cornelissen AM, Von den Hoff JW, Maltha JC, et al.** Effects of interferons on proliferation and collagen synthesis of rat palatal wound fibroblasts. *Arch Oral Biol* 1999;**44**:541–7.
- Coker RK, Laurent GJ.** Pulmonary fibrosis: cytokines in the balance. *Eur Respir J* 1998;**11**:1218–21.
- Ziesche R, Hofbauer E, Wittmann K, et al.** A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis [see comments]. *N Engl J Med* 1999;**341**:1264–9.
- Raghu G, Brown KK, Bradford WZ, et al.** A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2004;**350**:125–33.
- Honore I, Nunes H, Groussard O, et al.** Acute respiratory failure after interferon-gamma therapy of end-stage pulmonary fibrosis [see comment]. *Am J Respir Crit Care Med* 2003;**167**:953–7.
- Strieter RM, Starko KM, Enelow RL, et al.** Effects of interferon-gamma 1b on biomarker expression in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2004;**170**:133–40.
- Iyer SN, Gurujeyalakshmi G, Giri SN.** Effects of pirfenidone on transforming growth factor-beta gene expression at the transcriptional level in bleomycin hamster model of lung fibrosis. *J Pharmacol Exp Ther* 1999;**291**:367–73.
- Iyer SN, Gurujeyalakshmi G, Giri SN.** Effects of pirfenidone on procollagen gene expression at the transcriptional level in bleomycin hamster model of lung fibrosis. *J Pharmacol Exp Ther* 1999;**289**:211–8.
- Schelegle ES, Mansoor JK, Giri S.** Pirfenidone attenuates bleomycin-induced changes in pulmonary functions in hamsters. *Proc Soc Exp Biol Med* 1997;**216**:392–7.
- Raghu G, Johnson WC, Lockhart D, et al.** Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label phase II study. *Am J Respir Crit Care Med* 1999;**159**:1061–9.
- Pruerger RJ, Schwartz DA, Dayton CS, et al.** The relationship between alveolar macrophage TNF, IL-1, and PGE2 release, alveolitis, and disease severity in sarcoidosis. *Chest* 1993;**103**:832–8.
- Wilborn J, Crofford LJ, Burdick MD, et al.** Cultured lung fibroblasts isolated from patients with idiopathic pulmonary fibrosis have a diminished capacity to synthesize prostaglandin E2 and to express cyclooxygenase-2. *J Clin Invest* 1995;**95**:1861–8.
- Keerthisingam CB, Jenkins RG, Harrison NK, et al.** Cyclooxygenase-2 deficiency results in a loss of the anti-proliferative response to transforming growth factor-beta in human fibrotic lung fibroblasts and promotes bleomycin-induced pulmonary fibrosis in mice. *Am J Pathol* 2001;**158**:1411–22.
- Bonner JC, Rice AB, Moomaw CR, et al.** Airway fibrosis in rats induced by vanadium pentoxide. *Am J Physiol Lung Cell Mol Physiol* 2000;**278**:L209–16.
- Salas-Prato M, Assalian A, Mehdi AZ, et al.** Inhibition by rapamycin of PDGF- and bFGF-induced human tenon fibroblast proliferation in vitro. *J Glaucoma* 1996;**5**:54–9.
- Simler NR, Howell DC, Marshall RP, et al.** The rapamycin analogue SDZ RAD attenuates bleomycin-induced pulmonary fibrosis in rats. *Eur Respir J* 2002;**19**:1124–7.
- Murphy GJ, Nicholson ML.** Rapamycin has no effect on fibrosis-associated gene expression or extracellular matrix accumulation when administered to animals with

- established or early allograft vasculopathy. *J Thorac Cardiovasc Surg* 2003;**126**:2058–64.
58. **Katzenstein AL**, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med* 1998;**157**:1301–15.
 59. **Collard HR**, Ryu JH, Douglas WW, *et al*. Combined corticosteroid and cyclophosphamide therapy does not alter survival in idiopathic pulmonary fibrosis. *Chest* 2004;**125**:2169–74.
 60. **Derom F**, Barbier F, Ringoir S, *et al*. Ten-month survival after lung homotransplantation in man. *J Thorac Cardiovasc Surg* 1971;**61**:835–46.
 61. **Toronto Lung Transplant Group**. Unilateral lung transplantation for pulmonary fibrosis. *N Engl J Med* 1986;**314**:1140–5.
 62. **Ouwens JP**, Groen H, TenVergert EM, *et al*. Simulated waiting list prioritization for equitable allocation of donor lungs. *J Heart Lung Transplant* 2002;**21**:797–803.
 63. **D'Armini AM**, Callegari G, Vitulo P, *et al*. Risk factors for early death in patients awaiting heart-lung or lung transplantation: experience at a single European center. *Transplantation* 1998;**66**:123–7.
 64. **Trulock EP**, Edwards LB, Taylor DO, *et al*. The Registry of the International Society for Heart and Lung Transplantation: 21st official adult heart transplant report: 2004. *J Heart Lung Transplant* 2004;**23**:804–15.
 65. **Levine SM**, Anzueto A, Peters JI, *et al*. Single lung transplantation in patients with systemic disease. *Chest* 1994;**105**:837–41.
 66. **Rosas V**, Conte JV, Yang SC, *et al*. Lung transplantation and systemic sclerosis. *Ann Transplant* 2000;**5**:38–43.
 67. **King TE Jr**, Toozee JA, Schwarz MI, *et al*. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med* 2001;**164**:1171–81.
 68. **Collard HR**, King TE. Treatment of idiopathic pulmonary fibrosis: the rise and fall of corticosteroids. *Am J Med* 2001;**110**:326–8.
 69. **Kizer JR**, Zisman DA, Blumenthal NP, *et al*. Association between pulmonary fibrosis and coronary artery disease. *Arch Intern Med* 2004;**164**:551–6.
 70. **Collins J**, Kazerooni EA, Lacomis J, *et al*. Bronchogenic carcinoma after lung transplantation: frequency, clinical characteristics, and imaging findings. *Radiology* 2002;**224**:131–8.
 71. **Maurer JR**, Frost AE, Estenne M, *et al*. International guidelines for the selection of lung transplant candidates. The International Society for Heart and Lung Transplantation, the American Thoracic Society, the American Society of Transplant Physicians, the European Respiratory Society. *Transplantation* 1998;**66**:951–6.
 72. **Snell GI**, De Hoyos A, Winton T, *et al*. Lung transplantation in patients over the age of 50. *Transplantation* 1993;**55**:562–6.
 73. **Kanasky WF Jr**, Anton SD, Rodrigue JR, *et al*. Impact of body weight on long-term survival after lung transplantation. *Chest* 2002;**121**:401–6.
 74. **Durieux S**, Mercadal L, Orsel P, *et al*. Bone mineral density and fracture prevalence in long-term kidney graft recipients. *Transplantation* 2002;**74**:496–500.
 75. **Patel S**, Kwan JT, McCloskey E, *et al*. Prevalence and causes of low bone density and fractures in kidney transplant patients. *J Bone Miner Res* 2001;**16**:1863–70.
 76. **Snell GI**, Walters EH, Kotsimpos TC, *et al*. Idiopathic pulmonary fibrosis: in need of focused and systematic management. *Med J Aust* 2001;**174**:137–40.
 77. **Homma A**, Anzueto A, Peters JI, *et al*. Pulmonary artery systolic pressures estimated by echocardiogram vs cardiac catheterization in patients awaiting lung transplantation [see comment]. *J Heart Lung Transplant* 2001;**20**:833–9.
 78. **Snell GI**, Richardson M, Griffiths AP, *et al*. Coronary artery disease in potential lung transplant recipients >50 years old: the role of coronary intervention. *Chest* 1999;**116**:874–9.
 79. **Lee R**, Meyers BF, Sundt TM, *et al*. Concomitant coronary artery revascularization to allow successful lung transplantation in selected patients with coronary artery disease. *J Thorac Cardiovasc Surg* 2002;**124**:1250–1.
 80. **Nathan SD**, Barnett SD, Urban BA, *et al*. Pulmonary embolism in idiopathic pulmonary fibrosis transplant recipients. *Chest* 2003;**123**:1758–63.
 81. **Starnes VA**, Barr ML, Schenkel FA, *et al*. Experience with living-donor lobar transplantation for indications other than cystic fibrosis. *J Thorac Cardiovasc Surg* 1997;**114**:917–21.
 82. **Steen S**, Liao Q, Wierup PN, *et al*. Transplantation of lungs from non-heart-beating donors after functional assessment ex vivo. *Ann Thorac Surg* 2003;**76**:244–52.
 83. **Steen S**, Sjöberg T, Pierre L, *et al*. Transplantation of lungs from a non-heart-beating donor. *Lancet* 2001;**357**:825–9.
 84. **Sundaresan S**, Semenkovich J, Ochoa L, *et al*. Successful outcome of lung transplantation is not compromised by the use of marginal donor lungs. *J Thorac Cardiovasc Surg* 1995;**109**:1075–80.
 85. **Gabbay E**, Williams TJ, Griffiths AP, *et al*. Maximizing the utilization of donor organs offered for lung transplantation. *Am J Respir Crit Care Med* 1999;**160**:265–71.
 86. **Bhorade SM**, Vigneswaran W, McCabe MA, *et al*. Liberalization of donor criteria may expand the donor pool without adverse consequence in lung transplantation. *J Heart Lung Transplant* 2000;**19**:1199–204.
 87. **Bittner HB**, Dunitz J, Hertz M, *et al*. Hyperacute rejection in single lung transplantation: case report of successful management by means of plasmapheresis and antithymocyte globulin treatment. *Transplantation* 2001;**71**:649–51.
 88. **Brumble LM**, Milstone AP, Loyd JE, *et al*. Prevention of cytomegalovirus infection and disease after lung transplantation: results using a unique regimen employing delayed ganciclovir. *Chest* 2002;**121**:407–14.
 89. **Palmer SM**, Grinnan DC, Diane Reams B, *et al*. Delay of CMV infection in high-risk CMV mismatch lung transplant recipients due to prophylaxis with oral ganciclovir. *Clin Transplant* 2004;**18**:179–85.
 90. **Snell GI**, Rabinov M, Griffiths A, *et al*. Pulmonary allograft ischemic time: an important predictor of survival after lung transplantation. *J Heart Lung Transplant* 1996;**15**:160–8.
 91. **Ueno T**, Snell GI, Williams TJ, *et al*. Impact of graft ischemic time on outcomes after bilateral sequential single-lung transplantation. *Ann Thorac Surg* 1999;**67**:1577–82.
 92. **Snell GI**, Levvey BJ, Chin W, *et al*. Sirolimus allows renal recovery in lung and heart transplant recipients with chronic renal impairment. *J Heart Lung Transplant* 2002;**21**:540–6.
 93. **Gerhardt SG**, McDyer JF, Girgis RE, *et al*. Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: results of a pilot study. *Am J Respir Crit Care Med* 2003;**168**:121–5.
 94. **Cairn J**, Yek T, Banner NR, *et al*. Time-related changes in pulmonary function after conversion to tacrolimus in bronchiolitis obliterans syndrome. *J Heart Lung Transplant* 2003;**22**:50–7.
 95. **Verleden GM**, Buyse B, Delcroix M, *et al*. Cyclophosphamide rescue therapy for chronic rejection after lung transplantation. *J Heart Lung Transplant* 1999;**18**:1139–42.
 96. **Diamond DA**, Michalski JM, Lynch JP, *et al*. Efficacy of total lymphoid irradiation for chronic allograft rejection following bilateral lung transplantation. *Int J Radiat Oncol Biol Phys* 1998;**41**:795–800.
 97. **Dusmet M**, Maurer J, Winton T, *et al*. Methotrexate can halt the progression of bronchiolitis obliterans syndrome in lung transplant recipients. *J Heart Lung Transplant* 1996;**15**:948–54.
 98. **Snell GI**, Esmore DS, Williams TJ. Cytolytic therapy for the bronchiolitis obliterans syndrome complicating lung transplantation. *Chest* 1996;**109**:874–8.
 99. **Calvo V**, Borro JM, Morales P, *et al*. Antifungal prophylaxis during the early postoperative period of lung transplantation. Valencia Lung Transplant Group. *Chest* 1999;**115**:1301–4.
 100. **Charman SC**, Sharples LD, McNeil KD, Wallwork J. Assessment of survival benefit after lung transplantation by patient diagnosis [see comment]. *J Heart Lung Transplant* 2002;**21**:226–32.
 101. **Trulock EP**, Edwards LB, Taylor DO, *et al*. The Registry of the International Society for Heart and Lung Transplantation: 20th official adult lung and heart-lung transplant report: 2003. *J Heart Lung Transplant* 2003;**22**:625–35.
 102. **Haider Y**, Yonan N, Mogulkoc N, *et al*. Bronchiolitis obliterans syndrome in single lung transplant recipients: patients with emphysema versus patients with idiopathic pulmonary fibrosis. *J Heart Lung Transplant* 2002;**21**:327–33.
 103. **Venuta F**, Boehler A, Rendina EA, *et al*. Complications in the native lung after single lung transplantation. *Eur J Cardio-Thorac Surg* 1999;**16**:54–8.
 104. **Meyers BF**, Lynch JP, Trulock EP, *et al*. Single versus bilateral lung transplantation for idiopathic pulmonary fibrosis: a ten-year institutional experience. *J Thorac Cardiovasc Surg* 2000;**120**:99–107.
 105. **Ouwens JP**, van den Berg JW, van der BW, *et al*. Long-term survival despite early loss of graft function after single lung transplantation for pulmonary fibrosis. *J Heart Lung Transplant* 2002;**21**:395–401.
 106. **Williams TJ**, Snell GI. Early and long-term functional outcomes in unilateral, bilateral, and living-related transplant recipients. *Clin Chest Med* 1997;**18**:245–57.
 107. **Martinez JA**, Paradis IL, Dauber JH, *et al*. Spirometry values in stable lung transplant recipients. *Am J Respir Crit Care Med* 1997;**155**:285–90.
 108. **Kadikar A**, Maurer J, Kesten S. The six-minute walk test: a guide to assessment for lung transplantation. *J Heart Lung Transplant* 1997;**16**:313–9.
 109. **Williams TJ**, Grossman RF, Maurer JR. Long-term functional follow-up of lung transplant recipients. *Clin Chest Med* 1990;**11**:347–58.
 110. **Stavem K**, Bjortuft O, Lund MB, *et al*. Health-related quality of life in lung transplant candidates and recipients. *Respiration* 2000;**67**:159–65.