Key points

- › Lung transplantation is an established therapeutic option for selected patients suffering from end-stage lung diseases, providing survival and quality of life benefits.
- › Shortage of donor organs and chronic graft rejection in the form of bronchiolitis obliterans are the two major drawbacks in lung transplantation.
- › When to refer to the lung transplant centre is at least as crucial as whom to refer, *e.g.* patients with idiopathic pulmonary fibrosis have a high mortality on the waiting list and, therefore, this group of patients should be referred early.
- › The period of time on the waiting list should be used for active risk management: continuous optimisation of nutrition, comorbidities (*e.g.* osteoporosis), psychosocial issues and general health behaviour is important, and can be achieved through close collaboration with the lung transplant programme.

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Lung transplantation: who, when?

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Educational aims

- ▶ To provide information about the selection of appropriate patients for lung transplantation.
- ▶ To outline recommendations for chest physicians concerning who to refer and when.
- ▶ To better understand short- and long-term results after the procedure, considering underlying disease, quality of life and survival.
- ▶ To present future trends in lung transplant medicine.

Summary

Since the first successful lung transplantation was performed in the early 1980s, this procedure has emerged as a mainstay of therapy for patients suffering from end-stage lung diseases. Due to a shortage of donor organs, time on the waiting list is increasing in most transplant programmes and, hence, the timing of referral and listing is crucial. This review discusses the different aspects that should be considered when advising potential lung transplant recipients. Particular focus is given to the appropriate time of referral, matters of medical care whilst on the waiting list, post-transplant prognosis and quality of life issues.

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Since the first successful lung transplantation was performed in Toronto (Canada) in the early 1980s, this procedure has emerged as a mainstay of therapy for patients suffering from end-stage lung diseases, and lung transplant programmes now exist in many countries. Internationally, >1,400 transplants are performed per year. Chronic allograft rejection causing bronchiolitis obliterans syndrome and a shortage of donor organs are the two major drawbacks in contemporary lung transplantation medicine. Whilst the former remains the dominant cause of morbidity and mortality (affecting up to 50% of long-term survivors after transplantation), the latter causes the loss of many candidates on the waiting list.

Therefore, accounting for both resource limitation and ethical aspects, the selection of patients who can potentially benefit from favourable long-term outcomes represents a fundamental issue in transplantation medicine. In addition to considering absolute and relative contraindications in patients with end-stage lung disorders, the timing of referral and listing of appropriate candidates is crucial. While the remaining lifespan should exceed the expected waiting time on the list, the patients should ideally benefit in terms of both life expectancy and quality of life after transplantation. Due to the amount of variables to be considered, this process is a matter of ongoing research. In particular, quality of

life, therapy compliance, age at transplantation, and transplantation in underprivileged economic environments are examples of aspects that undoubtedly need further attention.

Selection of patients

1. Indications and referral

Lung transplantation is indicated in selected patients with chronic end-stage lung disease who are receiving optimal medical therapy but nevertheless have declining lung function. Lung transplant candidates should have no alternative medical or surgical therapies available to them, and their disease is usually associated with a significantly diminished quality of life and a poor prognosis (table 1). Ideally, potential candidates will be suffering from single organ failure with no additional medical illness, a stable social background and no psychopathological conditions. However, treating physicians will sometimes be faced with one or more comorbidities that result in a complex disease pattern rather than simple organ dysfunction. It must be emphasised that the referral of potential candidates to the lung transplant centre should not be delayed due to treatment of such associated conditions. Although it depends on the individual patient, in the current authors' experience, a potential candidate is unable to obtain appropriate information and sufficiently adapt psychologically in a time period shorter than 6 months. Accordingly, the time span between referral and listing should be suitably calculated, which may provide an opportunity for therapies aimed at potential accompanying diseases (e.g. osteoporosis, nutritional issues, psychological impairments, chronic infections, diabetes mellitus, systemic hypertension). Since waiting time on the list varies substantially among different transplant centres, the optimal time schedule for

a particular patient in terms of educational measures, further diagnostic steps, additional therapeutic interventions and listing should be established by the local multidisciplinary transplantation team. Therefore, patients who are appropriately referred before the actual need for listing can be periodically seen by the transplant centre, whilst continuing care is provided by the referring physician. As an advanced step, the waiting period on the list can be actively used for risk factor management by an experienced transplant team.

Providing counselling to patients about the risks and benefits of the procedure is of vast importance, and patients are given a significant amount of information to absorb and assimilate. Age limits for lung transplant candidates have been extended over the past few years, as, although older patients have slightly worse survival than younger patients, there is no evidence that this group regains less quality of life after transplantation.

2. Contraindications

Conditions that are potentially associated with high complication rates in the peri- and/or post-transplant period and, hence, most probably do not result in overall benefit for the patient are summarised in table 2.

Irreversible significant dysfunction of another major organ system is generally regarded as a contraindication for lung transplantation. This includes severe liver diseases (bilirubin $>35\text{ }\mu\text{m}\cdot\text{L}^{-1}$, factor V $<50\%$), significant renal impairment (creatinine clearance $<50\text{ mL}\cdot\text{min}^{-1}$) or heart disease (left ventricular ejection fraction $<30\%$ and/or untreatable coronary artery disease), or progressive neurological disorders. However, the option of a simultaneous liver, renal or heart transplantation can be discussed in selected patients. Additionally, atherosclerosis is generally a contraindication for the procedure.

A diagnosis of malignancy within the last 2 years, with the exception of basal cell and squamous cell carcinoma of the skin, is a contraindication for transplantation. At least a 5-year disease-free interval is required for extracapsular renal cell carcinoma, breast cancer ($\geq$ stage II), colon cancer ($>$ Dukes A) and melanoma ($\geq$ level III Clark).

Since rigorous compliance with medical care and treatment plans has a vital impact on survival, unstable and incompletely treatable psychiatric or psychopathological conditions are contraindications for transplantation.

Table 1 General eligibility for lung transplantation

Disease related

- Chronic progressive end-stage lung disease
- Under optimal alternative therapy
- Substantially diminished quality of life
- Poor prognosis (expected mean survival $<2\text{--}3$ years)
- Expected survival >6 months

Host related

- Stable psychosocial background
- Free of substance addiction >6 months
- Aged $<65\text{--}(70)$ years
- Ability to absorb and assimilate complex information
- Lacking contraindication

Transplantation medicine is constantly developing and disease-specific experiences may vary between different programmes; therefore, many relative contraindications, such as nutritional issues, concomitant infectious diseases or anatomical abnormalities should be discussed on the basis of an individual patient with the local transplant centre.

3. Disease-specific considerations

The impact of the underlying disease on recommended referral practice, waiting list mortality, and the short- and long-term outcome is substantial. Table 3 indicates the functional findings when lung transplantation is indicated. However, it is important to stress that this decision should be based on the sum of findings and information rather than relying on a single parameter. Guidelines for the selection of lung transplant candidates were published in 1998 [1] and an update is now under way.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is by far the most common indication for lung transplantation. In many centres, this disease accounts for >50% of all procedures performed [2]. Patients with COPD have better survival rates while awaiting lung transplantation compared to patients with other primary lung diseases. Consequently, the survival benefit is small in COPD. Since estimation of the survival of COPD patients is difficult, the characteristics of patients who are most likely to experience a survival benefit from lung transplantation have not yet been defined. Recently, Celli *et al.* [3] defined and consecutively evaluated a simple multidimensional clinical grading system, consisting of forced expiratory volume in one second (FEV₁), distance walked in 6 minutes, modified Medical Research Council (MMRC) dyspnoea scale, and body mass index (summarised in the BODE index). The BODE index was shown to be superior at predicting the risk of death among COPD patients compared with the simple measurement of FEV₁. Compared with other diagnostic categories, COPD patients have a similar gain of quality of life after lung transplantation. Since the primary aim of lung transplantation in COPD is improvement of quality of life, the option of lung volume-reduction surgery should always be considered. Patients with a heterogeneous, predominantly upper lobe disease and a low exercise capacity are most likely to benefit from this procedure. Conversely, patients with an FEV₁

Table 2 Contraindications for lung transplantation

Significant dysfunction of other organ systems

Liver disease (bilirubin >35 $\mu\text{mol} \cdot \text{L}^{-1}$, factor V <50%)
Renal impairment (creatinine clearance <50 $\text{mL} \cdot \text{min}^{-1}$)
Heart disease (left ventricular ejection fraction <30%)
Untreatable coronary artery disease
Progressive neurological disorders

Diagnosis of malignancy within the last 2 years

Disease-free interval (<5 years) after:
Extracapsular renal cell carcinoma
Breast cancer ($\geq$ stage II)
Colon cancer (>Dukes A)
Melanoma ($\geq$ level III Clark)

Documented non-compliance

Incompletely treatable psychopathological conditions

<20% predicted and either a carbon monoxide diffusing capacity of the lungs (DL_{CO}) <20% or homogenous disease have a high risk for unfavourable short-term outcome and, therefore, are unsuitable candidates for this procedure [4]. Surgical lung volume reduction might be the only surgical treatment option for older patients, whereas this therapy can be considered as a "bridging procedure" prior to lung transplantation in suitable younger candidates.

Table 3 Indications for lung transplantation

COPD

FEV₁ <20–25% predicted
Resting hypoxia (P_{a,O_2} <7.3 kPa) and/or hypercapnia (P_{a,CO_2} >6.7 kPa)
Elevated pulmonary artery pressure
Exacerbations in increasing frequency and severity
BODE index 7–10

Idiopathic pulmonary fibrosis

Consider referral at time of diagnosis
Symptomatic patients
Pulse oximetry <89% during 6-minute walk test
Progressive disease under drug treatment

Pulmonary arterial hypertension

FEV₁ <30% predicted
Resting hypoxia (P_{a,O_2} <7.3 kPa) and/or hypercapnia (P_{a,CO_2} >6.7 kPa)
Increasing numbers of hospitalisations
Recurrent major haemoptysis
Wasting

Cystic fibrosis

Functional class NYHA III or IV
6-minute walk distance <350 m
Cardiac index <2 $\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$
Mean right atrial pressure >15 mmHg
Mean pulmonary artery pressure >55 mmHg

P_{a,O_2} : arterial oxygen tension; P_{a,CO_2} : arterial carbon dioxide tension; NYHA: New York Heart Association.

A lung transplant recipient successfully climbing Mount Kilimanjaro 6 years after lung transplantation

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) typically shows rapid progression, and treatment trials are largely ineffective. Historically, response rates to immunosuppressive therapies are as high as 30%. However, these data have originated from studies performed prior to the current case definition of IPF, and more recent data suggest an even worse response to therapy of 10% maximum [5]. IPF patients have the highest mortality on the transplant waiting list, highlighting that referral is often too late. Conversely, in IPF patients, lung transplantation provides not only an improvement in quality of life, but also a clear survival benefit. Given the high waiting list mortality and the fact that corticosteroid-related morbidities are frequent medical problems in this population, IPF patients should be referred earlier to the lung transplant centre. The current authors believe that referral of potential transplant candidates suffering from IPF should be considered at the time of diagnosis. Different parameters have been related to the prognosis of IPF, such as age, smoking status, serial changes in lung function parameters, high-resolution computed tomography fibrosis scores and responses to therapy trials, *etc.* In particular, recent data have shown that a $DL_{CO} < 39\%$ predicted [6], a decrease in pulse oximetry $< 89\%$ during the 6-minute walk test with the patient breathing room air [7] or a decrease of forced vital capacity (FVC) during 6 months of follow-up [8] indicate poor prognosis. However, it must be emphasised that patients who maintain their FVC within 10% of their baseline values are also at risk of dying from their disease and, hence, spirometry is not a suitable tool to prove stability of disease in IPF patients. Response to therapy

is another potential pitfall in the treatment of patients suffering from IPF. Due to its generally low success rate, the outcome of a therapy trial should not be awaited before referring a patient. In case of improvement during a therapy trial, the schedule of these patients can easily be adapted during the evaluation for transplantation.

Other diffuse parenchymal lung diseases

A number of systemic diseases, including collagen vascular diseases, sarcoidosis or post-chemotherapy conditions, are associated with lung fibrosis. The clinical course in these patients is highly variable and each patient should be considered on an individual basis. Since the rate of progression is usually slower in these patients compared with IPF, it is prudent to follow the previously mentioned criteria regarding lung transplantation in appropriate candidates.

Cystic fibrosis

Due to the multisystem nature of cystic fibrosis (CF), many different factors have been linked to the prognosis of this disease. Beside lung function parameters, other factors have been recognised as major determinants of survival and, therefore, different aspects have to be considered when selecting CF patients for transplantation. A multiple logistic regression model [9] has shown that, in addition to FEV₁, diabetes mellitus, female sex, body weight, number of exacerbations and infection with *Burkholderia cepacia* are relevant prognostic variables for 5-year survival. Examples of other factors associated with poor prognosis are resting hypercapnia, perfusion disparity on ventilation/perfusion scans, increased resting heart rate, higher mean pulmonary artery pressure and increased cardiac index. Taken together, prediction models are diverse and complex in CF and, although numerous studies have investigated this topic, selection of appropriate transplant candidates remains individual. Despite additional disease-specific non-pulmonary problems, compared with other lung transplant recipients, appropriately selected CF patients have a favourable long-term prognosis (table 4). This might be established in younger patients and from previous experience with complex therapeutic interventions in this group of patients. While severe liver disease is a contraindication for isolated lung transplantation, a combined lung–liver transplantation should be discussed in selected cases. Due to high peri-transplant mortality, overt sepsis is an absolute contraindication to

Table 4 *Kaplan–Meier survival by diagnosis during the period of January 1990–June 2002*

	PPH	CF	AATD	COPD	IPF
Subjects n	737	1923	1356	4955	2119
Year %					
1	64.8	78.6	74.7	79.9	67.5
3	54.4	63.0	60.0	62.4	51.6
5	45.2	52.9	50.2	46.8	40.0
10	20.3	34.1	26.0	18.2	17.5
Conditional $t_{1/2}$ %	8.2	8.4	7.5	5.9	6.2

AATD: α_1 -antitrypsin deficiency; conditional $t_{1/2}$: conditional half-life in years, i.e. the estimated time point at which 50% of the recipients who survive to at least 12 months have died. Adapted from [2].

transplantation. Furthermore, as with other diseases, incompletely evaluated and insufficiently informed patients are inappropriate transplant candidates. Unfortunately, in this group of patients, lung transplant physicians are frequently faced with otherwise suitable candidates who just present too late due to patient's delay. Neglecting the severity of their own disease occurs regularly in CF patients and it is a challenge for primary caregivers to recognise this problem and to advise their patients appropriately.

Pulmonary arterial hypertension

Patients suffering from pulmonary arterial hypertension (PAH) in its idiopathic form or associated with other diseases generally have a poor prognosis and, therefore, are potential transplant candidates. Recently, encouraging advances in medical therapy of idiopathic [10, 11] and, to a lesser extent, associated forms [12] have been reported. As a consequence of the increasing complexity of vasodilator therapy and the low incidence of this disease, PAH should be treated in specialised centres where experience with medical therapy and with its limits are available. Guidelines for the diagnosis and treatment of PAH have been published recently [13]. An intense collaboration between the PAH team and the transplant team is mandatory to provide optimal and contemporary care for patients suffering from PAH. Prior to the introduction of the new vasodilators, the indication for transplantation was based on the universally poor survival rate and, therefore, was relatively unproblematic. Now, in many patients, transplantation can be delayed or even avoided. Since response to medical therapy does not depend on the initial haemodynamics, in general, all patients suffering

from PAH should have a therapy trial. The response to therapy can be assessed after 3 months, and patients with no clinical improvement or even deterioration should be considered for transplantation. It is not known if optimal medical treatment consists of combination therapy and, if so, what the combination is. However, in view of the serious consequences of therapy failure, a combination therapy is often established despite of scarcity of data supporting this practice. Since pulmonary thromboendarterectomy is an advantageous therapy option, it is mandatory to rule out chronic thromboembolic pulmonary hypertension by appropriate methods in every patient with PAH.

Orphan lung diseases

A variety of rare lung diseases presenting in advanced stages are potentially amenable to lung transplantation. Sarcoidosis, lymphangioleiomyomatosis and histiocytosis X are examples of diseases that can be treated by lung transplantation in well-selected patients. Due to multi-system involvement, in most cases, additionally affected organs have an impact on the evaluation for possible lung transplantation and, therefore, each patient should be considered on an individual basis. Although further discussion of these rare indications for transplantation is beyond the scope of this review, it should be noted that patients with well-advanced forms of sarcoidosis being considered for transplantation have a high risk of dying while awaiting transplantation. Compared with IPF, sarcoidosis is regularly diagnosed many years earlier and, hence, this high mortality on the waiting list probably reflects late consideration and referral for transplantation.

Outcome

1. General

When considering lung transplantation in a particular patient, weighing up outcome with and without the procedure is crucial. Long-term survival rates of lung transplant recipients are lower than those observed in kidney, heart and liver recipients. Lung transplant recipients have a higher incidence of acute and chronic rejection and infection than recipients of other solid organs. Since the lung is in direct contact with the outside environment, infectious agents and pollution can easily enter into the graft. The impaired mucociliary clearance of transplanted lungs is an additional factor, which predisposes the organ to non-alloimmune injuries. Although chronic allograft rejection is thought to be mediated by alloimmunological mechanisms, non-alloimmunological inflammatory conditions caused by infection or aspiration might also be important pathogenetic factors. Finally, these inflammatory injuries result in obliteration of the small airways, causing a progressive airflow obstruction.

Survival rates from three eras are shown in figure 1, which also shows the current authors' results. There has been a significant improvement in the two more recent eras compared with the earliest period (1988–1992). Most advances were achieved within the 1st year after transplantation, mainly by the prevention of technical failures and early infections. However, after the 1st year, further improvements are scarce, which is, at least in part, the consequence of the

persistently high prevalence of bronchiolitis obliterans syndrome, the clinical correlate of chronic graft rejection. Transplantation of older and sicker patients is also currently increasing, which might be an additional explanation for the lack of better long-term outcome. Kaplan-Meier survival curves of the International Society of Heart and Lung Transplantation (ISHLT) Registry of >14,000 lung transplant recipients, divided according to age groups, show a 5-year survival of patients aged 18–34, 35–49, 50–64 and >65 years of 50, 51, 44 and 35%, respectively. Due to the association between comorbidity and increasing age, long-term survival in older lung transplant recipients is less favourable. A further cause for this observation might be that older recipients are more likely to get a single lung transplant, which *per se* has a worse prognosis.

Interestingly, as shown in figure 2, the relationship between recipient age and 5-year mortality is not linear. While the poorer prognosis of the older recipient can be explained in several ways, the elucidation of the incline of the curve in the younger age group is more challenging. CF, which is the most common indication for lung transplantation in this age group, does not *per se* have a worse prognosis than diseases that are more prevalent in the older age group; therefore, other mechanisms might be involved. In particular, as previously shown in renal graft recipients, the prevalence of non-compliance seems to be high in adolescent patients. In lung transplant medicine, data concerning therapy compliance in this age group are scarce and further research in this area is highly warranted.

..... Zurich 1998–2004 (n=112)
 Zurich 1992–2004 (n=172)
 ISHLT 1998–2002 (n=6417)
 ISHLT 1993–1997 (n=6140)
 ISHLT 1988–1992 (n=2166)

Figure 1

Actuarial survival by era for adult lung transplantations performed during the period January 1988–December 2004, according to the ISHLT Registry and the Lung Transplant Programme of the University of Zurich. Reprinted in part with permission from [14].

Figure 2

Age-related mortality with 5 years of transplant in a multivariate logistic regression model during January 1995–June 1998. Reprinted with permission from [2].

Along with survival, improving quality of life is a major aim of lung transplantation. Many transplant-related aspects disadvantageously impact on the posttransplant quality of life. Allograft dysfunction is associated with a significant decline in quality of life [15], due to recurrence of shortness of breath, increased risk of infection and the psychological stress that is related to an intensified therapeutic regimen. When considering the quality of life of long-term survivors, drug-related morbidity is of major importance [16]. Beside increased risk of infection and malignancy, the direct consequences of immunosuppression, typical side-effects of calcineurin inhibitors (*e.g.* renal dysfunction, neurotoxicity, hypertrichosis) and corticosteroids (weight gain, osteoporosis, diabetes mellitus) are frequent drawbacks. Nevertheless, significant and durable improvements of quality of life have been shown in both cross-sectional and longitudinal studies [16–18].

2. Impact of underlying disease

Lung transplantation is performed in a wide variety of disease states. As shown in table 4, the underlying disease has a significant impact on long-term survival. Patients with COPD have the best short-term survival, and, although only few data are available, compared with other disease categories, these patients seem not to have more transplantation-related morbidity or lower quality of life [19]. It is noteworthy that patients with α_1 -antitrypsin deficiency seem to be more susceptible to sepsis compared with other lung transplant recipients. This risk persists beyond the first 6 months after transplantation [20]. Lung transplant recipients suffering from CF have both a favourable short- and long-term survival; however, patients infected with *B. cepacia* seem to have a worse short- and long-term prognosis

[20, 21]. With regards to quality of life, CF patients enjoy similar benefits compared with other patient groups. In view of the amount of potential comorbidities (*e.g.* osteoporosis, diabetes mellitus, hepatic and intestinal manifestations, rhinosinusitis, infection with antibiotic resistant organisms), this is a remarkable finding that might be explained by the young age of these patients, their lifelong expertise with disease issues and their alertness with regard to infections.

Since the prognosis of patients with IPF is extremely poor in most cases, the survival benefit after lung transplantation is significant, although absolute survival time is less satisfying compared with other lung transplant recipients. The latter observation can be explained with the older age of this group, and the fact that these patients receive single lung transplantation more frequently might be an additional cause. After surviving the first few most critical months after transplantation, lung transplant recipients suffering from PAH benefit from an excellent long-term survival and, in some transplant programmes, these patients have the highest overall long-term survival.

The risk of disease recurrence in the allograft is a well-known event that seldom has clinical implications. Diseases that have been pathologically proven to recur in the allograft include: sarcoidosis, histiocytosis, lymphangioleiomyomatosis and pulmonary alveolar proteinosis. With increasing long-term survival, this phenomenon might receive more attention in the future.

Outlook

The more that lung transplantation becomes a standard procedure and resource allocation becomes an issue, the more the aspects of costs must be included into the decision-making

process of "who" and "when". Heterogeneity of patient groups, international differences in healthcare systems, lack of unbiased controls, continuously improving survival rates, lack of assessing indirect costs and different allocation systems are examples of confounding factors that make economic evaluations difficult. Fundamental problems, such as potential discrimination of elderly persons with reduced life expectancies, additionally complicate cost-utility analysis and have important ethical implications. Although a comprehensive discussion of this matter is far beyond the scope of this review, cost issues are worth mentioning.

With regards to the costs from screening of potential transplant candidates and other pre-transplant expenses, waiting list mortality is detrimental and, hence, optimal referral practice should be mandatory and cost-effective.

Despite high physiological and psychological rehabilitation after successful lung transplantation, only a minority of patients return to full- or part-time work up to several years after transplantation (figure 3). In the current authors' experience, many lung transplant recipients would like to recommence working, but struggle due to sequelae from long-lasting pre-transplant sickness, unwillingness of employers or lack of training in the case of adolescent patients. Obviously, not only from an economical point of view, but also in terms of self-esteem and quality of life, more attention should be given to this subject. Current and future employment issues

should be included in the routine assessment in lung transplant programmes.

Although still the leading cause of morbidity and mortality in long-term survivors, encouraging options for the treatment of patients suffering from bronchiolitis obliterans syndrome (BOS) have become available in recent times. Low-dose azithromycin was shown to stabilise or even improve lung function in lung transplant recipients with established BOS [22]. Although the mechanism of action of this drug in BOS is not completely understood, it is thought to be the result of anti-inflammatory properties rather than direct microbiological action. Most promising results were also reported after fundoplication in lung transplant recipients [23]. These results support the hypothesis that gastro-oesophageal reflux is an important non-alloimmune dependent mechanism leading to BOS, which, under ideal circumstances, may be partly or completely reversible.

The negative impact of BOS on quality of life and survival is well known. Even though data are still scarce, the economic consequences of chronic allograft rejection are considerable [24]. Measures to decrease the incidence of BOS are highly warranted also from an economic standpoint. Close collaboration between transplant teams and referral community, in terms of pre-transplant evaluation, time of referral and post-transplant follow-up strategy, is important to provide optimal benefit to both individual patients and healthcare resources.

Figure 3

Employment status on the 1-year, 3-year, 5-year and 7-year annual follow-ups. Since all follow-ups between April 1994 and June 2003 were included, the data for each follow-up year do not include the same patients. Reprinted with permission from [2].

Suggested further reading

Maurer JR, Frost AE, Estenne M, Higenbottam T, Glanville AR. 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. *J Heart Lung Transplant* 1998; 17: 703–709.

This multi-authored text, written by internationally renowned experts, describes general health guidelines and disease-specific criteria, which are generally felt to identify patients with end-stage lung disease who will probably benefit from lung transplantation. An update of this text is under way.

Trulock EP, Edwards LB, Taylor DO, Boucek MM, Keck BM, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: twenty-second official adult lung and heart-lung transplant report - 2005. *J Heart Lung Transplant* 2005; 24: 956–967.

The registry of the ISHLT is the world's most comprehensive record of heart and lung transplant activities. Data from every transplant centre in the USA and many other centres are summarised in this annually published paper. For further details, visit www.isHLT.org.

Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001; 153: 345–352.

The authors used information from the Cystic Fibrosis Foundation Patient Registry (CFFPR), which has collected longitudinal data on ~90% of CF patients diagnosed in the USA since 1986. They developed multivariate logistic regression models by using data on 5,820 patients randomly selected from 11,630 in the CFFPR in 1993. The model provides insights into the complex nature of CF and supplies a rigorous tool for clinical practice and research.

Rutherford RM, Fisher AJ, Hilton C, et al. Functional status and quality of life in patients surviving 10 years after lung transplantation. *Am J Transplant* 2005; 5: 1099–1104.

This paper provides single-centre experience with patients surviving 10 years after lung transplantation and discusses functional outcome and quality of life in this group of patients.

de Perrot M, Chaparro C, McRae K, et al. Twenty-year experience of lung transplantation at a single center: influence of recipient diagnosis on long-term survival. *J Thorac Cardiovasc Surg* 2004; 127: 1493–1501.

This study examines the long-term patient outcomes of 521 lung transplantations in a single centre between 1983 and 2003. The authors summarise the relevant procedures of their programme and provide comprehensive information concerning complications and survival.

Nathan SD. Lung transplantation: disease-specific considerations for referral. *Chest* 2005; 127: 1006–1016.

The author of this review summarises recent advances in the understanding of the various primary diseases, potential alternative therapies and the latest post-transplant statistics after lung transplantation.

Useful web links

International Society of Heart and Lung Transplantation
www.isHLT.org
 Eurotransplant International Foundation
www.eurotransplant.nl

Educational questions

1. Who benefits most from lung transplantation in terms of survival and quality of life?
2. Effective medical treatment of PAH became available in the last few years. Which patients should still be considered for lung transplantation?
3. Which disease is associated with the highest mortality on the lung transplant waiting list?
4. Which diseases recur in the transplanted lung and what are the clinical consequences?
5. What are the functional consequences of chronic allograft rejection?

References

1. Maurer JR, Frost AE, Estenne M, Higenbottam T, Glanville AR. 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*. *J Heart Lung Transplant* 1998; 17: 703–709.
2. Trulock EP, Edwards LB, Taylor DO, Boucek MM, Keck BM, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: twenty-second official adult lung and heart-lung transplant report - 2005. *J Heart Lung Transplant* 2005; 24: 956–967.
3. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005–1012.
4. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; 348: 2059–2073.
5. Nicholson AG, Colby TV, du Bois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 2000; 162: 2213–2217.
6. Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. *Am J Respir Crit Care Med* 2003; 168: 531–537.
7. Lama VN, Flaherty KR, Toews GB, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; 168: 1084–1090.
8. Flaherty KR, Mumford JA, Murray S, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; 168: 543–548.
9. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001; 153: 345–352.
10. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; 106: 1477–1482.
11. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; 347: 322–329.
12. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000; 132: 425–434.
13. Galie N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. *The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology*. *Eur Heart J* 2004; 25: 2243–2278.
14. Trulock EP, Edwards LB, Taylor DO, Boucek MM, Keck BM, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: twenty-first official adult lung and heart-lung transplant report - 2004. *J Heart Lung Transplant* 2004; 23: 804–815.
15. van Den Berg JW, Geertsma A, van Der Bij W, et al. Bronchiolitis obliterans syndrome after lung transplantation and health-related quality of life. *Am J Respir Crit Care Med* 2000; 161: 1937–1941.
16. Rodrigue JR, Baz MA, Kanasky WF Jr, Macnaughton KL. Does lung transplantation improve health-related quality of life? The University of Florida experience. *J Heart Lung Transplant* 2005; 24: 755–763.
17. Gross CR, Savik K, Bolman RM 3rd, Hertz MI. Long-term health status and quality of life outcomes of lung transplant recipients. *Chest* 1995; 108: 1587–1593.
18. Rutherford RM, Fisher AJ, Hilton C, et al. Functional status and quality of life in patients surviving 10 years after lung transplantation. *Am J Transplant* 2005; 5: 1099–1104.
19. TenVergert EM, Vermeulen KM, Geertsma A, et al. Quality of life before and after lung transplantation in patients with emphysema versus other indications. *Psychol Rep* 2001; 89: 707–717.
20. de Perrot M, Chaparro C, McRae K, et al. Twenty-year experience of lung transplantation at a single center: influence of recipient diagnosis on long-term survival. *J Thorac Cardiovasc Surg* 2004; 127: 1493–1501.
21. Liou TG, Adler FR, Huang D. Use of lung transplantation survival models to refine patient selection in cystic fibrosis. *Am J Respir Crit Care Med* 2005; 171: 1053–1059.
22. Yates B, Murphy DM, Forrest IA, et al. Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med* 2005; 172: 772–775.
23. Davis RD Jr, Lau CL, Eubanks S, et al. Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. *J Thorac Cardiovasc Surg* 2003; 125: 533–542.
24. van Den Berg JW, van Enkevort PJ, TenVergert EM, Postma DS, van der Bij W, Koeter GH. Bronchiolitis obliterans syndrome and additional costs of lung transplantation. *Chest* 2000; 118: 1648–1652.

Suggested answers

1. Patients with end-stage lung disease due to idiopathic lung fibrosis, PAH and CF have a poor spontaneous survival and, therefore, gain survival benefits from lung transplantation. Conflicting data exist as to whether patients with emphysema gain survival benefit after lung transplantation. In terms of quality of life, the benefit is substantial and independent of underlying disease.
2. Since response to medical therapy does not depend on the initial haemodynamics, in general, all patients suffering from PAH should have a therapy trial. The response to therapy can be assessed after 3 months, and patients with no clinical improvement or even deterioration should be considered for transplantation. In any case, it is mandatory to rule out chronic thromboembolic pulmonary hypertension, since pulmonary thromboendarterectomy is an advantageous therapeutic option.
3. IPF typically shows that rapid progression and medical treatment trials are largely ineffective. Referral for evaluation for lung transplantation should be considered at the time of diagnosis.
4. Sarcoidosis, histiocytosis, lymphangioleiomyomatosis and pulmonary alveolar proteinosis are diseases that have been pathologically proven to recur in the allograft. Disease recurrence is rarely of clinical significance after lung transplantation.
5. BOS, the clinical correlate of chronic allograft rejection, is characterised by progressive airflow obstruction due to small airway destruction. Additionally, these patients are extremely prone to infectious complications.