# Essentials in Lung Transplantation

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*Editor*

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*This work is dedicated to our patients, their carers and our colleagues who, by working together, honour the greatest gift, organ donation, and thereby sustain life and hope.*

# Preface

This work presents a comprehensive summary of the basic tenets of lung transplantation with an update on recent developments in the field. The emphasis is to provide an approachable and easily digested product that relies heavily on teaching through visual images. Each of the authors is an Australian and many are recognised experts in the area. Lung transplantation is now a core activity in each state of Australia with almost 3000 transplants performed throughout Australia. With the growth of donor resources which have doubled over the last 10 years, patients with life-threatening advanced lung diseases can look forward with some security to improvements in survival and quality of life. This work examines the operational principles which underpin that success and show how an evidenced-based approach combined with wisdom born of experience leads to better outcomes in day-to-day management.

Unlike other books in the field, this work focuses on simplicity and elegance of style with ample visual images to demonstrate the core messages. Importantly this work provides a unique Australian viewpoint and discusses the relevance of international trends and strategies in the context of the local environment.

Sydney, NSW, Australia — Allan R. Glanville

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# Chapter 1
# Who and When to Transplant: What Has Changed?

**Isuru N. S. Seneviratne and Peter Hopkins**

## 1.1 Introduction

Lung transplantation needs to be considered for all patients with advanced lung disease whose clinical condition continues to deteriorate despite maximal medical or surgical therapy [1].

It is generally accepted that referral for lung transplantation should typically occur early in patients who have a lung disease that is amenable to transplantation. Such patients will have an impaired ability to perform activities of daily living and a reduced life expectancy over the next 2 years. It is important to note that referral to a transplant centre may not mean that the patient will necessarily be listed for transplant. Early referral may however, allow identification and management of modifiable risk factors to facilitate progression to lung transplantation. For example, a patient with class I obesity or a patient with physical deconditioning could be supported to optimise weight loss or enrol in pulmonary rehabilitation respectively, to improve their functional status before listing for transplantation.

Following lung transplant evaluation, a mutual decision in favour for transplantation needs to occur between the patient, patient's family and transplant specialists before a patient is placed on the transplant list.

Chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF) are the three most common indications for transplant [2] and account for approximately 80% of all procedures performed worldwide (Fig. 1.1) [3].

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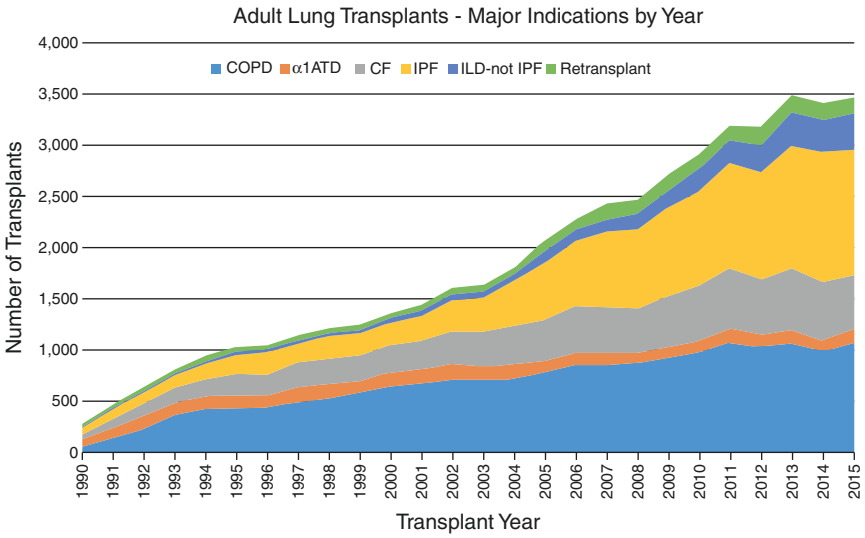


**Fig. 1.1** Adult lung transplants—major indications by year

## 1.2 General Inclusion and Exclusion Criteria for Lung Transplantation

General criteria for recipient selection have been developed by the International Society for Heart and Lung Transplantation (ISHLT) [1] and include:

1. A risk of death from lung disease within 2 years if lung transplantation is not performed in excess of 50%
2. A high (>80%) likelihood of surviving at least 90 days after lung transplantation
3. A high (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function

In addition to these General criteria, disease specific criteria also exist to better stratify/quantify patients' disease burden and the need for lung transplantation (see Sect. 1.4 and Table 1.1).

International consensus guidelines [1] for absolute and relative exclusion criteria for lung transplantation are detailed in Table 1.2. It is important to recognise that these criteria serve only as a guideline. As clinical experience grows with lung transplantation and with the development of new treatments and improvements in existing therapeutic techniques (for lung transplantation and overall general health and disease management) these criteria as continuously being tested and new boundaries are being established. Examples of this include the approach to pre-transplant malignancy, in an era where we are seeing more people being cured of their malignancy with very little long term complications from the cancer or treatment undertaken; an age value as a contraindication to proceeding with

**Table 1.1** Quick reference guide of specific clinical condition criteria for transplant

| |
|---|
| • *COPD* that is progressive despite smoking cessation, optimization of medications, pulmonary rehabilitation, and supplemental oxygen, a BODE index [4] of 5–6; $PaCO_2$ >50 mmHg (6.6 kPa) and/or $PaO_2$ < 60 mmHg (8 kPa), or $FEV_1$ <25% of predicted |
| • At the time of a confident radiographic diagnosis of *idiopathic pulmonary fibrosis* (IPF) or a histologic diagnosis of IPF or *fibrosing nonspecific interstitial pneumonia* (NSIP), regardless of lung function |
| • *Interstitial lung disease* (ILD) associated with rheumatic disease, sarcoidosis, or pulmonary Langerhans cell histiocytosis and New York Heart Association (NYHA) functional class III or IV (ie, symptoms with minimal exertion or severe limitation with symptoms at rest) or rapidly progressive respiratory impairment |
| • *ILD* with forced vital capacity (FVC) <80% predicted, a diffusion capacity for carbon monoxide (DLCO) <40% predicted, or the requirement for supplemental oxygen, at rest or with exertion |
| • *Pulmonary vascular disease* and NYHA functional class III or IV; during escalation of therapy e.g. incorporation of intravenous prostaglandin therapy |
| • Patients with *pulmonary veno-occlusive disease* (PVOD) or *pulmonary capillary hemangiomatosis* should be evaluated at the time of diagnosis |
| • *Cystic fibrosis* patients with an $FEV_1$ <30% of predicted, a six-minute walk distance <400 m, development of pulmonary hypertension, and/or life-threatening haemoptysis despite bronchial embolization |

**Table 1.2** Absolute and relative exclusion criteria for lung transplantation

| *Absolute exclusion criteria* |
|---|
| 1. Recent history of malignancy: A minimum of 2-years (ideally 5-years) disease-free interval combined with a low predicted risk of recurrence after lung transplantation (please see special considerations for lung transplantation) |
| 2. Untreatable significant dysfunction of another major organ system (e.g., heart, liver, kidney, or brain) unless combined organ transplantation is considered |
| 3. Uncorrected atherosclerotic disease with suspected or confirmed end-organ ischemia or dysfunction and/or coronary artery disease not amenable to revascularisation |
| 4. Acute medical instability, including, but not limited to, acute sepsis, myocardial infarction, and liver failure |
| 5. A bleeding diathesis that cannot be corrected |
| 6. Chronic infection with highly virulent and/or resistant microbes that are poorly controlled pre-transplant |
| 7. Evidence of active Mycobacterium tuberculosis infection |
| 8. Significant chest wall or spinal deformity expected to cause severe restriction after transplantation |
| 9. Class II or III obesity (body mass index [BMI] ≥35.0 $kg/m^2$) |
| 10. Current non-adherence to medical therapy or a history of repeated or prolonged episodes of non-adherence to medical therapy that are perceived to increase the risk of non-adherence after transplantation |
| 11. Psychiatric or psychologic conditions associated with the inability to cooperate with the medical/allied health care team and/or adhere with complex medical therapy |
| 12. Absence of an adequate or reliable social support system |

(continued)

**Table 1.2** (continued)

| |
|---|
| 13. Severely limited functional status with poor rehabilitation potential. |
| 14. Substance abuse or dependence (e.g., alcohol, tobacco, marijuana, or other illicit substances). Convincing evidence of risk reduction behaviours (e.g. active long-term participation in therapy for substance abuse and/or dependence) should be required before offering lung transplantation. Ongoing abstinence should be verified with serial blood and urine testing of substances that are of concern |
| *Relative exclusion criteria* |
| 1. Age >65 years in association with low physiologic reserve and/or other relative contraindications (please see special consideration for lung transplant) |
| 2. Class I obesity (BMI 30.0–34.9 kg/m$^2$), particularly truncal (central) obesity |
| 3. Progressive or severe malnutrition |
| 4. Severe, symptomatic osteoporosis |
| 5. Extensive prior chest surgery with lung resection |
| 6. Mechanical ventilation and/or extracorporeal life support (ECLS). However, carefully selected candidates without other acute or chronic organ dysfunction may be successfully transplanted |
| 7. Colonization or infection with highly resistant or highly virulent bacteria, fungi, and certain strains of mycobacteria (e.g., chronic extrapulmonary infection expected to worsen after transplantation) |
| 8. For patients infected with hepatitis B and/or C, a lung transplant can be considered in patients without significant clinical, radiologic, or biochemical signs of cirrhosis or portal hypertension and who are stable on appropriate therapy. Lung transplantation in candidates with hepatitis B and/or C should be performed in centres with experienced hepatology units |
| 9. For patients infected with human immunodeficiency virus (HIV), a lung transplant can be considered in those with controlled disease with undetectable HIV-RNA, and compliant on combined anti-retroviral therapy. Lung transplantation in HIV-positive candidates should be performed in centres with expertise in the care of HIV-positive patients |
| 10. Infection with Burkholderia cenocepacia, Burkholderia gladioli, and multi-drug resistant Mycobacterium abscesses. For patients with these infections to be considered suitable transplant candidates, the patients should be evaluated by centres with significant experience managing these infections in the transplant setting, and patients should be aware of the increased risk of transplant because of these infections |
| 11. Atherosclerotic disease burden sufficient to put the candidate at risk for end-organ disease after lung transplantation. With regard to coronary artery disease, some patients will be candidates for percutaneous coronary intervention or coronary artery bypass graft (CABG) preoperatively or, in some instances, combined lung transplant and CABG |
| 12. Other medical conditions that have not resulted in end-stage organ damage, such as diabetes mellitus, systemic hypertension, epilepsy, central venous obstruction, peptic ulcer disease, or gastroesophageal reflux, should be optimally treated before transplantation |
| 13. Extensive prior thoracic surgery with lung resection |

Adapted from Weill D et al. A consensus document for the selection of lung transplant candidates [1]

transplant in a generation where people are living longer and remaining healthier for a longer period.

Because of this changing dynamic of health and medicine, it is important that all patients that meet inclusion criteria for lung transplantation be referred for transplantation discussion and/or evaluation to allow a detailed review of possible contraindications and to assess the actual impact these will have on achieving a favourable outcome following lung transplantation.

## 1.3 Special Considerations for Lung Transplantation

### *1.3.1 Nutritional Status*

It is now well established that nutritional status can adversely affect post-transplant survival. Given this the ISHLT consensus guidelines state that class I obesity (BMI 30–34.9 kg per $m^2$) is a relative contraindication for lung transplantation, while class II or III obesity (BMI ≥35 kg per $m^2$) is an absolute contraindication [1].

In addition to obesity, there is strong data surrounding poor post-transplant outcomes, in particular primary graft dysfunction, in malnourished candidates [2, 5]. This appears to be especially the case in those individuals with COPD and CF [4, 6, 7]. As such, it is now clear that these individuals should be as vigorously evaluated as those individuals with an elevated BMI and aggressive attempts to improve the nutritional status prior to lung transplant are warranted.

### *1.3.2 Frailty and Sarcopaenia*

Frailty and sarcopaenia are characterised by loss of physiologic and cognitive reserves that predispose to adverse outcomes from acute stressors [8]. Though frailty correlates with increasing age, it is not an inevitable consequence of ageing. It is important to note that frailty is a dynamic condition, and is potentially reversible.

Two major frailty models have been described—the frailty phenotype and the frailty index [8]:

1. The frailty phenotype defines frailty as a distinct clinical syndrome meeting three or more of five phenotypic criteria: weakness, slowness, low level of physical activity, self-reported exhaustion, and unintentional weight loss (see Table 1.3).
2. The frailty index defines frailty as cumulative deficits identified in a comprehensive geriatric assessment.

**Table 1.3** Frailty phenotype [9]

| *Criteria* |
|---|
| 1. Decreased grip strength |
| 2. Self-reported exhaustion |
| 3. Unintentional weight loss of more than 4.5 kg over the past year |
| 4. Slow walking speed |
| 5. Low physical activity |
| *Definition* |
| – Positive for frail phenotype: ≥3 criteria present |
| – Intermediate/pre-frail: one or two criteria present |
| – Non-frail: no criteria present |

Data shows that approximately one third of lung transplant candidates are frail [10] and a large proportion of these individuals are over the age of 50 years [11]. Recent data has shown that pre-transplant frailty was independently associated with decreased survival after lung transplantation [12]. This result builds on the information of previously published data, which has shown a clear link between 6-min walk distance (which assesses aspects of the frailty phenotype) and lung transplant outcomes [13, 14]. Frailty assessment should therefore be an integral part of transplant assessment, not just to improve post-transplant outcomes but also because it may represent an important area for intervention to improve candidate selection and lung transplant outcomes.

### *1.3.3 Malignancy*

Until recently, malignancy within the prior 5 years has been considered a contraindication for transplantation given the potential for immunosuppressive agents to accelerate malignant potential. Advances in cancer therapeutics have enabled many patients to achieve complete cure of their underlying malignancy and then progress onto the need for lung transplantation for their underlying lung disease. This waiting period of 5 years has the potential to impact adversely on patient outcomes as they wait for this period to lapse prior to formal listing for lung transplantation. It is clear that the disease-free pre-transplant interval has the largest effect on mortality and post-transplant recurrence [15]. However additional factors including cancer type (e.g. haematological malignancy versus prostate cancer [whereby pre-transplant haematological malignancy has the worst prognosis post transplantation [15, 16]]), histological subtype and tumour size are important considerations in the risk stratification process with regard to disease-free survival post-transplant. The changing oncological landscape has challenged the dogma of considering cancer-survivors for transplant and now an individualised approach that includes shared-decision making with oncologists is needed to determine the actual risk of recurrence within the context of the post-transplant risk factors.

With vastly expanding oncological treatment modalities, comes the increase in treatment-related lung injury. This lung injury maybe severe enough to necessitate the need for lung transplantation and examples include bleomycin-induced lung fibrosis and more recently obliterative bronchiolitis following stem cell transplant for haematological malignancy. These cases add an increased degree of complexity to the malignancy scenario due to the potential multi-system complications of the inciting treatment and adverse effects of the medical treatments utilised to manage the initial adverse event (e.g. steroids for pneumonitis with the seqela of osteoporosis, diabetes, etc.). The ever-increasing cohort of case reports and case series demonstrates that these patients can be successfully transplanted with good outcomes but require meticulous management and discussion in the per-transplant and post-transplant phases through a mutli-specialty, multi-disciplinary approach.

### 1.3.4 Mechanical Bridge to Transplantation Including Extracorporeal Life Support (ECLS)

The use of strategies to support an acutely decompensated patient until a suitable organ becomes available has increased in recent years. With advancements in technology and clinical expertise with these mechanical strategies, we are now seeing improved outcomes for these patients.

Of these strategies mechanical ventilation is still the most common bridge used [1] but there is increased interest in the use of ECLS as a bridge to transplant. Both of these strategies require patients to be bed-bound and often sedated. This reduces their ability to participate actively in physiotherapy and can lead to severe deconditioning and may compromise their suitability for transplantation. It is generally accepted that post-transplant mortality increases proportionately to time mechanical support is required and caution should be exercised in transplanting candidates who have prolonged need for mechanical support. Thus, there is always a dilemma with regards to timing of transplantation between ensuring clinical stability following the initial insult and preventing the deleterious effects of prolonged mechanical support.

In an ideal situation patients that a bridged to transplant with mechanical support would have undergone a comprehensive transplant assessment and all medical and psychosocial risk factors identified before bridge therapy is initiated. However, the reality is that of an unexpected and abrupt deterioration compelling the need for mechanical support. Knowing this it is important to recognise that outcomes are generally poorer in patients who are initiated on a mechanical support without warning for respiratory failure. This is in part due to the inability to complete a detailed medical and psychological evaluation from a medical perspective but also as it does not allow the patient and family time to fully considered lung transplantation and the implications for the long term.

Current International consensus guidelines are unable to provide clear indications and contraindications to the use of mechanical support, in particular ECLS as a bridge to transplant due to the paucity of published data. Regardless, it is well accepted by centres that the use of mechanical support is an integral part of pre-transplantation medicine and is a situation that undoubted will become more common in the future and is an area in need of further study and development to improve outcomes further.

### 1.3.5 Pulmonary Artery Hypertension (PAH)

Typically patients with PAH in addition to their lung vasculature abnormality have a failing right ventricle at the time of referral for transplant assessment. In the past, these patients have commonly been managed with a combined Heart-Lung transplantation due to the concerns regarding myocardial dysfunction, in particular the right ventricle in the post-transplant period.

It is now clear that PAH represents a heterogeneous population not only due to the underlying primary mechanism but also the consequences on right and/or left ventricular function [17]. In line with this, it is now known that some patients will have a more favourable outcome with Heart-Lung transplantation while others will have comparable outcomes with isolated bilateral lung transplantation. The rational for this that even though the right ventricle may be dysfunctional pre-transplant it has the ability to remodel after lung transplantation and return to normal/near-normal function.

A recent review article [17] recommends that patients with congenital heart disease and Eisenmenger's syndrome, severe right ventricular dysfunction (ejection fraction 10–25%) and/or left ventricular dysfunction (ejection fraction 32–55%) should undergo Heart-Lung transplantation. It is recommended that all other PAH patients should be managed with bilateral lung transplantation. This approach in addition to decreasing waiting list times has the added advantage of enhancing organ utilisation for other recipients.

## 1.4 Specific Clinical Condition Criteria

### *1.4.1 Chronic Obstructive Pulmonary Disease*

Individuals with COPD should be referred for transplant assessment when the patient continues to deteriorated despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy [1].

Other specific indication for referral for transplant assessment include [1]:

1. BODE index of 5–6.
2. $PaCO_2$ >50 mmHg or 6.6 kPa and/or $PaO_2$ <60 mmHg or 8 kPa.
3. FEV1 <25% predicted.

Prior to or concurrently with the lung transplant assessment, evaluation for lung volume reduction should be undertaken as this can delay the need for lung transplant by almost 3 years [18, 19]. Lung transplantation surgery can be performed following lung volume reduction surgery and carries little additional risk [20, 21]. With the emergence of bronchoscopic procedures for lung volume reduction in individuals with heterogeneous emphysema, this may provide a less invasive and hazardous therapy to improve symptoms and quality of life compared with lung transplant and lung volume reduction surgery. It is important to note that successful lung volume reduction may result in significant improvements in functional and nutritional status and in many instances can improve the patient's suitability as a transplant candidate and outcomes following lung transplantation [19].

The clinical course of individuals with COPD is typically very protracted and survival outcomes with advanced stage disease is typically better than other respiratory diseases for which lung transplant is undertaken. With this, it is an ongoing challenge to determining the right time to list these individuals for lung transplantation.

Indication for listing as per international consensus guidelines [1] include:

1. Significant deterioration in quality of life
2. BODE index >7
3. FEV1 15–20% predicted
4. Three or more severe exacerbations during the preceding year
5. One severe exacerbation with acute hypercapnic respiratory failure
6. Moderate to severe pulmonary hypertension
7. Recipient characteristic which would make procurement of an appropriate organ difficult e.g. Patient height, blood group, highly sensitised (i.e. a patient that has a large number of antibodies [that may have occurred through previous pregnancy, previous blood transfusion] present to various HLA antigens that would likely cause antibody mediated rejection of the transplanted organ)

### *1.4.2 Interstitial Lung Disease (ILD)*

It is well described in respiratory literature that ILD, and in particular idiopathic pulmonary fibrosis (IPF), has a worse prognosis with respect to other lung conditions that require lung transplantation. The propensity of these individuals to deteriorate rapidly underpins the need for early referral for transplant assessment. The most recent American Thoracic Society consensus document highlights that transplantation and supplemental oxygen were the only treatments strongly recommended for patients with IPF, and a transplant discussion was recommended at the time of diagnosis [22].

Other recommendations for referral for transplant assessment include [1]:

1. Histopathologic or radiographic evidence of usual interstitial pneumonitis (UIP) or fibrosing non-specific interstitial pneumonitis (NSIP), regardless of lung function.
2. Abnormal lung function: forced vital capacity (FVC) <80% predicted or diffusion capacity of the lung for carbon monoxide (DLCO) <40% predicted.
3. Any dyspnoea or functional limitation attributable to lung disease.
4. Any oxygen requirement, even if only during exertion.
5. For inflammatory ILD, failure to improve dyspnoea, oxygen requirement, and/or lung function after a clinically indicated trial of medical therapy.

Timing of listing of individuals with IPF has become more challenging in recent years due to the availability of anti-fibrotic agents (pirfenidone, nintedanib) which have been shown to reduce disease progression and improve survival [23, 24]. While these therapies have the potential to delay the need for lung transplantation, long term data is still lacking. Studies of anti-fibrotic agents have primarily been limited to IPF, but work is now underway to examine their utility in other types of ILD.

Indication for listing patients with ILD as per international consensus guidelines include [1]:

1. Decline in FVC ≥10% during 6 months of follow-up (note: a 5% decline is associated with a poorer prognosis and may warrant listing).
2. Decline in DLCO ≥15% during 6 months of follow-up.
3. Desaturation to <88% or distance <250 m on 6-min walk test or >50 m decline in 6-min-walk distance over a 6-month period.
4. Pulmonary hypertension.
5. Hospitalization because of respiratory decline, pneumothorax, or acute exacerbation.

#### 1.4.2.1 Special Considerations

- *Single vs Bilateral Lung Transplantation*

  Although single lung transplantation is regularly done for individuals with ILD, studies have shown that bilateral lung transplant may result in improved long-term survival [25–29]. In addition to the demonstrated survival benefits of bilateral lung transplantation, bilateral lung transplantation is preferred in the setting of structural lung abnormalities such as cysts, bullae, and bronchiectasis which can develop in the advanced staged of ILD and can act as a nidus for infection. In addition, there is also the risk of malignancy developing in the native lung.
- *Telomerase associated Idiopathic pulmonary fibrosis and telomerase mutations*
  Telomeres are a functional complex at the end of linear eukaryotic chromosomes. They are essential for maintaining the integrity and stability of linear eukaryotic genomes. Telomere length regulation and maintenance contribute to normal human cellular aging and human diseases [30]. It is now known that mutations in the telomeres are associated with IPF and also with hematologic manifestations, such as myelodysplasia. Individuals with telomerase mutations appear to have increased rates of haematological, liver and arthritic complications post-transplant and these may necessitate the need for adjustment of the immunosuppressive regimen [31, 32]. Despite these risks, long-term survival is possible, but requires a cautious approach when considering these patients for transplant with heightened vigilance to monitor for other complications associated with telomere mutation.

- *Collagen vascular disorder associated ILD*

  ILD is commonly associated with collagen vascular disorders such as scleroderma and rheumatoid arthritis. In some instances, the ILD is the prominent process and hence may warrant transplantation. The multi-system nature of collagen vascular disorders requires a thorough evaluation of extra pulmonary manifestations that may impact transplant eligibility.

  As an example, many centres regard systemic sclerosis (SSc) as a relative, and in some instances as an absolute contraindication to lung transplantation because of concerns about oesophageal dysmotility and gastroparesis increasing the risk of aspiration. Data does however suggest that outcomes post-transplantation may be similar to other patients with ILD. Thus carefully selected patients with SSc can undergo lung transplantation with good outcomes utilising specific medical and surgical interventions to control oesophageal dysmotility and gastroparesis post-transplant.

### *1.4.3 Cystic Fibrosis (CF)*

Predicting survival in individuals with cystic fibrosis is challenging as there are no variables that consistently and accurately predictive poor outcome. Transplantation should be considered in CF patients who have a 2-year predicted survival of <50% and who have functional limitations classified as New York Heart Association Class III or IV [1].

Other variables that should prompt a transplant assessment as per international consensus guidelines include [1]:

1. A FEV1 that has fallen to 30% or a patient with advanced disease and a rapidly falling FEV1 despite optimal therapy (particularly in a female patient), infected with non-tuberculous mycobacterial (NTM) disease or B cepacia complex (see section below) and/or with diabetes.
2. A 6-min walk distance of less than 400 m.
3. Development of pulmonary hypertension in the absence of a hypoxic exacerbation (as defined by a systolic pulmonary arterial pressure (PAP) >35 mmHg on echocardiography or mean PAP >25 mmHg measured by right heart catheterization).
4. Clinical decline characterised by increasing frequency of exacerbations associated with any of the following:
   (a) An episode of acute respiratory failure requiring non-invasive ventilation.
   (b) Increasing antibiotic resistance and poor clinical recovery from exacerbations.
   (c) Worsening nutritional status despite supplementation.

(d) Pneumothorax.
(e) Life-threatening haemoptysis despite bronchial embolisation.

Indications for listing [1]:

1. Chronic respiratory failure with:
   (a) hypoxia alone (partial pressure of oxygen [$PaO_2$] <8 kPa or < 60 mmHg).
   (b) Hypercapnia (partial pressure of carbon dioxide [$PaCO_2$] >6.6 kPa or >50 mmHg).
2. Long-term non-invasive ventilation therapy.
3. Pulmonary hypertension.
4. Frequent hospitalization.
5. Rapid lung function decline.
6. World Health Organization Functional Class IV.

#### 1.4.3.1 Specific Considerations

- *Non-tuberculous Mycobacteria (NTM) disease*

  In recent years there has been increased rates of NTM isolation in patients with CF. CF patients with nontuberculous mycobacteria cultured from sputum prior to transplantation are at increased risk of post-transplant infection. With increasing clinical experience with these pathogens it has been established that specific NTM are more pathogenic and have a greater impact post-transplant than others. The highest risk is seen in those infected with *Mycobacterium abscessus* [33] whereas species such as *Mycobacterium avium* complex (MAC—comprising of *M. avium, M. intracellulare and M. chimera*) only have a marginal impact on outcomes post lung transplant. Recommendations from ISHLT, based on case series and expert opinions, suggest the following:

  1. All patients with CF who are referred for transplantation should be evaluated for NTM pulmonary disease.
  2. Patients with NTM disease who are being evaluated for transplantation should have the organism confirmed according to microbiology guidelines and begin treatment before transplant listing.
  3. Treatment should be performed by, or in collaboration with, a physician experienced in the management of such patients.
  4. Progressive pulmonary or extrapulmonary disease secondary to NTM despite optimal therapy or an inability to tolerate optimal therapy is a contraindication for transplant listing.

- *Burkholderia cepacia complex (Bcc)*

  Patients with CF who are infected with Bcc have been shown to have a more rapid progression of respiratory disease and thus are more likely to require lung transplantation but have poorer outcomes after transplantation. However, it is now known that certain genomovars, or subspecies, may have greater virulence than others and thus

impact transplant outcomes [34, 35]. The Bcc subspecies *Burkholderia cenocepacia* in particular have a significantly worse survival after transplantation compared to uninfected patients with CF, and the increased mortality is directly attributable to Bcc infection. Hence Infection with Bcc is considered a relative contraindication to lung transplantation. Taking this into account the following recommendations are made [1]:

1. All patients with CF referred for transplantation should be evaluated for the presence of Bcc.
2. Patients with species other than *B. cenocepacia* do not constitute an increased risk for mortality after transplantation and can be listed, provided that other criteria are met.
3. Patients with *B cenocepacia* have an increased risk of mortality secondary to recurrent disease after transplantation. It is recommended that centres continuing to accept such patients should have an active research program assessing novel approaches to prevent and control recurrent disease and should be experienced in management of these patients.

### *1.4.4 Pulmonary Vascular Diseases*

With the developments of targeted therapies for the treatment of pulmonary hypertension, the timing of referral for transplant for pulmonary vascular disease is less clear. Medical therapies (e.g. prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors) now have the ability to stabilise patients whom in the past would certainly have died unless they proceeded to lung transplantation. Additionally, the advent of novel therapies (such as selexipag, riociguat) may continue to change this landscape.

Recommendation for referral for transplant assessment [1]:

1. NYHA Functional Class III or IV symptoms during escalating therapy.
2. Rapidly progressive disease (assuming weight and rehabilitation concerns not present).
3. Use of parenteral targeted pulmonary arterial hypertension (PAH) therapy regardless of symptoms or NYHA Functional Class.
4. Known or suspected pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis.

Timing of transplant listing:

1. NYHA Functional Class III or IV despite a trial of at least 3 months of combination therapy including prostanoids.
2. Cardiac index of <2 l/min/m$^2$.
3. Mean right atrial pressure of >15 mmHg.
4. 6-min walk test of <350 m.
5. Development of significant haemoptysis, pericardial effusion, or signs of progressive right heart failure (renal insufficiency, increasing bilirubin, brain natriuretic peptide, or recurrent ascites).

## 1.5 Lung Retransplantation

Lung retransplantation represents only a small proportion of those that undergo lung transplantation. ISHLT registry data shows that since 1995 lung retransplantation accounted for 4% of all lung transplants undertaken and for the 2015 year just under 8% of all lung transplants were retransplantation. However, with improvements in the overall health status of post-transplant patients has seen an increase in the frequency of repeat transplant in recent years.

In general, the same clinical criteria used for selection for the initial lung transplantation should be adopted with particular emphasis on the presence of significant renal dysfunction. This and other co-morbidities significantly increase the risk of mortality in retransplant candidates.

As with the initial lung transplantation a bilateral or single lung transplant can be undertaken. As mentioned previously single lung transplant can increase the risk of the remaining 'native' lung acting as a nidus for infection. The failed allograft may also represent a source of ongoing immune stimulation, and its removal would offer intuitive advantages [1]. Given these reasons, complete removal of a failed allograft is advisable.

Specific prognostic factors that have been identified include [1]:

1. Patients retransplanted for bronchiolitis obliterans syndrome (BOS) have better survival than those transplanted for primary graft dysfunction or airway complications.
2. Patients who are >2 years out from initial transplantation have better outcomes than patients retransplanted earlier.
3. Patients retransplanted for BOS have been seen to have more rapid declines in airflow than patients transplanted for other indications.
4. Patients retransplanted in <2 years after the initial transplantation also have an even greater risk of developing BOS.

Despite improving survival rates of retransplant candidates, overall survival remains inferior to survival seen after initial transplantation. With this is mind consideration must be given to the ethical issues surrounding lung allocation to retransplantation candidates i.e. allocation of a lung to a patient who has already received a lung transplant versus an individual who has not. Another factor to consider is that it is generally accepted that priority is given to younger patients regarding retransplantation; however at the same time categorically placing older patients at a disadvantage is inappropriate. These aspects, in addition to the medical issues surrounding transplantation make this an ethically challenging area.

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