Guidelines for the selection of lung-transplant candidates

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Purpose of review
Lung transplantation can improve survival and quality of life in select patients with end-stage lung disease. Because of the limited availability of donor lungs and limited post-transplant survival of recipients, selection of candidates that are most likely to benefit from transplantation is of utmost importance.

Recent findings
Since the revision of 2006 international guidelines for the selection of lung-transplant candidates, new literature has emerged to improve our understanding of disease-specific prognosis and the impact of nonpulmonary comorbidities on post-transplant outcomes. Further published data on the cumulative effect of multiple comorbidities have allowed transplant professionals to better define the high-risk recipient. Applying each of the above principles to the evaluation of potential lung-transplant recipients will allow optimal allocation of donor organs to recipients that are most likely to benefit.

Summary
This article will review the most recent literature in the field in order to provide an updated framework for the optimal selection of candidates for lung transplantation.

Keywords
candidates, lung transplantation, outcomes, selection

INTRODUCTION

Lung transplantation is a therapeutic option for patients with end-stage lung disease who have failed all other forms of medical or surgical therapy [1]. There is strong evidence supporting the quality of life and survival benefits of lung transplantation in appropriately selected recipients [1–3]. Despite advances in the field, lung transplantation remains a less than perfect treatment strategy resulting in a median post-transplant survival of less than 6 years and the need for lifelong immunosuppression, which confers risk of infection and systemic side effects [4▪▪]. The selection of candidates for lung transplantation requires careful consideration of both expected benefit to the intended recipients alongside the limitations of a scarce resource. Although the number of transplants performed has increased yearly over the past 20 years, the estimated number of patients who die of lung disease outweighs the number of suitable donor lungs available for transplant both in the USA and worldwide by a ratio of greater than 1000 : 1 [4▪▪,5,6]. As such there rests an ethical responsibility to allocate these limited resources to candidates that have the best likelihood for a successful outcome. Therefore, candidates for transplant should have severe enough disease that transplant confers an expected survival benefit, but not be so ill that they may not survive the waiting period for transplant or have unacceptable risk of postoperative mortality.

The International Society of Heart and Lung Transplantation put forth guidelines for the selection of lung-transplant candidates in 2006 based primarily on review of retrospective registry data, predictive models and expert consensus opinion, as few randomized clinical trials exist with regards to this topic [7]. Since this time, there have been new data with regards to disease-specific indications for transplant as well as more information on outcomes of patients previously thought to be at higher risk for increased post-transplant mortality. In the USA, the implementation of the Lung Allocation Score (LAS) has prioritized recipients at greatest risk of death on

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KEY POINTS

- Disease-specific mortality predictors should be used to determine urgency of transplant.
- Early evaluation of transplant candidates may provide opportunity to modify risk factors that could impact post-transplant outcomes.
- Patients with the most urgent need for transplant, such as high LAS scores or need for mechanical ventilation, are also at risk for worse post-transplant outcomes.

wait list in conjunction with expected transplant benefit and is being evaluated for urgent candidates in Eurotransplant [8,9▪]. After briefly summarizing the guidelines previously put forth in 2006 (given below), this article reviews recently published literature that may impact selection of candidates and future revisions of these guidelines.

Summary of The International Society for Heart and Lung Transplantation (ISHLT) 2006 disease-specific indications for transplantation [7]:

New York Heart Association (NYHA) class III or IV symptoms in addition to:

(1) COPD
  (a) Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) index greater than 7
  (b) Acute hypercapnea
  (c) Pulmonary hypertension
  (d) Forced expiratory volume in 1 s (FEV_1) below 20% and diffusing capacity for carbon monoxide (DLCO) below 20%
(2) Cystic fibrosis
  (a) FEV_1 less than 30%
  (b) Frequent exacerbations
  (c) Hypercapnea or hypoxia
  (d) Pulmonary hypertension
  (e) Recurrent hemoptysis or pneumothorax
(3) Idiopathic pulmonary fibrosis
  (a) DLCO less than 40%
  (b) Ambulatory hypoxia
  (c) 10% or greater decline in forced vital capacity (FVC) over 6 months
(4) Pulmonary arterial hypertension
  (a) Progression on maximal medical therapy
  (b) 6 minute walk test (MWT) less than 350 m
  (c) Cardiac index (CI) below 2 l/min
  (d) right atrial pressure (RAP) above 15 mmMg

Summary of 2006 ISHLT contraindications to transplantation [7]:

(1) Absolute
  (a) Malignancy in past 2 years
  (b) Noncurable chronic infection (HIV, hepatitis B)
  (c) Medical noncompliance
  (d) Lack of social support system
  (e) Active or recent substance use
  (f) Advanced dysfunction of another organ system
  (g) Chest wall deformity
(2) Relative
  (a) Age greater than 65
  (b) Critical condition
  (c) Limited functional status
  (d) Obesity
  (e) Severe osteoporosis
  (f) Mechanical ventilation
  (g) Colonization with highly resistant organisms

DISEASE-SPECIFIC INDICATIONS FOR TRANSPLANT

The timing of referral and listing for lung transplantation depend not only on disease severity but also on anticipated rate of deterioration and predicted mortality. Given a median survival of 5–6 years, in general, most candidates for lung transplant should have a pretransplant predicted mortality that meets or exceeds their estimated post-transplant survival.

CHRONIC OBSTRUCTIVE LUNG DISEASE

Worldwide, chronic obstructive lung disease (COPD) remains the most common indication for lung transplantation, accounting for approximately 35% of all transplants performed [4▪▪]. As a chronic disease generally characterized by slow progression, candidate selection for COPD requires careful consideration of mortality predictors, as many patients may not derive a survival benefit from transplant on the basis of low FEV_1 alone, despite severe symptoms of disease [10,11]. Predictors of early mortality from COPD include acute hospitalizations for hypercapnea, a BODE index score of above 7, patients with combined FEV_1 and DLCO of less than 20%, or pulmonary hypertension despite oxygen therapy [12–15]. The 2006 ISHLT guidelines reflect an assessment of these predictors as factors that would predict a survival benefit with transplantation.

More recent studies have focused on the societal and quality-of-life considerations that may impact selection of candidates with COPD. Eskander *et al.* [16▪] evaluated the magnitude of improvement in quality of life after transplant based

on pretransplant BODE index. They noted dramatic improvements that were similar in magnitude for patients with pretransplant BODE scores of 5–6 or 7–10, despite differences in predicted post-transplant survival between groups [16▪]. Although the quality-of-life benefit might lead one to consider transplant as a therapeutic option in patients who may not otherwise receive a survival benefit, this rationale must be balanced against societal allocation of a limited resource. Thabut *et al.* [11] demonstrated that the survival benefit of transplant for COPD depends not only on pretransplant recipient characteristics but also on the choice of procedure, with general results suggesting that the survival benefit of lung transplant is greater with double lung transplant (DLT) than with single lung transplant (SLT) in COPD [11]. Subsequently Munson *et al.* [17▪▪] developed a Markov model to compare the effect of single vs. bilateral lung-transplant strategies on wait list outcomes among patients listed for lung transplantation. Although the SLT strategy resulted in fewer wait list deaths with similar post-transplant survival in both groups, the strategy that maximized survival depended upon the relative benefit of BLT vs. SLT for COPD, donor interval, and wait list size.

Since COPD remains a leading indication for lung transplantation, optimal selection of these patients is important to maximize utilization of organs while maintaining the greatest benefit for those who need it the most. If future advances substantially increase the donor organ supply and improve post-transplant outcomes, then patients with less severe COPD could potentially derive a benefit as well.

CYSTIC FIBROSIS

Although advances in medical management over the past 20 years have substantially improved life expectancy from a median age of 26 to almost 40 years in patients diagnosed with cystic fibrosis (CF), transplantation remains an important option in the management of these patients [18,19]. The heterogeneous nature of this disease has provided challenges to reliably determine optimal timing for transplantation. Despite the development of both simple and complex multivariate models using data from the CF registry to predict CF-related mortality, these models have shown limited utility in validation studies, with positive predictive values of less than 50% [20–22]. The ISHLT guidelines identify factors from these studies that, when taken together, warrant transplant referral such as FEV_1 less than 30%, frequent exacerbations requiring antibiotics, hemoptysis, hypercapnea, and hypoxia, and acknowledge that the timing of transplant listing must 'take into account several indicators of disease severity'. More recently, Loeve *et al.* [23▪] assessed a 4-category Severe Advanced Lung Disease – computed tomography (CT) scan scoring system on transplant wait list mortality and found that an inflammatory/infectious pattern correlated with survival and added to the predictive value of the LAS. As with prior predictive models, it remains to be determined whether this radiographic scoring system can be further validated to be used as a reliable tool in determining the timing of transplantation.

Recent studies have examined the effects of CF-associated comorbidities such as *Burkholderia* colonization and diabetes on post-transplant mortality. Historically, CF recipients colonized with *Burkholderia cepacia* complex (BCC) species had been excluded from transplant based on studies from the 1990s demonstrating poor outcomes [1]. However, the recent identification of distinct strains within the BCC complex has led to the observation that post-transplant mortality in CF recipients with *Burkholderia* varies by species and strain [24,25]. In two separate studies, recipients with non-*Cenocepacia* BCC had comparable survival to uninfected recipients, suggesting that these patients could be transplanted safely [24,25]. Recipients with *B. gladioli* and *B. cenocepacia* had exceedingly worse outcomes, although strain-specific variations may exist. In a small series of 43 patients with CF, Van Meerkerk *et al.* [26] noted markedly increased mortality (44 vs. 6%) in transplant recipients with pre-existing diabetes. These findings need to be further confirmed in larger multicenter studies, and potentially correlated with other measures of diabetic control and complications. Taken together, these studies continue to highlight the ongoing challenge in determining optimal timing of transplantation for this group. It is important to recognize that despite the challenges of selecting the proper timing for transplantation in CF patients, this group as a whole enjoys some of the best outcomes from lung transplantation [4▪▪]. The reason for this is not entirely clear but perhaps is in part due to the relatively younger age of recipients.

INTERSTITIAL LUNG DISEASE

With few effective treatments currently available, idiopathic pulmonary fibrosis (IPF) is the second most common indication for transplantation worldwide [4▪▪]. This progressive disease may behave in one of the several patterns including a chronic progressive course, one with periods of stability followed by acute sudden decline, and an

accelerated rapidly progressive course [27]. With a median survival of only 3 years from time of diagnosis and an unpredictable clinical course, ISHLT guidelines recommend referral for transplantation at the time of diagnosis, and recommended early listing for transplantation based on the following predictors of mortality: DLCO of less than 40% predicted, desaturation with ambulation, and greater than 10% decline in FVC over 6 months [7]. In the US the implementation of the LAS has prioritized patients with IPF, dramatically reducing the wait list mortality in this population [28]. Richards *et al.* [29▪▪] recently developed profiles of plasma protein expression to better stratify patients at increased risk of early death. Whereas these findings have not been validated in other clinical trials, such profiles could add an important prognostic tool in determining the timing of transplant among patients with IPF [29▪▪]. Finally, clinical trials of new agents such as pirfenidone and the tyrosine kinase inhibitor BIBF-1120 may slow the progression of IPF by a modest degree, although their impact on mortality remains to be determined [30▪▪,31▪▪]. There are less data about the timing of transplantation for other interstitial lung diseases, although in general patients with NYHA class III–IV symptoms with objective decline in lung function may be appropriate candidates.

PULMONARY HYPERTENSION

Although advances in the medical management of pulmonary arterial hypertension has doubled survival in patients diagnosed from pulmonary hypertension, registry data suggest that median survival in the USA remains less than 10 years from time of diagnosis [32,33▪]. However, unlike other indications for transplant, the LAS has not reduced wait list mortality in this group of candidates [32]. It is also important to note that this group of patients has the highest perioperative mortality of any group following transplantation and are the most likely to develop primary graft dysfunction during the perioperative period [4▪▪]. With these challenges taken together with the recent advances in medical treatment, fewer patients with pulmonary hypertension are transplanted currently compared to prior decades. Furthermore, because this was the smallest group of patients to receive lung transplants, few data existed to best identify the determinants for pre and post-transplant mortality [7]. This in turn made the modeling for the LAS perhaps less well refined for this group of patients compared to others. The ISHLT guidelines currently recommend listing for transplant if patients have 6MWT less than 350 m, CI less than 2 l/min, or RAP greater than 15, and failing therapy despite maximal medical management [7]. Since these guidelines were published, researchers have developed and validated a more contemporary prognostic equation that incorporates the above and additional factors including renal function, DLCO, portal hypertension, and heart rate to more accurately predict survival [34–36]. Incorporation of these tools into revisions of urgency-based transplant lists such as the LAS may reduce deaths on the wait list in this group of patients. In the interim, in the US, if a lung-transplant team does not feel that a patient's LAS score accurately reflects his/her severity of illness, the team can appeal to the United Network for Organ Sharing Thoracic Board to potentially raise the score to the 90th percentile.

POTENTIAL BARRIERS TO TRANSPLANTATION

Since the 2006 ISHLT guidelines were published, several retrospective studies have examined outcomes of patients who underwent transplantation with previously stated contraindications. In particular, new literature regarding age, renal disease, obesity, coronary artery disease (CAD), and gastric motility may provide additional insights about post-transplant outcomes in these populations. United Network for Organ Sharing (UNOS) registry analysis of the impact of age on post-transplant survival from 1999 to 2006 showed that 1-year mortality increased by 37% above age 60 and more than doubled in recipients over the age of 70 [37]. Furthermore, less than one-third of the elderly recipients returned to a normal functional status at last follow-up. Although interpretation of these data is limited by significant baseline differences among age cohorts, the overall outcomes suggest that transplantation in elderly should continue to be approached with a careful assessment of risk and anticipated benefit. Arnaoutakis *et al.* [38▪] conducted a single-center study using the Rifle Criteria (risk, injury, failure, loss, end stage) (RIFLE) grading system for acute kidney injury (AKI) and found greater than 50% post-transplant mortality in recipients transplanted with RIFLE-F severity of AKI. Although the study noted a 30% 1-year mortality in recipients RIFLE-I severity (Cr increased x2), a larger sample size may be needed to determine if these findings are statistically significant.

MODIFIABLE RISK FACTORS

Sherman *et al.* [39▪] reported their single-center experience with lung transplantation in patients with CAD, demonstrating equivalent cardiac,

pulmonary outcomes and 5-year mortality in a cohort of 27 recipients with critical discrete coronary lesions and normal ejection fraction compared to matched controls without CAD. Although prospective studies are needed to further confirm these findings, the larger cohort size and assessment of longer-term outcomes provide stronger data to suggest that select candidates with revascularized CAD can have acceptable outcomes after lung transplant. Several independent groups have demonstrated the negative impact of obesity and underweight status on post-transplant mortality, with progressively steeper effects in recipients with BMI above 30 [40,41]. These findings are not meant to be interpreted as strict exclusion criteria for transplant, but rather may represent opportunities to optimize comorbidities during the pretransplant period to maximize post-transplant survival. Baldwin *et al.* [42▪] examined 6000 adults who underwent lung transplantation from 2000 to 2008, and found that hypoalbuminemia, particularly in CF and IPF recipients, correlated with increased mortality after transplant. Further prospective studies are needed to determine whether correction of hypoalbuminemia prior to transplant could improve post-transplant outcomes. Collectively these data highlight the need for early evaluation of transplant candidates to identify and potentially optimize comorbidities that may impact post-transplant outcomes.

HIGH-RISK RECIPIENTS

The implementation of the LAS has allowed patients previously too sick to survive to transplant to receive the highest wait list scores [8]. As such, there is a growing body of retrospective literature on the outcomes of recipients that are hospitalized in ICUs, receiving mechanical ventilation and extracorporeal membrane support. Unadjusted retrospective analyses of ISHLT registry data have consistently identified mechanical ventilation as a risk factor for post-transplant mortality, with unadjusted 1-year survivals of 62% compared with 1-year survival of 80% among all recipients [4▪▪,43,44▪]. Mason *et al.* [43] used propensity score analyses to account for differing baseline characteristics between these cohorts and noted persistently worse outcomes for patients on mechanical ventilator support. Increasingly, extracorporeal membrane support has been used as a bridge to lung transplantation as an alternative to mechanical ventilation. Although separate single-center studies of lung transplant recipients bridged to transplant with extracorporeal membrane oxygenation (ECMO) by Bermudez *et al.* [46▪], and Lang *et al.* [45] report post-transplant 1-year survival ranging from 60 to 74%, cumulative ISHLT registry data suggest a 50% 1-year mortality in ECMO recipients [4▪▪,45,46▪]. Other emerging studies of 'awake' ECMO, with potential for concomitant physical rehabilitation, have demonstrated feasibility, and in one study, superior outcomes compared with bridged-to transplant with conventional mechanical ventilation [47▪,48,49▪]. Whereas data in recent era are encouraging, extrapolation of all of these studies to clinical practice is severely limited by the small sample size, retrospective, single-center experiences, and baseline differences in the pretransplant characteristics between control and treatment cohorts. Furthermore, the overall inferior outcomes in the face of limited donor availability suggests that the use of rescue therapies to bridge to transplant can not be routinely considered until further improvements in post-transplant outcomes are demonstrated.

The concept of a 'high-risk threshold' at which a patient's severity of illness significantly compromises their post-transplant survival has been further demonstrated in studies of the LAS scoring system and others. Several studies have shown that extremely high LAS scores (>60) are associated with worse post-transplant outcomes, although a net survival benefit for the individual is preserved [2,50▪,51]. Russo *et al.* developed a risk stratification system based on parameters entered in the UNOS database which assesses the cumulative impact of multiple predictors of mortality [44▪]. In this model, which assigned point scores to mortality predictors such as age, steroid dependence, and hospitalization, the high-risk group had 56% 1-year survival compared to 80% 1-year survival in the overall cohort. Although further validation of this model is needed, it represents an important attempt to objectively define 'the high-risk candidate.'

CONCLUSION

Lung transplantation can be a life-saving option for patients with end-stage lung disease in appropriately selected recipients. However, despite reductions in wait list mortality, there still remain far fewer donors than candidates in need of lung transplantation. As urgency-based transplant wait lists prioritize patients that are at increased risk for post-transplant mortality, one must also weigh the judicious allocation of a donor lungs against an individual patient's needs to best use this limited resource. An understanding of disease-specific prognostic factors and other comorbidities that may affect post-transplant survival is critical in determining the patients' expected survival benefit and thus, suitability for transplant. Future studies are needed

to further validate predictive models of pretransplant risk factors on disease-specific and posttransplant mortality, and prospectively examine the impact of pretransplant risk factors on posttransplant outcomes.

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Conflicts of interest

The authors have no relevant financial disclosures or conflicts of interest.

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