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ISHLT CONSENSUS

A consensus document for the selection of lung transplant candidates: 2014—An update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation

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The appropriate selection of lung transplant recipients is an important determinant of outcomes. This consensus document is an update of the recipient selection guidelines published in 2006.

The Pulmonary Council of the International Society for Heart and Lung Transplantation (ISHLT) organized a Writing Committee of international experts to provide consensus opinion regarding the appropriate timing of referral and listing of candidates for lung transplantation. A comprehensive search of the medical literature was conducted with the assistance of a medical librarian. Writing Committee members were assigned specific topics to research and discuss. The Chairs of the Writing Committee were responsible for evaluating the completeness of the literature search, providing editorial support for the manuscript, and organizing group discussions regarding its content.

The consensus document makes specific recommendations regarding the timing of referral and of listing for lung transplantation. These recommendations include discussions not present in previous ISHLT guidelines, including lung allocation scores, bridging to transplant with mechanical circulatory and ventilator support, and expanded indications for lung transplantation.

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In the absence of high-grade evidence to support decision making, these consensus guidelines remain part of a continuum of expert opinion based on available studies and personal experience. Some positions are immutable. Although transplant is rightly a treatment of last resort for end-stage lung disease, early referral allows proper evaluation and thorough patient education. Subsequent waiting list activation implies a tacit agreement that transplant offers a significant individual survival advantage. It is both the challenge and the responsibility of the transplant community globally to ensure organ allocation maximizes the potential benefits of a scarce resource, thereby achieving that advantage.
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The International Society for Heart and Lung Transplantation (ISHLT) has developed 2 previous editions of International Guidelines for the Selection of Lung Transplant Candidates. Published in 1998 and 2006,[1,2] these guidelines represented the best and most current information present at the time relevant to the appropriate selection of patients being evaluated for lung transplantation. Given the continued evolution of the field, the Pulmonary Transplantation Council presents a Third Edition of the Consensus Report for the Selection of Lung Transplant Candidates.

The goal of this current edition is to assist physicians, both those who refer candidates and those who work in the lung transplant field, in properly identifying patients who are the most likely to benefit from lung transplantation. Although physicians caring for patients with advanced lung disease outside of a transplant center do not make the final decision regarding listing a patient for transplant, it is imperative that physicians involved with these sorts of patients become familiar with the criteria for lung transplant referral and listing.

Referral for transplant and placement on the waiting list are 2 distinct processes, but there is general agreement that referral to a lung transplant program should occur early in patients who have a lung disease that is amenable to transplantation. None of the parameters listed in this document informing on the timing of referral or listing should be used in isolation. Instead, the entire clinical situation of the patient should be considered. However, early referral does give the transplant program maximal flexibility in performing the formal evaluation and in making the second more important step—placing the patient on the active waiting list.

The decision to place a patient on the active waiting list is a critical one, particularly the timing of the decision, given that a patient should not be exposed to the risk of the transplant surgery until all other viable treatment options are exhausted. Listing a patient for a lung transplant is an explicit acknowledgement that a patient has a limited life expectancy without a transplant and an expectation that the risk-to-benefit ratio favors lung transplantation rather than conventional medical treatment. We also discuss the concept of removing patients from the waiting list, either temporarily or permanently, when circumstances are noted to have changed the overall risk-to-benefit ratio for the patient and/or do not represent appropriate donor lung use. A predictably futile or poor outcome transplant is not an appropriate use of a precious resource. As be discussed further later on, the listing decision involves numerous factors that require an understanding not only of the clinical course of the patient but also of local factors influencing the expected wait times at a specific center.

This report discusses general indications and contraindications (relative and absolute) and disease-specific selection criteria, some of which are unchanged from previous selection guidelines. As in previous editions, the current report largely represents a consensus of expert opinion and does not meet the true definition of "guidelines," as defined by the ISHLT. However, an effort has been made to include a discussion of areas supported by robust scientific data. In light of the evolving nature of the field, important areas of emphasis of this edition include factors influencing recipient selection that were not present in previous recipient selection editions, such as lung allocation changes, pediatric lung transplantation, the use of mechanical ventilation and circulation support for bridging potential transplant recipients and ex vivo perfusion for better assessment and recruitment of donor lungs, and the broadening of selection criteria (especially with regard to age, comorbidities, retransplantation, and recipient infectious disease issues). The presence of pre-existing recipient infections and their impact on post-transplant outcomes is an evolving area of study, and there is a paucity of data on which to rely. In this context, it is ultimately the prerogative and responsibility of individual centers to determine whether a patient with a particular type of infection is deemed a suitable candidate at a specific program and, if a candidate, what clinical parameters are most heavily considered. Transplantation should occur at centers experienced in the treatment and management of these infections.

How to use this document

The decision to place a patient on the waiting list for a lung transplant is complex, reflecting consideration not only of clinical and psychosocial characteristics of the individual patient but also program-specific factors and regional considerations (e.g., the influence of a lung allocation system). The referral of a patient to a transplant center should not be interpreted by the patient, referring physician, or the program as an automatic endorsement of listing that individual, either at the time of referral or at some point in the future. Instead, referral should simply imply that a

patient has met the minimum clinical characteristics that might warrant transplant consideration. Recognizing this, this document to the extent possible attempts to separate the referral decision and the listing decision.

Given that the level of the evidence informing decisions about recipient selection is largely based on expert opinion and that this document represents a consensus of that expert opinion, the recommendations contained herein should not be considered definitive. Further, the Committee does not believe it is appropriate to consider its recommendations to be interpreted as a standard of care by physicians, patients, or third-party payers or in legal proceedings. The selection of appropriate lung transplant candidates is too multifaceted to lend itself well to strict, proscriptive guidelines and instead should be the result of a process that carefully considers the unique aspects of each patient and each transplant program.

Methods

At the ISHLT Annual Scientific Meeting in 2012, the Pulmonary Transplantation Council of the ISHLT proposed revising the recipient selection criteria, which were last updated in 2006. The Council leadership solicited interest in participating in the formulation of this document. A Writing Committee was proposed and approved by the Standards and Guidelines Committee in late 2012. The Writing Committee reflected the diverse nature of the Pulmonary Transplantation Council with regard to geographic distribution and level of experience. The ISHLT Board of Directors approved the project in early 2013.

A comprehensive search of the medical literature was conducted with the assistance of a medical librarian. The search included articles published in English from 1980 through 2013. The search terms included (Patient Selection [mesh] *or* select* [ti] *or* scor* [ti] *or* registry [ti] *or* candidat* [ti] *or* allocat* [ti] *or* "patient selection" [tiab] *or* recruit* [ti] *or* "patient recruitment" [tiab] *or* "subject recruitment" [tiab] *or* "subject selection" [tiab]) *and* ("lung transplantation" [mesh] *or* "lung transplant" [tiab] *or* "lung transplants" [tiab] *or* "lung transplantation" [tiab] *or* (lung* [ti] *and* transplan* [ti])) *and* English [lang] *not* (letter [pt] *or* editorial [pt]).

Writing Committee members were assigned specific topics to research and discuss. The Chairs of the Writing Committee were responsible for evaluating the completeness of the literature search, providing editorial support for the manuscript, and organizing group discussions regarding its content. Each member of the Writing Committee had an opportunity to review the entire document and provide input before completion of the final manuscript.

Given that this document is a consensus document rather than a guideline, grading of levels of evidence and recommendations was not undertaken. Instead, as noted previously, a comprehensive literature search and consensus expert opinion have been presented. In all instances, the Writing Committee adhered to the ISHLT Standards and Guidelines Document Development Protocol (update January 2013).

General candidacy considerations

Lung transplantation should be considered for adults with chronic, end-stage lung disease who meet all the following general criteria:

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

Contraindications

Because lung transplantation is a complex therapy with a significant risk of perioperative morbidity and mortality, it is important to consider the overall sum of contraindications and comorbidities. The following lists are not intended to include all possible clinical scenarios but rather to highlight common areas of concern.

Absolute contraindications

- Lung transplantation should not be offered to adults with a recent history of malignancy. A 2-year disease-free interval combined with a low predicted risk of recurrence after lung transplantation may be reasonable, for instance, in non-melanoma localized skin cancer that has been treated appropriately. However, a 5-year disease-free interval is prudent in most cases, particularly for patients with a history of hematologic malignancy, sarcoma, melanoma, or cancers of the breast, bladder, or kidney. Unfortunately, for a portion of patients with a history of cancer, the risk of recurrence may remain too high to proceed with lung transplantation even after a 5-year disease-free interval.
- Untreatable significant dysfunction of another major organ system (e.g., heart, liver, kidney, or brain) unless combined organ transplantation can be performed.
- Uncorrected atherosclerotic disease with suspected or confirmed end-organ ischemia or dysfunction and/or coronary artery disease not amenable to revascularization.
- Acute medical instability, including, but not limited to, acute sepsis, myocardial infarction, and liver failure.
- Uncorrectable bleeding diathesis.
- Chronic infection with highly virulent and/or resistant microbes that are poorly controlled pre-transplant.
- Evidence of active *Mycobacterium tuberculosis* infection.
- Significant chest wall or spinal deformity expected to cause severe restriction after transplantation.
- Class II or III obesity (body mass index [BMI] ≥ 35.0 kg/m^2).
- 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.
- Psychiatric or psychologic conditions associated with the inability to cooperate with the medical/allied health care team and/or adhere with complex medical therapy.
- Absence of an adequate or reliable social support system.
- Severely limited functional status with poor rehabilitation potential.

- Substance abuse or dependence (e.g., alcohol, tobacco, marijuana, or other illicit substances). In many cases, convincing evidence of risk reduction behaviors, such as meaningful and/or long-term participation in therapy for substance abuse and/or dependence, should be required before offering lung transplantation. Serial blood and urine testing can be used to verify abstinence from substances that are of concern.

Relative contraindications

- Age >65 years in association with low physiologic reserve and/or other relative contraindications. Although there cannot be endorsement of an upper age limit as an absolute contraindication, adults >75 years old are unlikely to be candidates for lung transplantation in most cases. Although age by itself should not be considered a contraindication to transplant, increasing age generally is associated with comorbid conditions that are either absolute or relative contraindications.
- Class I obesity (BMI 30.0–34.9 kg/m^2), particularly truncal (central) obesity.
- Progressive or severe malnutrition.
- Severe, symptomatic osteoporosis.
- Extensive prior chest surgery with lung resection.
- Mechanical ventilation and/or extracorporeal life support (ECLS). However, carefully selected candidates without other acute or chronic organ dysfunction may be successfully transplanted.
- 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).
- 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 centers with experienced hepatology units.
- For patients infected with human immunodeficiency virus (HIV), a lung transplant can be considered in patients with controlled disease with undetectable HIV-RNA, and compliant on combined anti-retroviral therapy. The most suitable candidates should have no current acquired immunodeficiency syndrome–defining illness. Lung transplantation in HIV-positive candidates should be performed in centers with expertise in the care of HIV-positive patients.
- Infection with *Burkholderia cenocepacia*, *Burkholderia gladioli*, and multi-drug–resistant *Mycobacterium abscessus* if the infection is sufficiently treated preoperatively and there is a reasonable expectation for adequate control postoperatively. For patients with these infections to be considered suitable transplant candidates, the patients should be evaluated by centers 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.
- 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. The preoperative evaluation, type of coronary stent used (bare metal vs drug eluting), and degree of coronary artery disease deemed acceptable vary among transplant centers.
- 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.

Special surgical considerations

Previous surgery

Recommendations:

- Previous surgery is not a contraindication to lung transplantation.
- Pleurodesis is the most troublesome situation but is not a contraindication.
- Pneumothorax in a patient who may become a future transplant recipient should be given the best immediate management. The choice of intervention is unlikely to affect future acceptance for transplantation.
- Higher rates of bleeding, reexploration, and renal dysfunction are to be expected in patients with previous chest procedures. These conditions may be exacerbated by longer cardiopulmonary bypass times.
- In otherwise well-selected patients, medium-term and long-term outcome is not affected by previous chest procedures.
- Conversely, older patients (>65 years old) with other comorbidities have poorer outcomes, and the previous intrapleural procedure should be taken into account during selection.

Some patients referred for lung transplantation will have undergone previous chest surgery. If one includes prior chest tube insertion, the percentage of referred patients may be up to 40%[3,4] or for up to 90% in conditions such as lymphangioleiomyomatosis (LAM).[4] Surgery may be coincidental, for instance, previous CABG, but usually is related as a diagnostic or therapeutic step in pre-transplant management. Examples of the latter range from simple video-assisted thoracoscopic biopsy in interstitial disease to previous lung volume reduction surgery (LVRS). Conditions associated with recurrent pneumothorax, such as cystic fibrosis (CF) or LAM, may have required pleurodesis, previous lung resection, or pneumonectomy.

The evidence for any effect of previous interventions is entirely based on retrospective institutional or local registry reports and so is prone to publication bias. Small series (14 and 18 patients)[5,6] have described successful lung transplant after chest surgery. The largest more recent experience[3]

described 238 patients, although 115 merely had earlier chest drain insertion. Numerous accounts concentrate on conditions such as LAM[4] or CF,[7] in which pneumothorax is a disease-specific pre-transplant complication.

Some broad conclusions can be taken from the published literature. Any previous surgery, but particularly pleurodesis (surgical or chemical), is associated with greater blood loss and early post-operative morbidity such as renal dysfunction and primary graft dysfunction. The incidence of phrenic nerve damage, chylothorax, and re-exploration is also greater. Where multivariate analysis can be applied,[3] age >65 years, pulmonary hypertension, transfusion >20 units, and prolonged cardiopulmonary bypass all are predictors of early death. Previous cardiac surgery appears to have little specific effect, but reported experience is very small.

Several reports have examined the specific issue of previous LVRS. Early experience indicated that LVRS had no effect,[8] but in a more recent account,[9] 25 of 177 patients who received transplants for chronic obstructive pulmonary disease (COPD) had undergone previous LVRS and had poorer outcomes. There were the expected higher rates of bleeding and early morbidity but also significantly worse early graft function and poorer results in older, frailer patients.

Mechanical bridges to transplant

ECLS recommended:

- Young age.
- Absence of multiple-organ dysfunction.
- Good potential for rehabilitation.

ECLS not recommended:

- Septic shock.
- Multi-organ dysfunction.
- Severe arterial occlusive disease.
- Heparin-induced thrombocytopenia.
- Prior prolonged mechanical ventilation.
- Advanced age.
- Obesity.

"Bridge to lung transplantation" refers to strategies to manage with artificial support an acutely decompensating patient until a suitable organ is available.[10,11] Ideally, bridge to lung transplantation should be applied with the intent to prolong the pre-transplant life expectancy of patients, increasing the chances to receive a lung transplant, and to improve the likelihood of a successful post-transplant outcome by improving pre-transplant clinical stability.[12] It is also preferable that patients bridged to transplant in this way have already been fully evaluated by the transplant team and all medical and psychosocial risk factors identified before bridge therapy is initiated. Less favorable outcomes are generally seen in patients who present de novo with respiratory failure and are placed on a mechanical support system without the benefit of the transplant team and the patient having fully considered transplant as a therapeutic option.

Mechanical ventilation today has been the most commonly used bridging strategy to lung transplant,[13–15] but ventilated patients are particularly susceptible to ventilator-induced lung injury and ventilator-associated pneumonia. Patients are required to be bed-bound and often sedated, which reduces their ability to undergo adequate physiotherapy. This situation can lead to severe deconditioning and may compromise their suitability for transplantation. Although often successful, mechanical ventilation is far from the "ideal bridge" to lung transplant.

Since the beginning of the lung transplant era, ECLS has been recognized as a potential bridge to lung transplant for patients with respiratory failure. However, the initial clinical experience in the 1980s and 1990s was discouraging with a high mortality rate and a high incidence of complications associated with the application of ECLS.[16] Substantial improvements in ECLS technology in recent years have led to renewed enthusiasm for ECLS as a bridge to lung transplant. Current ECLS devices can provide different modes and configurations of support with the appropriate level of pulmonary (and cardiac) support for each patient's physiologic need with significantly less morbidity and fewer complications.[10–12,17]

In the modern era of ECLS, several recently published case series have shown that the post-transplant mortality rate of selected patients bridged to transplant with ECLS is comparable to that of patients transplanted without pre-transplant ECLS.[14,18–21] Despite these promising results, the application of ECLS as bridge to transplant remains controversial. In addition to the historically poor outcomes, bridging patients to transplant with ECLS is associated with substantial resource utilization in both the pre-transplant and post-transplant phase and with important complications, including bleeding, vascular access problems, and infection. However, the transplant benefit is likely greater in this patient group, given the high pre-transplant mortality associated with the need for this level of support. Regardless, it is well accepted by centers using ECLS that post-transplant mortality increases in relation to time on ECLS pre-transplant, and caution should be exercised in transplanting candidates who have prolonged need for ECLS.

Recently, newer ECLS systems have maintained patient stability with fewer complications. As a bridge to lung transplant, ECLS is being progressively used as an alternative to mechanical ventilation to avoid the injurious adverse effects of mechanical ventilation, rather than as a rescue treatment for patients refractory to mechanical ventilation. Fuehner et al[22] published one of the first reports showing that the post-transplant survival rate in patients bridged to lung transplant with ECLS was higher than in historical control patients bridged with invasive mechanical ventilation (80% vs 50%, $p = 0.02$). In this study, ECLS was applied in awake non-intubated patients who were allowed to ambulate while on ECLS and receive active physical therapy (22). An analysis of data from the United Network for Organ Sharing (UNOS) showed 1-year survival in patients bridged to transplant using ECLS substantially improved from 30% in 2005 to 75% in 2010, at which time

survival was superior to survival in patients who were transplanted off of a ventilator.

Indications and contraindications to ECLS as a bridge to transplant cannot be firmly established because only relatively small case series have been published to date. However, recommendations for the use of ECLS have been published.[10,12]

Overall, these data suggest that ECLS is effective in supporting patients with advanced respiratory failure and in improving clinical stability of patients, which should ultimately improve post-transplant outcomes. Clinical advances in this field are needed because the mortality rate of patients on the lung transplant waiting list is still in the range of 20%.[23] Bridging to transplant using ECLS requires ongoing assessment of the potential recipient for candidacy because frequently neurologic events, organ failure, and infectious complications preclude candidacy for transplantation.

Disease-specific candidate selection

Interstitial lung disease

Timing of referral:

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

Timing of listing:

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

Indications

ILD, and in particular idiopathic pulmonary fibrosis (IPF), carries the worst prognosis among the common disease indications for lung transplantation. Recent worldwide changes in allocation of donor lungs, including the Lung Allocation Score (LAS) in the United States and Eurotransplant, have dramatically increased lung transplant rates for candidates with ILD. Despite this, waiting list mortality remains high. In phase 3 trials of patients with IPF, pirfenidone was shown to reduce disease progression, as reflected by lung function, exercise tolerance, and survival.[24] In the most recent American Thoracic Society consensus document, 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.[25] The evidence reviewed here focuses on IPF as the most common and life-threatening subtype of ILD, while recognizing that fibrosing NSIP and other types of progressive ILD refractory to treatment may carry a similar prognosis.

Prognosis in IPF is generally poor; retrospective cohort studies indicate a median survival of 2 to 3 years from diagnosis, and only 20% to 30% patients survive >5 years after diagnosis.[25,26] This poor prognosis underscores the importance of early referral of patients with IPF so that listing and transplantation can be achieved rapidly in the setting of an unexpected decline.[27]

Prognostic factors in IPF have been reviewed in detail more recently,[26] and consistent clinical predictors of worse survival include older age, dyspnea, low or declining pulmonary function,[28–30] pulmonary hypertension, concomitant emphysema, extensive radiographic involvement, low exercise capacity or exertional desaturation,[27,31] and UIP on histopathology. Clinical prediction models such as the CRP (clinical, radiologic, and physiologic) score have not been widely used in practice.[32] du Bois et al[29] assessed numerous risk factors in a large cohort of patients with IPF and developed a practical 4-item risk scoring system that includes age, respiratory hospitalization, percentage predicted FVC, and 24-week change in FVC. If validated, particularly in patients with IPF who are potential lung transplant candidates, this model could be a useful aid in referral and listing decisions.

Special considerations

ILD severe enough to warrant consideration of lung transplantation may be associated with collagen vascular diseases such as scleroderma and rheumatoid arthritis. Data regarding specific predictors of prognosis in this setting are limited.[33,34] If the lung disease has not responded to appropriate treatment and there are no extrapulmonary contraindications to transplantation, it is reasonable to use similar guidelines to those proposed for idiopathic ILD.

Cystic fibrosis

Timing of referral:

- FEV_1 that has fallen to 30% or a patient with advanced disease with a rapidly falling FEV_1 despite optimal therapy (particularly in a female patient), infected with

non-tuberculous mycobacterial (NTM) disease or *B cepacia* complex (see previous comment on *B cenocepacia* and subsequently) and/or with diabetes.
- A 6-minute walk distance <400 m.
- Development of pulmonary hypertension in the absence of a hypoxic exacerbation (as defined by a systolic pulmonary arterial pressure (PAP) >35 mm Hg on echocardiography or mean PAP >25 mm Hg measured by right heart catheterization).
- Clinical decline characterized by increasing frequency of exacerbations associated with any of the following:
  - An episode of acute respiratory failure requiring non-invasive ventilation.
  - Increasing antibiotic resistance and poor clinical recovery from exacerbations.
  - Worsening nutritional status despite supplementation.
  - Pneumothorax.
  - Life-threatening hemoptysis despite bronchial embolization.

Timing of listing:

- Chronic respiratory failure.
  - With hypoxia alone (partial pressure of oxygen [Pao_2] <8 kPa or <60 mm Hg).
  - With hypercapnia (partial pressure of carbon dioxide [$Paco_2$] >6.6 kPa or >50 mm Hg).
- Long-term non-invasive ventilation therapy.
- Pulmonary hypertension.
- Frequent hospitalization.
- Rapid lung function decline.
- World Health Organization Functional Class IV.

Indications

Transplantation should be considered for suitable patients with CF who have a 2-year predicted survival of $<50\%$ and who have functional limitations classified as New York Heart Association Class III or IV. However, predicting survival using objective data has been difficult, with no single factor sufficiently predictive of poor survival in patients with CF. Much of the data apply to the general CF population rather than the population that meets other criteria for transplantation, and the CF transplant candidate data come from relatively small cohorts. A measurement of lung function over time to assess disease progression has been the most useful predictor.[35] The FEV_1 has been the most frequently used variable in assessing early mortality. In 1992, Kerem et al[36] reported that FEV_1 $<30\%$ of predicted was associated with a 2-year mortality rate of approximately 40% in men and 55% in women.

Mayer-Hamblett et al[37] used the Cystic Fibrosis Foundation registry to develop a model identifying the best clinical predictors of mortality in patients with CF. They found that age, height, FEV_1, respiratory microbiology, number of hospitalizations, and number of home intravenous antibiotic courses were significant predictors of 2-year mortality, but their multivariate logistic regression model was not a better predictor of early mortality than FEV_1 alone.[37]

Another study evaluated patients with CF referred for transplantation at four lung transplant centers. Using a univariate analysis, the authors reported a relationship between early mortality and FEV_1 $<30\%$ of predicted and elevated $Paco_2$ >50 mm Hg (6.6 kPa). They also noted the need for and the use of nutritional supplements as an indicator of increased early mortality. Patients who had FEV_1 $<30\%$ of predicted had an increased early mortality only when Paco2 was >50 mm Hg.[38] In a single-center study, Milla and Warwick[39] also found that the rate of decline was a better predictor of early mortality than FEV_1 alone.

Using the Cystic Fibrosis Foundation database, Liou et al[40] developed a 5-year survival model. The authors evaluated the impact of different variables on survival and correlated it with a change in the FEV_1 percentage predicted. Female sex, diabetes mellitus, *B cepacia* infection, and the number of exacerbations negatively affected the survival of patients with CF, whereas FEV_1 percentage predicted alone was *not* a sufficient predictor of early mortality.

Other preoperative characteristics that have been shown to affect survival after lung transplantation include exercise tolerance and pulmonary hypertension. A 6-minute walk distance <400 m and pulmonary hypertension have been associated with a poorer prognosis.[41–44] The development of a pneumothorax and the presence of NTM disease (in particular *M abscessus*) also increase the rate of decline in lung function and/or mortality in the setting of advanced lung disease.[45,46]

Specific considerations

NTM disease

An increase in incidence of patients with CF culturing NTM has been observed.[45] The following recommendations are made, although it is recognized that this is a subject where the evidence is predominantly based on case series[47,48]:

- All patients with CF who are referred for transplantation should be evaluated for NTM pulmonary disease.
- 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.
- Treatment should be by, or in collaboration with, a physician experienced in the treatment of such patients.
- Progressive pulmonary or extrapulmonary disease secondary to NTM despite optimal therapy or an inability to tolerate optimal therapy is a contraindication for transplant listing.

B cepacia complex

Patients with CF who are infected with *B cepacia* complex have been shown to have a more rapid progression of respiratory disease associated with a more rapid fall in

FEV_1. Patients with *B cepacia* complex infection also have a less favorable outcome after transplantation, although most of the increased risk has been shown to be confined to patients infected with *B cenocepacia*.[49–51]

The following recommendations are made:

- All patients with CF referred for transplantation should be evaluated for the presence of *B cepacia*.
- 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.
- Patients with *B cenocepacia* have an increased risk of mortality secondary to recurrent disease after transplantation. It is recommended that centers 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. A full discussion with the patients of the increased risk associated with these infections should occur.

COPD

Timing of referral:

- Disease is progressive, despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy.
- Patient is not a candidate for endoscopic or surgical LVRS. Simultaneous referral of patients with COPD for both lung transplant and LVRS evaluation is appropriate.
- BODE index of 5 to 6.
- $Paco_2 > 50$ mm Hg or 6.6 kPa and/or $Pao_2 < 60$ mm Hg or 8 kPa.
- $FEV_1 < 25\%$ predicted.

Timing of listing (presence of one criterion is sufficient):

- BODE index ≥ 7.
- $FEV_1 < 15\%$ to 20% predicted.
- Three or more severe exacerbations during the preceding year.
- One severe exacerbation with acute hypercapnic respiratory failure.
- Moderate to severe pulmonary hypertension.

Indications

Accounting for 40% of all lung transplantations performed worldwide, COPD (non–α_1-antitrypsin deficiency [A1ATD] and A1ATD) is the most common indication.[52] The clinical course of COPD is typically very protracted, and even at an advanced stage, short-term and intermediate-term survival is better than in the other diseases for which transplants are commonly performed. Apart from survival, in patients with COPD, often the most important clinical feature is a significant decrement in the quality of life. As a result, and considering the prevalence of end-stage COPD and the continuing donor organ shortage, it remains challenging to determine the point at which lung transplantation should be offered to patients with COPD and whether quality of life issues should also be taken into account when making that decision.

In a study including 609 patients with severe emphysema randomly assigned to the medical therapy arm of the National Emphysema Treatment Trial (NETT), Martinez et al[53] identified the following factors that were associated with increased mortality in a multivariate analysis: increasing age, oxygen utilization, lower total lung capacity and higher residual volume (% predicted), lower maximal cardiopulmonary exercise testing workload, greater proportion of emphysema in the lower lung zone vs the upper lung zone, and lower upper-to-lower-lung perfusion ratio. The modified BODE score, which is a composite score of body mass index (B), airway obstruction (% predicted FEV_1) (O), dyspnea (D), and exercise capacity (E), was also associated with a higher mortality. In some studies, the original BODE score, developed by Celli et al,[54] assigned a score from 0 to 10, with a higher score indicating more severe disease and a worse survival (a BODE score of 7–10 was associated with a mortality of 80% at 4 years, whereas a score of 5–6 conferred a mortality of 60% at 4 years) and proved to be a better indicator of survival than the spirometric staging system.[55] Either the original or the modified BODE can be used, depending on local center preference and expertise.

The presence of 3 or more exacerbations in a 1-year period negatively affects survival in patients with COPD.[56] The increased mortality risk is independent of the baseline severity of the disease as measured by the BODE index.[57] Patients with COPD and acute hypercapnic respiratory failure have an in-hospital mortality of >10%, and patients who survived the hospital admission have a mortality rate of 43% and at 1 year and 49% at 2 years post-admission.[58]

The 2006 ISHLT international guidelines for the selection of lung transplant candidates adopted the BODE index as a useful tool to evaluate COPD candidates for lung transplantation.[1] The role of the BODE score and its survival effect in lung transplantation for COPD was evaluated by Lahzami et al,[59] who showed that most patients with COPD had an individual survival benefit from lung transplantation regardless of their pre-transplant BODE score, although a global survival benefit was seen only in patients with a BODE score of ≥ 7, suggesting that this is the appropriate population to transplant. Patients with a BODE score of 5 to 6, although not expected to derive a survival benefit, experienced similar quality of life benefits from transplant as patients with a BODE score of 7 to 10. Although lung transplant candidates with COPD are different compared with the original COPD population as assessed in the original report of the BODE index by Celli et al (younger age and non-smoking), it does not prevent the BODE index from being useful in the assessment of COPD candidates for lung transplantation.[60]

Special considerations

A specific issue to the COPD population is the impact of bronchoscopic lung volume reduction (BLVR) or LVRS on

listing for lung transplantation. In certain patients (FEV_1 <25% but >20%, DLCO >20%, and heterogeneous emphysema distribution on computed tomography [CT] scan), LVRS may be offered first, reserving transplantation for patients failing to improve with LVRS or patients experiencing a functional decline after a period of sustained improvement. Successful LVRS or BLVR and the associated improvement in functional and nutritional status in some instances can improve the patient's suitability as a transplant candidate.[8,61]

Pulmonary vascular diseases

Timing of referral:

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

Timing of transplant listing:

- NYHA Functional Class III or IV despite a trial of at least 3 months of combination therapy including prostanoids.
- Cardiac index of <2 liters/min/m^2.
- Mean right atrial pressure of >15 mm Hg.
- 6-minute walk test of <350 m.
- Development of significant hemoptysis, pericardial effusion, or signs of progressive right heart failure (renal insufficiency, increasing bilirubin, brain natriuretic peptide, or recurrent ascites).[1,61,62]

Indications

The timing of referral for transplant for pulmonary vascular disease is difficult. The development of targeted medical therapy has led to a marked change in the timing for referral and listing for patients with idiopathic pulmonary arterial hypertension (IPAH) or pulmonary hypertension from other causes. Medical therapies including prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors have proven efficacy in the management of patients with IPAH, and, as such, most patients who would have been listed for transplant in the pre-prostanoid era may not require transplant listing while awaiting clinical response to medical therapy.[63,64] Because of the generally good response to medical therapy, transplant centers still vary considerably in referral, listing and transplantation of patients with IPAH. In patients who are deteriorating rapidly, transplant bridging strategies are an option but a more difficult one in this patient group.

Equations to predict waiting list mortality in patients with IPAH are under development. One such registry with a published equation, the U.S. Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), identified the following factors to be associated with increased mortality: NYHA Functional Class IV, male gender with age >60 years old, increased pulmonary vascular resistance (PVR), PAH associated with portal hypertension, or a family history of PAH.[65] NYHA Functional Class III, increased mean right atrial pressure, decreased resting systolic blood pressure or an elevated heart rate, decreased 6-minute walk distance, increased brain natriuretic peptide, renal insufficiency, PAH associated with connective tissue diseases, decreased DLCO, and the presence of pericardial effusion were also associated with increased mortality. Despite criticism that this registry did not reflect actual lung transplant waiting list populations, it provided insight into risk factors for mortality.

Special transplant circumstances

Lung retransplantation

Lung retransplantation accounts for a small percentage of lung transplants performed annually. However, its frequency has increased in recent years. This trend has been particularly prevalent in North America and coincided with the introduction of the LAS system in 2005 in the United States. Although many of these patients would previously have been too ill to survive prolonged waiting times, the LAS system has allowed them priority access to available donor organs.[66,67]

The criteria for candidate selection for lung retransplantation generally mirror the criteria used for selection for initial lung transplantation. Particular attention should be paid to the presence of significant renal dysfunction, which, if present, increases the hazard ratio for mortality considerably among retransplantation candidates. The presence of additional comorbidities increases risk by a multivariate analysis.[68,69]

Retransplantation candidates may be considered for bilateral or single-lung transplantation. If the initial transplant was a single-lung transplant, consideration must be given to whether leaving the previous allograft in situ is desirable. The failed allograft may represent a source of ongoing immune stimulation, and its removal would offer intuitive advantages. Previous reports have also identified the retained allograft as a source of fatal infection in nearly one quarter of retransplantation recipients.[70] These factors would suggest that removal of a failed allograft is advisable. Ipsilateral single-lung retransplantation has been associated with a higher acute risk of death compared with contralateral single-lung retransplantation.[68] However, these comparisons are confounded by factors such as the original indication and timing for retransplantation. Nonetheless, the most recent trend has been toward more frequent bilateral retransplantation. This trend may relate to a desire to remove failed allografts in an era when initial bilateral lung transplantation is increasingly more common.

Factors have been identified that influence short-term and long-term outcomes after lung retransplantation.[71,72] Patients retransplanted for bronchiolitis obliterans syndrome

(BOS) manifest better survival than patients transplanted for primary graft dysfunction or airway complications. Generally, patients who are >2 years out from initial transplantation fare better than patients retransplanted earlier. Patients retransplanted for BOS generally demonstrate more rapid declines in airflow than patients transplanted for other indications. However, patients retransplanted in <2 years after the initial transplantation also have an even greater risk of developing BOS.[69]

It is generally accepted that patients who were mechanically ventilated immediately before retransplantation have inferior survival outcomes. More recent analysis[73] has suggested that when patients retransplanted <30 days after initial transplantation are excluded, mechanical ventilation does not remain an independent risk factor for poor outcome. However, in centers performing a high volume of retransplant operations, poorer outcomes have been observed in patients who are hospitalized, with or without the need for mechanical ventilation.

Survival after lung retransplantation may have improved over time but remains inferior to survival seen after initial transplantation. For the individual patient, retransplantation should be analyzed as a time-dependent survival risk factor. Consideration must also be given to ethical issues surrounding lung allocation to retransplantation candidates. Prioritization of younger patients in consideration for retransplantation is consistent with public preference. However, categorically placing older patients at a disadvantage is inappropriate.

Heart-lung transplantation

Patients with advanced cardiac and lung diseases not amenable to either isolated heart or lung transplant may be candidates for combined heart-lung transplantation. Most commonly, patients with irreversible myocardial dysfunction or congenital defects with irreparable defects of the valves or chambers in conjunction with intrinsic lung disease or severe PAH are considered for heart-lung transplantation.[74,75]

PAH and elevated PVR, defined as a PVR > 5 Woods units, a PVR index >6, or a transpulmonary pressure gradient 16 to 20 mm Hg, should be considered as relative contraindications to isolated cardiac transplantation. If the pulmonary artery systolic pressure is >60 mm Hg in conjunction with any of these 3 variables, the risk of right heart failure and early death is increased. If the PVR can be reduced to <2.5 with a vasodilator but the systolic blood pressure falls to <85 mm Hg, the patient remains at high risk of right heart failure and mortality after isolated cardiac transplantation. Mechanical circulatory support may be considered to improve these indices and still enable cardiac transplantation and obviate the need for heart-lung transplantation.

In most patients with pulmonary hypertension associated with right ventricular failure, isolated bilateral lung transplantation is associated with comparable or better results than heart-lung transplantation.[11,76] In the absence of objective assessment of infarcts or fibrotic changes of the right ventricle, heart-lung transplantation is usually not indicated. Exceptions may occur, such as when the heart size occupies most of the thoracic cavity and would critically limit the available thoracic volume for the lung allografts.

In patients with intrinsic cardiac diseases such as coronary artery disease, valvular heart disease, or septal defects,[77] without intrinsic myocardial dysfunction, corrective cardiac surgery with concomitant lung transplant is preferable to heart-lung transplantation. Patients with sarcoidosis involving the heart and lungs may be best managed with heart-lung transplantation.

The timing of transplantation, particularly in patients with congenital heart disease, can be challenging. However, indices of right ventricular failure such as persistent NYHA Functional Class IV symptoms on maximal medical therapy, with cardiac index of <2 liters/min/m^2 and right arterial pressure >15 mm Hg, are indications to proceed with transplant listing. Certain anomalies such as pulmonary venous stenosis or PVOD in conjunction with the need to replace the heart respond poorly to medical management and often require earlier transplant listing.

Multi-organ transplant

There is an expanding pool of potential candidates with multi-system organ dysfunction who might benefit from simultaneous lung transplant and transplantation of another solid organ. Concurrent thoracic and abdominal transplantation was reviewed more recently by Wolf et al,[78] who analyzed 122 simultaneous lung-liver transplants (typically for CF) and 41 lung-kidney transplants (typically for restrictive lung disease or pulmonary hypertension). The authors concluded such patients had high waiting list mortality at 34% and 35%, respectively, although having reached transplantation, the simultaneous procedure conferred a significantly enhanced 5-year survival at 59% and 56%, respectively. These survival figures are higher than those of lung transplantation alone (50% at 5 years in the United States; $p < 0.01$), although less than those of abdominal transplantation alone. These differences may reflect the expertise of the centers attempting such transplants. These pooled results are consistent with other small case series from the United States and Europe.[79,80]

Combined lung and kidney transplant

The most common combination of thoracic and abdominal transplantation is kidney transplantation after lung transplantation. Cassuto et al[81] reviewed the UNOS deceased donor experience and noted 362 lung transplant recipients had been listed for kidney transplant at a mean of 6.5 years after lung transplant. This statistic indicates that staged kidney transplants relatively soon after transplant are rare with most representing the failure of a second organ system secondary to the effects of calcineurin inhibitors.

When considering the overall survival benefit, kidney transplantation after lung transplantation was poorest of the solid-organ combinations and related to the lung allograft, with 80% dying with a functional kidney graft. A living-related kidney transplant effectively doubles the survival compared with a deceased donor with a longer wait time. Lonze et al[82] subsequently produced a similar analysis, reinforcing the high waiting list mortality and the need to consider living-related and extended donor criteria kidneys to optimize access to transplantable kidneys. Most lung transplant recipients with end-stage renal disease do not survive to get a cadaveric kidney, and the impact of the renal failure on lung function is a significant component of the patient's respiratory decline.

Combined lung and liver transplant

The referral of lung transplant candidates with advanced liver and lung disease is increasing. In some instances, the liver and lung disease are part of the same disease process, such as in CF and A1ATD, but in other patients, the disease process affecting each organ is separate. The information available regarding combined liver-lung transplant is derived from case series and the UNOS database, and the number of cases currently reported is small (<100).[79,80,83–87] Based on the information available, candidates for combined lung-liver transplant should meet lung disease–specific criteria for lung transplant listing and have advanced liver disease as demonstrated by biopsy-proven cirrhosis and a portal gradient >10 mm Hg. Combined liver-lung transplant should not be considered in patients with albumin <2.0 g/dl, international normalized ratio >1.8, or the presence of severe ascites or encephalopathy.

In some patients with less severe liver or lung disease, listing for a combined transplant may be appropriate if post-transplant organ dysfunction would be anticipated if the patient were to receive either single organ alone. In this situation, multiple factors may influence the decision regarding combined transplant or liver or lung transplant alone, including anticipated waiting time for the combined and single organ, anticipated level of liver or lung dysfunction after undergoing a single-organ transplant, amount of bleeding expected in patients with liver disease, rate of expected progression of the liver or lung disease after transplantation of the other organ, and presence of comorbidities that could complicate the postoperative recovery of the combined transplant recipient.

Esophageal dysfunction/scleroderma

Lung transplantation for systemic sclerosis (SSc) remains controversial. Despite previous inclusion as an acceptable indication for transplant in the ISHLT guidelines for lung transplantation,[1] many centers continue to consider SSc a contraindication because of concerns about esophageal dysmotility and gastroparesis increasing the risk of aspiration. Two more recent reports suggest that patients with SSc, even in the presence of esophageal disease, have similar 1-year and 5-year survival rates as other patients with ILD.[88,89] Rates of acute rejection were increased in patients with SSc in one report[88] and no different in the other.[89] Freedom from BOS was similar between the 2 groups in both reports. Carefully selected patients with SSc can undergo successful lung transplantation. Care to rule out intrinsic renal disease and measures to control esophageal dysmotility post-transplant with medical or surgical therapy are warranted.

Adenocarcinoma in situ and minimally invasive adenocarcinoma

Recommendations for referral and listing:

- Diffuse parenchymal tumor involvement causing lung restriction and significant respiratory compromise.
- Significantly reduced quality of life.
- Failure of conventional medical therapies.

With regard to transplantation, the following evaluation and management is suggested:

- Before listing for lung transplantation, the tumor should be biopsied and/or tissue from a previous resection thoroughly examined to exclude more invasive disease.
- Patients should undergo thorough staging with chest and abdominal CT, brain magnetic resonance imaging, bone scanning, and positron emission tomography. These tests should be repeated regularly (every 3 months is suggested) to detect metastases that would result in removing the patient from the waiting list.
- At the time of lung transplantation, a backup recipient should be available so that if mediastinal nodal involvement or spread beyond the pleura is detected, the operation should be discontinued, and the substitute recipient should receive the lungs.

The rationale of lung transplantation for adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), either pure lepidic growth (AIS) or predominant lepidic growth, was developed when these tumors were referred to as diffuse bronchioloalveolar carcinoma (BAC). Regardless of nomenclature, lung transplant has been performed based on the tumor being confined to the lungs. Although survival after resection for localized disease is quite good, the results of chemotherapy for diffuse, bilateral disease is poor with survival beyond 2 years from the time of diagnosis rare. Some centers have performed lung transplantation in patients with diffuse BAC.[90,91]

A report by de Perrot et al[90] in 2004 characterized the international experience with lung transplantation for BAC. The survival of patients undergoing lung transplantation and heart-lung transplantation for BAC was 39% at 5 years and 31% at 10 years (26 patients) compared with survival of 53% at 5 years and 31% at 10 years reported by the ISHT in the 2013 Registry report.[52]

A major concern about lung transplantation for BAC is the incidence of recurrent tumor. The survey by de Perrot et al[90] found that of the 22 patients who survived the

operation, 13 (59%) developed a recurrence of BAC 5 to 49 months after transplantation. Zorn et al[91] also saw a high recurrence rate in the small series, where tumor recurred in 6 of 8 patients. One feature of the recurrences is the demonstration of their recipient origin,[92,93] suggesting that the mechanism of the recurrence may be contamination of the donor lungs from retention of malignant cells in the airways after excision of the recipient lungs.

In the current era, the survival of patients after lung transplantation for BAC based on the small worldwide experience appears to be marginally inferior to survival after lung transplantation for other conditions. Nevertheless, compared with the natural history of diffuse and bilateral BAC and the ineffectiveness of chemotherapy, survival after lung transplantation is far superior to that of the natural history of the disease, despite high recurrence rates of BAC after lung transplantation.

Pediatric candidate selection

Timing of referral (similarities with adult candidates):

- A progressive lung disease on maximal medical therapy.
- A short predicted life expectancy.
- A poor quality of life.[94,95]
- Because the waiting times, particularly for smaller children, are longer, potential candidates should be referred to a transplant center as early as possible.
- Appropriate child and family support in place. It is essential that the child, in particular, commits to the transplant procedure and close long-term follow-up.[94]

Appropriate selection of pediatric (<18 years old) candidates and timing for listing is crucial to maximize the overall survival of children and adolescents with end-stage lung disease undergoing lung transplantation.[94–96] Assessment of pediatric candidates for lung transplantation presents a specific challenge—recognizing unique aspects concerning the underlying lung disease, surgical approaches, effects of immunosuppressive treatment and infections on the developing immune system, and the child's somatic growth.[94]

CF lung disease is the leading indication for lung transplantation in pediatric patients, but indications vary considerably by age group.[94,95,97] In infants, congenital heart disease is the main indication. In children 1 to 10 years old, CF and IPAH are the most frequent underlying diseases.[97] In general, absolute medical and surgical contraindications for children undergoing lung transplants are mostly extrapolated from adult data and are therefore similar; however, relative contraindications may vary from center to center, such as chronic pre-transplant pulmonary infection with specific pathogens (i.e., *B cepacia* complex). Because non-adherence is a leading cause of chronic graft dysfunction in adolescent transplant recipients, potential non-adherence to medical therapy needs to be addressed at the transplant assessment. Mechanical ventilation and ECLS as a bridge to transplantation in children is considered a relative contraindication in some centers, but more recent data regarding the use of ECLS in pediatric cases show that such pediatric candidates might not generally be disadvantaged if selected very carefully. Some negative predictors of survival in adult lung transplant recipients may be less relevant in the pediatric setting.

Specific issues regarding the selection and assessment of children for a rarely performed living donor lobar lung transplant are beyond the scope of this document. Living donor lobar lung transplants remain an acceptable therapy option in experienced centers for pediatric patients unlikely to survive on the waiting list.[98]

Removal from the waiting list

One of the more vexing clinical decisions surrounding recipient management regards the patient currently listed for a transplant but in whom clinical circumstances have changed that raise concerns about the suitability of the patient's continued transplant candidacy. Although by definition all of these patients were at one time considered appropriate transplant candidates, potential recipients must be continually monitored for changes in status that would diminish the advisability of a transplant. It is imperative that all wait-listed patients be regularly evaluated, subjectively and objectively, ensuring that candidate selection is not simply a one-time static determination but rather a continuous process. This is especially important in patients bridged by mechanical ventilation and/or ECLS, who more frequently develop changes in clinical status that would preclude the likelihood of an acceptable transplant outcome.

Development of any of the above-discussed absolute or relative contraindications should prompt a reevaluation of a patient's transplant candidacy. In terms of removal from the waiting list, either temporarily or permanently, the most common reasons are important changes in weight or rehabilitation status, renal failure, a new virulent pathogen unresponsive to anti-microbial therapy, demonstrable medical non-compliance, or patient ambivalence toward transplantation. Positive developments that should lead to consideration of removal from the waiting list include response to medical therapy (most common in patients with pulmonary hypertension) and/or improvement in quality of life status that would alter the risk/benefit equation away from transplantation at the current time.

Conclusions

The current 2014 consensus document represents a continuum of thought processes developed previously in the 1998 and 2006 Guidelines but extends the scope of referral and active listing criteria to consider pediatric recipients, mechanical bridge to transplant in particular with ECLS, and retransplantation to fine-tune organ donor allocation and maximize community benefits of a scarce resource. In effect, the Writing Group's response to these challenging new areas exemplifies the natural tendency of clinicians working in this area to extend the envelope of care to patients once thought unsuitable for lung transplantation, while collecting prospective data regarding situations where

known risk outweighs putative benefit, knowledge of which decision making threshold is the cornerstone of good clinical practice in an ever-changing field. Although community expectation may partly drive resource allocation and behavior, it is also true that the transplant community has the responsibility to choose wisely, and where individual experienced centers demonstrate capability with higher risk patients, good practice principles should ensure that overt extrapolation beyond sensible boundaries should not occur in less experienced centers.

Finally, these are international guidelines, and each reader perforce must be cognizant of local referral systems and organ allocation systems, which vary considerably throughout the world. As a case in point, the still evolving LAS in the United States has changed irrevocably the landscape of lung transplantation therein and set a benchmark for national organ allocation, which tool has perhaps altered clinician referral and listing behavior, as a result of which the recipient community collectively may obtain a greater survival benefit.

Disclosure statement

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