Lung transplantation: indications and contraindications

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Abstract: The selection of appropriate recipients for lung transplantation is an evolving discipline. As experience with the procedure has developed over the last decades, the identification of transplant candidates has also changed as transplant centers strive to safely provide the therapy to as many patients possible. The International Society for Heart and Lung Transplantation (ISHLT) has developed three editions of recipient selection guidelines. Published in 1998, 2006, and 2015, these guidelines represented the best information relevant to the appropriate selection of lung transplant candidates. A discussion of areas supported by the most robust scientific data will be undertaken, but in many aspects of recipient selection, there is a paucity of data upon which to rely. Therefore, it is ultimately the prerogative and responsibility of individual centers to determine, after carefully weighing the best evidence available, whether a patient is deemed a suitable candidate at a specific program. All possible indications and contraindications for transplantation will be reviewed with attention also given to the appropriate timing of referral and listing of patients with advanced lung disease to a transplant center.

Keywords: Interstitial lung disease (ILD); chronic obstructive pulmonary disease (COPD); pulmonary arterial hypertension; cystic fibrosis (CF)

"Because donated organs are a severely limited resource, the best potential recipients should be identified. The probability of a good outcome must be highly emphasized to achieve the maximum benefit for all transplants."

OPTN/UNOS Ethics Committee General Considerations in Assessment for Transplant Candidacy. HRSA; 2010.

This chapter will discuss lung transplant indications and contraindications, representing a consensus of expert opinion developed over the years. The International Society for Heart and Lung Transplantation (ISHLT) has developed three editions of recipient selection guidelines. Published in 1998, 2006, and 2015 (1-3), these guidelines represented the best information relevant to the appropriate selection of lung transplant candidates. Although an effort will be made to include a discussion of areas supported by robust scientific data, as in many aspects of recipient selection, there is a paucity of data upon which to rely. Therefore, it is ultimately the prerogative and responsibility of individual centers to determine, after carefully weighing the best evidence available, whether a patient is ultimately deemed a suitable candidate at a specific program.

Recipient considerations

Lung transplantation should be considered for adults with advanced lung disease who meet the following general criteria:

(I)   High (>50%) risk of death due to lung disease within 2 years if lung transplantation is not performed;

(II) High (>80%) likelihood of surviving at least 90 days after lung transplantation;

(III) High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided there is adequate graft function.

Contraindications

Lung transplantation is a complex therapy with a significant

risk of perioperative morbidity and mortality. Therefore, it is prudent to consider all contraindications and comorbidities. The following lists are not intended to cover all possible clinical scenarios, but do 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 skin cancers other than melanoma that have been treated appropriately. However, a 5-year disease-free interval should be demonstrated in most cases, particularly for those with a history of hematologic malignancy, sarcoma, melanoma, or cancers of the breast, bladder, or kidney. Unfortunately, for some 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;

❖ Poorly controlled significant dysfunction of another major organ system (e.g., heart, liver, kidney or brain) unless a multi-organ transplant is being considered;

❖ Uncorrected coronary artery disease with end-organ ischemia or dysfunction and/or coronary artery disease not amenable to revascularization;

❖ An unstable medical condition, including but not limited to acute sepsis, myocardial infarction, and liver failure;

❖ Uncorrectable bleeding disorder;

❖ Poorly controlled infection with a virulent and/or resistant microbes;

❖ Evidence of active *Mycobacterium tuberculosis* infection;

❖ A chest wall or spinal deformity expected to cause severe restriction after transplantation;

❖ Class II or III obesity (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 psychological issues likely rendering the patient unable to comply with a complicated medical regimen;

❖ Inadequate social support system;

❖ Functionally limited with inability to participate in a rehabilitation program;

❖ A history of illicit substance abuse or dependence (e.g., alcohol, tobacco, marijuana, or other illicit substances). Convincing evidence of risk reduction behaviors (such as participation in therapy for substance abuse and/or dependence) should be demonstrated before lung transplantation is considered. Periodic blood and urine testing can be utilized to verify abstinence.

Relative contraindications

❖ Age over 65 years in association with low physiological reserve and/or other relative contraindications. Although there cannot be endorsement of an upper age limit as an absolute contraindication, adults older than 75 years of age are less likely to be candidates for lung transplantation. Although age alone should not exclude a patient from receiving a lung transplant, increasing age often is associated with comorbid conditions that are either absolute or relative contraindications;

❖ Class I obesity (BMI 30.0 to 34.9 kg/m^2), particularly truncal (central) obesity;

❖ Significant malnutrition;

❖ Significant 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 with resistant or highly virulent pathogens;

❖ For candidates infected with hepatitis B and/or C, lung transplant can be considered in patients without significant clinical, radiological, or biochemical signs of cirrhosis or portal hypertension and who are stable on appropriate therapy. Lung transplantation in hepatitis B and/or C candidates should be performed in centers with experienced hepatology units;

❖ For patients infected with human immunodeficiency virus (HIV), lung transplant can be considered in those with controlled disease with undetectable HIV-RNA, and adherent with anti-retroviral therapy (cART). 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. In order for patients with these infections to be considered suitable transplant candidates, 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 due to these infections;

❖ Coronary artery disease burden sufficient to put the candidate at risk for end-organ disease after lung transplantation. The preoperative evaluation, type of coronary stent used, and extent of coronary artery disease considered acceptable varies among transplant centers;

❖ Extrapulmonary conditions that have not resulted in significant organ damage, such as diabetes mellitus, systemic hypertension, epilepsy, central venous obstruction, peptic ulcer disease, or gastroesophageal reflux should be well-controlled before transplantation.

Special surgical considerations

Previous surgery

Recommendations

❖ Previous surgery is not a contraindication to lung transplantation;

❖ Previous pleurodesis can present operative challenges 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, re-exploration and renal dysfunction are to be expected in patients with previous chest procedures. This may be exacerbated by longer cardiopulmonary bypass times;

❖ In otherwise well selected patients, medium and long-term outcome is not affected by previous chest procedures;

❖ Conversely, older patients (>65) with other co-morbidities 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) (5). Surgery may be coincidental, for instance previous coronary artery bypass grafting (CABG), but usually related as a diagnostic or therapeutic step in pre-transplant management. Examples of the latter range from simple video-assisted thoracoscopic (VATS) 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. There have been small series (14 and 18 patients) (5,6) describing successful lung transplant after chest surgery. The largest recent experience (7) described 238 patients, although 115 merely had earlier chest drain insertion. A number of accounts concentrate on conditions such as LAM (5) or CF (8) where 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 higher blood loss and early post-operative morbidity such as renal dysfunction and primary graft dysfunction. There is also a higher incidence of phrenic nerve damage, chylothorax and re-exploration. Not surprisingly, where multivariate analysis can be applied (4), the combinations of age >65 years, pulmonary hypertension, transfusion >20 units and prolonged cardiopulmonary bypass are all predictors of early death. Previous cardiac surgery appears to have little specific effect, but reported experience is very small.

The specific issue of previous LVRS is examined in several papers. Early experience indicated that LVRS had no effect (9), but a more recent account (10), where 25 out of 177 patients transplanted for chronic obstructive pulmonary disease (COPD) had undergone previous LVRS had poorer outcomes. There were the expected higher rates of bleeding and early morbidity, but also a 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 the acutely decompensating patient until a suitable organ is available (11). Ideally, bridge to lung transplantation should be applied with the intent to prolong both the pre-transplant life expectancy of patients increasing the chances to receive a lung transplant and improving the likelihood of a successful post-transplant outcome by improving pre-transplant clinical stability. 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 prior to initiating bridge therapy. Less favorable outcomes are generally seen in those patients who present *de novo* with respiratory failure and are placed on a mechanical support system without the benefit of having 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 (12-16), but ventilated patients are particularly susceptible to ventilator-induced lung injury and ventilator-associated pneumonia and requires patients to be bed-bound and often sedated, which reduces their ability to undergo adequate physiotherapy. This can lead to severe deconditioning and may compromise their suitability for transplantation. Thus, while 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 1980's and 1990's was discouraging with a high mortality rate and a high incidence of complications associated with the application of ECLS (17). In recent years, substantial improvements in the ECLS technology 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 physiological need with significantly less morbidity and complications (11-13,17,18).

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 (17-23). 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 both in the pre and post-transplant phase and is associated with important complications (bleeding, vascular access problems, infection). However, it should be noted that the transplant benefit is likely higher 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 utilizing 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 side effects of mechanical ventilation, rather than as a rescue treatment for patients' refractory to mechanical ventilation. Fuehner and colleagues (23) have published one of the first reports showing that in patients bridged to lung transplant with ECLS the post-transplant survival rate 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 (23). In a recent analysis of the UNOS data, 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 those who were transplanted off a ventilator.

Indications and contraindications to ECLS as a bridge to transplant cannot be firmly established as only relatively small case series have been published to date. However, recommendations for the use of ECLS have been published (11,13).

ECLS is effective in supporting potential recipients with advanced respiratory failure and to improve patients' clinical stability, which should ultimately improve post-transplant outcomes. Clinical advancements in this field are needed, as the mortality rate of patients on the lung transplant waiting list is still in the range of 20% (24). Bridging to

transplant using ECLS requires ongoing assessment of the potential recipient for candidacy as frequently neurologic events, organ failure and infectious complications preclude candidacy for transplantation.

Disease-specific indications and considerations

IPF

Indications

Interstitial lung disease (ILD), and specifically idiopathic pulmonary fibrosis (IPF), carries the worst prognosis among the common disease indications for lung transplantation. Worldwide changes in donor lung allocation, including the Lung Allocation Score (LAS) in the USA and in 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 (25). In the most recent American Thoracic Society (ATS) 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 (26). The evidence reviewed here will focus on IPF as the most common and life-threatening subtype of ILD, while recognizing that fibrosing nonspecific interstitial pneumonia (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 2–3 years from diagnosis, and only 20–30% patients survive more than 5 years after diagnosis (26,27). This underscores the importance of early referral of IPF patients so that listing and transplantation can be achieved rapidly in the setting of an unexpected decline (28).

Prognostic factors in IPF have recently been reviewed in detail (26) and consistent clinical predictors of worse survival include older age, dyspnea, low or declining pulmonary function (28-31), pulmonary hypertension, concomitant emphysema, extensive radiographic involvement, low exercise capacity or exertional desaturation (28,32), and usual interstitial pneumonitis (UIP) on histopathology. Clinical prediction models such as the clinical, radiologic, and physiologic (CRP) score have not been widely used in practice (33). Also, du Bois and colleagues assessed numerous risk factors in a large cohort of IPF patients and developed a practical 4-item risk scoring system, which

includes age, respiratory hospitalization, percent predicted FVC, and 24-week change in forced vital capacity (FVC) (30). If validated, particularly in IPF patients 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 (34,35). 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.

CF

Indications

Transplantation should be considered for suitable CF patients who have less than a 50% 2-year predicted survival and whom have functional limitations classified as New York Heart class III or IV. Predicting survival using objective data, however, has been difficult with no single factor sufficiently predictive of poor survival in CF patients. Much of the data applies to the general CF population rather than the population that meets other criteria for transplantation and the CF transplant candidate data comes from relatively small cohorts. A measurement of lung function over time to assess disease progression has been the most useful predictor (36). The FEV_1 has been the most frequently used variable in assessing early mortality. In 1992, Kerem et al. reported that an FEV_1 less than 30% of predicted was associated with a 2-year mortality rate of approximately 40% in men and 55% in women (37).

Mayer-Hamblett and colleagues utilized the Cystic Fibrosis Foundation registry to develop a model identifying the best clinical predictors of mortality in the CF patients. They found that age, height, FEV_1, respiratory microbiology, number of hospitalizations, and the 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 the FEV_1 alone (38). Another study evaluated CF patients referred for transplantation at four lung transplant centers. Using a univariate analysis, the authors reported a relationship between early mortality and

an FEV_1 less than 30% of predicted and an elevated $PaCO_2$ >50 mmHg (6.6 kPa). They also noted the need for and the use of nutritional supplements as an indicator of increased early mortality. Those patients who had an FEV_1 less than 30% of predicted had an increased early mortality only when their PCO_2 was greater than 50 mmHg (39). Milla and Warwick in their single-center study also found that the rate of decline was a better predictor of early mortality than the FEV_1 alone (40). Using the Cystic Fibrosis Foundation database, Liou and colleagues developed a 5-year survival model (41). The authors evaluated the impact of various variables on survival and correlated it with a change in the FEV_1 percent predicted. They found that the female sex, diabetes mellitus, *Burkholderia cepacia* infection, and the number of exacerbations negatively impacted the survival of the CF patient whereas FEV_1 percent predicted alone was not a sufficient predictor of early mortality.

Other preoperative characteristics that impact survival following lung transplantation are exercise tolerance and pulmonary hypertension. A 6-minute walk distance less than 400 meters and pulmonary hypertension have been associated with poor outcomes (42-45). The development of a pneumothorax and the presence of non-tuberculous mycobacterial (NTM) disease (in particular *M. abscessus*) also increase declines in lung function and or mortality in those with advanced lung disease (46,47).

Specific considerations

Non-tuberculous mycobacteria

There has been an observed increase in incidence of patients with CF culturing NTM (45). The following recommendations are made, though it is recognized that this is a subject where the evidence is predominantly based on case series (48,49):

(I) All patients with CF who are referred for transplantation should be evaluated for NTM pulmonary disease;

(II) Patients with NTM disease who are being evaluated for transplantation should have the organism confirmed according to microbiology guidelines and commence treatment before transplant listing;

(III) Treatment should be by, or in collaboration with, a physician experienced in the treatment of such patients;

(IV) Patients with progressive pulmonary or extrapulmonary disease due to NTM despite

optimal therapy or an inability to tolerate optimal therapy is a contraindication for transplant listing.

Burkholderia cepacia complex

CF patients who are infected with *B. cepacia* have been shown to have a more rapid progression of respiratory disease associated with a more rapid fall in FEV_1. *Burkholderia cepacia* complex patients also have a less favorable outcome post transplantation, though the majority of the increased risk has been shown to be confined to those patients infected with the species *Burkholderia cenocepacia* (50-52).

The following recommendations are made:

❖ All patients with CF referred for transplantation should be evaluated for the presence of B. cepacian;

❖ Patients with species other than *B. cenocepacia* do not constitute an increased risk for mortality after transplantation and can be listed providing other criteria are met;

❖ Patients with *B. cenocepacia* have an increased risk of mortality due 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. Further, a full discussion with the patients of the increased risk associated with these infections should occur.

Indications

With 40% of all lung transplantations performed worldwide, COPD (non-A1ATD and A1ATD) is the most common indication (53). The clinical course of COPD is typically very protracted, and even at an advanced stage, short—and intermediate—survival is better than the other commonly transplanted diseases. Apart from survival, in patients with COPD, the most important clinical feature is a decline in the quality of life. As a result, considering the prevalence of end-stage COPD and the continuing donor organ shortage, it remains challenging to decide when to list COPD patients and whether quality of life issues should also be taken into account when making that decision.

In a recent study including 609 patients with severe emphysema randomized to the medical therapy arm of the National Emphysema Treatment Trial (NETT), Martinez *et al.* identified the following factors, which 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 versus the upper lung zone and lower upper-to-lower-lung perfusion ratio. Also, the modified BODE score, which is a composite score of body mass index (B), %predicted FEV_1 (airway obstruction, O), dyspnea (D) and exercise capacity (E) was associated with a higher mortality (54). In some studies, the original BODE score, developed by Celli *et al.* (55) 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 (56). Either the original or 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 impacts survival in COPD patients (57). Moreover, the mortality risk is independent of the severity of the disease as measured by the BODE index (58). COPD patients with acute hypercapnic respiratory failure have an in-hospital mortality of >10% and subjects who survived the hospital admission have a 43% and 49% mortality rate at 1 and 2 years post admission (59).

The role of the BODE score and its impact on lung transplantation survival for COPD has recently been evaluated by Lahzami *et al.* who showed that the majority of COPD patients had survival benefit from lung transplantation regardless of their pre-transplant BODE score, although a global survival benefit was only seen in patients with a BODE score of 7 or more (60), suggesting that this is the appropriate population to transplant. Patients with a BODE index of 5–6, while not expected to derive a survival benefit, experienced similar quality of life benefits from transplant to patients with a BODE index of 7–10. Although lung transplant candidates with COPD are different compared to the original COPD population as assessed in the BODE index paper 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 (61).

Special considerations

A specific issue to the COPD population is the impact of bronchoscopic [bronchoscopic lung volume reduction (BLVR)] or LVRS on listing for lung transplantation. In certain patients (FEV_1 <25%, but >20%, DL_{CO} >20% and heterogeneous emphysema distribution on CT scan) LVRS may be offered first, reserving transplantation for those patients failing to improve with LVRS or in those experiencing a lung function decline after a period of sustained improvement. Successful LVRS with improvement in functional and nutritional status can improve the patient's suitability as a transplant candidate (9,62).

Pulmonary hypertension

Indications

The timing of referral for transplant for pulmonary vascular disease remains 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 the prostanoids, endothelin receptor antagonists and phosphodiesterase inhibitors have proven efficacy in the management of IPAH patients and, as such, the majority of 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 (63-65). Because of the generally good response to medical therapy, transplant centers still vary considerably in referral, listing and transplantation of IPAH patients. However, in patients who are deteriorating rapidly, transplant bridging strategies are an option but a more difficult one in this patient group.

Equations to predict waitlist 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: 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 (66). Functional class III, increased mean right atrial pressure, decreased resting systolic blood pressure or an elevated heart rate, decreased six-minute walk distance, increased brain natriuretic peptide, renal insufficiency, PAH associated with connective tissue diseases, a decreased carbon monoxide diffusing capacity or the presence of a pericardial effusion were also associated with increased mortality. Despite criticism that this Registry did not reflect actual lung transplant waitlist 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 true in North America and coincided with the introduction of the lung allocation scoring (LAS) system in 2005 in the United States. While many of these patients would previously have been too ill to survive prolonged wait times, the LAS system has allowed them priority access to available donor organs (67,68).

The criteria for candidate selection for lung retransplantation generally mirror those utilized for selection for initial lung transplantation. Important considerations include the presence of significant renal dysfunction, which, if present, increases the hazard ratio for mortality considerably among retransplantation candidates. The presence of additional comorbidities also increases risk by a multivariate analysis (69,70).

Retransplantation candidates may be considered for bilateral lung 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 (71). These factors would suggest that failed allograft removal is advisable. Ipsilateral single lung retransplantation has been associated with a higher acute risk of death when compared to contralateral single lung retransplantation (69). However, these comparisons are somewhat 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 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 and long-term outcomes after lung retransplantation (72,73). Patients retransplanted for bronchiolitis obliterans syndrome (BOS) manifest better survival than those transplanted for primary graft dysfunction or airway complications. Generally, patients that are more than two years out from initial transplantation fare better than those retransplanted earlier. Those retransplanted for BOS in general demonstrate more rapidly declines in airflow than those transplanted for other indications. However, those retransplanted less than 2 years following initial transplantation also have an even greater risk of developing BOS (70).

It is generally accepted that those patients who were mechanically ventilated immediately prior to retransplantation have inferior survival outcomes. More recent analysis (73) have suggested that when patients retransplanted less than 30 days of initial transplantation are excluded, mechanical ventilation is not an independent risk factor for poor outcomes. 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 that seen after initial transplantation. In fact, 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 transplant

Patients with end-stage lung and heart diseases not amenable to either isolated heart or lung transplant may be candidates for heart-lung transplantation. In most circumstances, patients with irreversible myocardial dysfunction or congenital defects with irreparable defects of the valves or chambers in conjunction with intrinsic lung disease or severe pulmonary artery hypertension are considered for heart-lung transplantation (74-76).

Pulmonary artery hypertension and elevated PVR should be considered as relative contraindications to isolated cardiac transplantation defined as a PVR is >5 Woods units, a PVR index is >6 or a transpulmonary pressure gradient (TPG) 16–20 mmHg. If the pulmonary artery systolic pressure (PAS) exceeds 60 mmHg in conjunction with any of the aforementioned 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 mmHg, the patient remains at high risk of right heart failure and mortality after isolated cardiac transplantation. Mechanical circulatory

support can improve these parameters and still make heart transplantation a possibility, obviating the need for heart lung transplantation.

In the clinical scenario of pulmonary hypertension and right ventricular failure, isolated double lung transplantation is associated with similar outcomes as seen in heart-lung transplantation (77). 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 the majority 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 both 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 class IV symptoms on maximal medical therapy, with cardiac index of less than 2 liters/min/m^2 and right arterial pressure exceeding 15 mmHg are indications to proceed with transplant listing. Certain anomalies such as pulmonary venous stenosis or pulmonary veno-occlusive disease (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 multisystem organ dysfunction who might benefit from simultaneous lung transplant and transplantation of another solid organ. Concurrent thoracic and abdominal transplantation was recently reviewed by Wolf *et al.* (78), who analyzed 122 simultaneous lung-liver transplants (typically for cystic fibrosis) 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 actually higher than those of lung transplantation alone [50% at 5 years in the USA (P<0.01)], although less than

that of abdominal transplantation alone. This may reflect the expertise of the centers attempting such transplants. These pooled results are consistent with other small case series from the USA and Europe (79,80).

Combined lung and kidney transplant

The most common combination of thoracic and abdominal transplantation is kidney transplantation following lung transplantation. Cassuto and coworkers (81) have 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 post-lung transplant. It is clear from this statistic that staged kidney transplants relatively soon after transplant are rare with most representing the failure of a second organ system due to the effects of calcineurin inhibitors.

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

Combined lung and liver transplant

The referral of lung transplant candidates with both 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 (less than 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 mmHg. Combined liver lung transplant should not be considered

in those patients with albumin <2.0 g/dL, international normalized ratio (INR) >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 and include: anticipated wait 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 those with liver disease, rate of expected progression of the liver or lung disease after transplantation of the other organ, and presence of co-morbidities which 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), due to concerns about esophageal dysmotility and gastroparesis increasing the risk of aspiration, many centers continue to consider SSc a contraindication. Two recent reports suggest that patients with SSc, even in the presence of esophageal disease, have similar 1 and 5-year survival rates to other ILD patients (88,89). Rates of acute rejection were increased in SSc patients in one report (88) and no different in the other (89). Importantly, incidence of BOS was similar between the two groups in both reports. Carefully selected SSc patients 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 (AIS) and minimally invasive adenocarcinoma (MIA)

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:

- ❖ Prior to 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 computer tomography, 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 delisting of the patient;
- ❖ 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 a substitute recipient should receive the lungs.

The rationale of lung transplantation for AIS and 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. While survival after resection for localized disease is quite good, the results of chemotherapy for diffuse, bilateral disease is poor with survival beyond two years from the time of diagnosis quite uncommon. Hence, some centers have performed lung transplantation in patients with diffuse BAC (90,91).

In 2004, a report by de Perrot and colleagues (90) characterized the international experience with lung transplantation for BAC. The survival of patients undergoing lung transplantation and heart/lung transplantation for BAC at 5 and 10 years (26 patients) was 39% and 31% respectively, as compared to the survival reported by the International Society for Heart and Lung Transplantation in the 2013 Registry report (53) where the survival at 5 years was 53% and at 10 years was 31%.

One of the major concerns about lung transplantation for BAC is the incidence of recurrent tumor. In the survey by de Perrot (90), of the 22 patients that survived the operation, 13 (59%) developed a recurrence of BAC between 5 and 49 months after transplantation. Zorn and colleagues (91) also saw a high recurrence rate in the small series, where tumor recurred in 6 of 8 patients. One of the interesting features 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.

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

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Footnote

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References

1. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:745-55.

2. International guidelines for the selection of lung transplant candidates. The American Society for Transplant Physicians (ASTP)/American Thoracic Society(ATS)/ European Respiratory Society(ERS)/International Society for Heart and Lung Transplantation(ISHLT). Am J Respir Crit Care Med 1998;158:335-9.

3. Weill D, Benden C, Corris PA, et al. 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. J Heart Lung Transplant 2015;34:1-15.

4. Shigemura N, Bhama J, Gries CJ, et al. Lung transplantation in patients with prior cardiothoracic surgical procedures. Am J Transplant 2012;12:1249-55.

5. Reynaud-Gaubert M, Mornex JF, Mal H, et al. Lung transplantation for lymphangioleiomyomatosis: the French experience. Transplantation 2008;86:515-20.

6. Detterbeck FC, Egan TM, Mill MR. Lung transplantation after previous thoracic surgical procedures. Ann Thorac Surg 1995;60:139-43.

7. Dusmet M, Winton TL, Kesten S, et al. Previous intrapleural procedures do not adversely affect lung transplantation. J Heart Lung Transplant 1996;15:249-54.

8. Curtis HJ, Bourke SJ, Dark JH, et al. Lung transplantation outcome in cystic fibrosis patients with previous pneumothorax. J Heart Lung Transplant 2005;24:865-9.

9. Senbaklavaci O, Wisser W, Ozpeker C, et al. Successful lung volume reduction surgery brings patients into better condition for later lung transplantation. Eur J Cardiothorac Surg 2002;22:363-7.

10. Shigemura N, Gilbert S, Bhama JK, et al. Lung transplantation after lung volume reduction surgery. Transplantation 2013;96:421-5.

11. Cypel M, Keshavjee S. Extracorporeal life support as a bridge to lung transplantation. Clin Chest Med 2011;32:245-51.

12. de Perrot M, Granton JT, McRae K, et al. Outcome of patients with pulmonary arterial hypertension referred for lung transplantation: a 14-year single- center experience. J Thorac Cardiovasc Surg 2012;143:910-8.

13. Strueber M. Bridges to lung transplantation. Curr Opin Organ Transplant 2011;16:458-61.

14. Gottlieb J, Warnecke G, Hadem J, et al. Outcome of critically ill lung transplant candidates on invasive respiratory support. Intensive Care Med 2012;38:968-75.

15. de Perrot M, Granton JT, McRae K, et al. Impact of extracorporeal life support on outcome in patients with idiopathic pulmonary arterial hypertension awaiting lung transplantation. J Heart Lung Transplant 2011;30:997-1002.

16. Vermeijden JW, Zijlstra JG, Erasmus ME, et al. Lung transplantation for ventilator-dependent respiratory failure. J Heart Lung Transplant 2009;28:347-51.

17. Diaz-Guzman E, Hoopes CW, Zwischenberger JB. The evolution of extracorporeal life support as a bridge to lung transplantation. ASAIO J 2013;59:3-10.

18. Javidfar J, Brodie D, Iribarne A, et al. Extracorporeal membrane oxygenation as a bridge to lung transplantation and recovery. J Thorac Cardiovasc Surg 2012;144:716-21.

19. Toyoda Y, Bhama JK, Shigemura N, et al. Efficacy of extracorporeal membrane oxygenation as a bridge to lung transplantation. J Thorac Cardiovasc Surg 2013;145:1065-70; discussion 1670-1.

20. Shafii AE, Mason DP, Brown CR, et al. Growing experience with extracorporeal membrane oxygenation as a bridge to lung transplantation. ASAIO J 2012;58:526-9.

21. Hoopes CW, Kukreja J, Golden J, et al. Extracorporeal membrane oxygenation as a bridge to pulmonary transplantation. J Thorac Cardiovasc Surg 2013;145:862-

7; discussion 867-8.

22. Bittner HB, Lehmann S, Rastan A, et al. Outcome of extracorporeal membrane oxygenation as a bridge to lung transplantation and graft recovery. Ann Thorac Surg 2012;94:942-9; author reply 949-50.

23. Fuehner T, Kuehn C, Hadem J, et al. Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. Am J Respir Crit Care Med 2012;185:763-8.

24. Snyder JJ, Salkowski N, Skeans M, et al. The equitable allocation of deceased donor lungs for transplant in children in the United States. Am J Transplant 2014;14:178-83.

25. King TE, Jr., Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083-92.

26. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788-824.

27. Brown AW, Shlobin OA, Weir N, et al. Dynamic patient counseling: a novel concept in idiopathic pulmonary fibrosis. Chest 2012;142:1005-10.

28. du Bois RM, Weycker D, Albera C, et al. Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. Am J Respir Crit Care Med 2011;183:1231-7.

29. Collard HR, King TE Jr, Bartelson BB, et al. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003;168:538-42.

30. du Bois RM, Weycker D, Albera C, et al. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;184:459-66.

31. Flaherty KR, Andrei AC, Murray S, et al. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med 2006;174:803-9.

32. Lederer DJ, Arcasoy SM, Wilt JS, et al. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2006;174:659-64.

33. King TE Jr, Tooze JA, Schwarz MI, et al. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med 2001;164:1171-81.

34. Bongartz T, Nannini C, Medina-Velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis and rheumatism 2010;62:1583-91.

35. Bouros D, Wells AU, Nicholson AG, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med 2002;165:1581-6.

36. Rosenbluth DB, Wilson K, Ferkol T, et al. Lung function decline in cystic fibrosis patients and timing for lung transplantation referral. Chest 2004;126:412-9.

37. Kerem E, Reisman J, Corey M, et al. Prediction of mortality in patients with cystic fibrosis. N Engl J Med 1992;326:1187-91.

38. Mayer-Hamblett N, Rosenfeld M, Emerson J, et al. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. Am J Respir Crit Care Med 2002;166:1550-5.

39. Augarten A, Akons H, Aviram M, et al. Prediction of mortality and timing of referral for lung transplantation in cystic fibrosis patients. Pediatric transplantation 2001;5:339-42.

40. Milla CE, Warwick WJ. Risk of death in cystic fibrosis patients with severely compromised lung function. Chest 1998;113:1230-4.

41. Liou TG, Adler FR, Cahill BC, et al. Survival effect of lung transplantation among patients with cystic fibrosis. JAMA 2001;286:2683-9.

42. Kadikar A, Maurer J, Kesten S. The six-minute walk test: a guide to assessment for lung transplantation. J Heart Lung Transplant 1997;16:313-9.

43. Tuppin MP, Paratz JD, Chang AT, et al. Predictive utility of the 6-minute walk distance on survival in patients awaiting lung transplantation. J Heart Lung Transplant 2008;27:729-34.

44. Venuta F, Rendina EA, Rocca GD, et al. Pulmonary hemodynamics contribute to indicate priority for lung transplantation in patients with cystic fibrosis. J Thorac Cardiovasc Surg 2000;119:682-9.

45. Venuta F, Tonelli AR, Anile M, et al. Pulmonary hypertension is associated with higher mortality in cystic fibrosis patients awaiting lung transplantation. J Cardiovasc Surg (Torino) 2012;53:817-20.

46. Esther CR Jr, Esserman DA, Gilligan P, et al. Chronic Mycobacterium abscessus infection and lung function decline in cystic fibrosis. J Cyst Fibros 2010;9:117-23.

47. Flume PA, Mogayzel PJ Jr, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: pulmonary complications: hemoptysis and pneumothorax. Am J Respir Crit Care

Med 2010;182:298-306.

48. Lobo LJ, Chang LC, Esther CR Jr, et al. Lung transplant outcomes in cystic fibrosis patients with pre-operative Mycobacterium abscessus respiratory infections. Clin Transplant 2013;27:523-9.

49. Chernenko SM, Humar A, Hutcheon M, et al. Mycobacterium abscessus infections in lung transplant recipients: the international experience. J Heart Lung Transplant 2006;25:1447-55.

50. De Soyza A, Corris PA. Lung transplantation and the Burkholderia cepacia complex. J Heart Lung Transplant 2003;22:954-8.

51. De Soyza A, McDowell A, Archer L, et al. Burkholderia cepacia complex genomovars and pulmonary transplantation outcomes in patients with cystic fibrosis. Lancet 2001;358:1780-1.

52. De Soyza A, Meachery G, Hester KL, et al. Lung transplantation for patients with cystic fibrosis and Burkholderia cepacia complex infection: a single- center experience. J Heart Lung Transplant 2010;29:1395-404.

53. Yusen RD, Christie JD, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: thirtieth adult lung and heart- lung transplant report--2013; focus theme: age. J Heart Lung Transplant 2013;32:965-78.

54. Martinez FJ, Foster G, Curtis JL, et al. Predictors of mortality in patients with emphysema and severe airflow obstruction. Am J Respir Crit Care Med 2006;173:1326-34.

55. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350:1005-12.

56. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. Am J Respir Crit Care Med 1995;152:S77-121.

57. Soler-Cataluña JJ, Martinez-Garcia MA, Roman Sanchez P, et al. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005;60:925-31.

58. Soler-Cataluña JJ, Martinez-Garcia MA, Sanchez LS, et al. Severe exacerbations and BODE index: two independent risk factors for death in male COPD patients. Respir Med 2009;103:692-9.

59. Connors AF Jr, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med 1996;154:959-67.

60. Lahzami S, Bridevaux PO, Soccal PM, et al. Survival impact of lung transplantation for COPD. Eur Respir J 2010;36:74-80.

61. Marchand E. The BODE index as a tool to predict survival in COPD lung transplant candidates. Eur Respir J 2010;36:1494-5; author reply 1495.

62. Kreider M, Hadjiliadis D, Kotloff RM. Candidate selection, timing of listing, and choice of procedure for lung transplantation. Clin Chest Med 2011;32:199-211.

63. Gottlieb J. Lung transplantation for interstitial lung diseases and pulmonary hypertension. Semin Respir Crit Care Med 2013;34:281-7.

64. Conte JV, Gaine SP, Orens JB, et al. The influence of continuous intravenous prostacyclin therapy for primary pulmonary hypertension on the timing and outcome of transplantation. J Heart Lung Transplant 1998;17:679-85.

65. Robbins IM, Christman BW, Newman JH, et al. A survey of diagnostic practices and the use of epoprostenol in patients with primary pulmonary hypertension. Chest 1998;114:1269-75.

66. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164-72.

67. Eberlein M, Garrity ER, Orens JB. Lung allocation in the United States. Clin Chest Med 2011;32:213-22.

68. Egan TM, Murray S, Bustami RT, et al. Development of the new lung allocation system in the United States. Am J Transplant 2006;6:1212-27.

69. Kawut SM, Lederer DJ, Keshavjee S, et al. Outcomes after lung retransplantation in the modern era. Am J Respir Crit Care Med 2008;177:114-20.

70. Novick RJ, Stitt LW, Al-Kattan K, et al. Pulmonary retransplantation: predictors of graft function and survival in 230 patients. Pulmonary Retransplant Registry. Ann Thorac Surg 1998;65:227-34.

71. Kawut SM. Lung retransplantation. Clin Chest Med 2011;32:367-77.

72. Strueber M, Fischer S, Gottlieb J, et al. Long-term outcome after pulmonary retransplantation. J Thorac Cardiovasc Surg 2006;132:407-12.

73. Aigner C, Jaksch P, Taghavi S, et al. Pulmonary retransplantation: is it worth the effort? A long-term analysis of 46 cases. J Heart Lung Transplant 2008;27:60-5.

74. Choong CK, Sweet SC, Guthrie TJ, et al. Repair

of congenital heart lesions combined with lung transplantation for the treatment of severe pulmonary hypertension: a 13-year experience. J Thorac Cardiovasc Surg 2005;129:661-9.

75. Faro A, Mallory GB, Visner GA, et al. American Society of Transplantation executive summary on pediatric lung transplantation. Am J Transplant 2007;7:285-92.

76. Fadel E, Mercier O, Mussot S, et al. Long-term outcome of double-lung and heart-lung transplantation for pulmonary hypertension: a comparative retrospective study of 219 patients. Eur J Cardiothorac Surg 2010;38:277-84.

77. Januszewska K, Malec E, Juchem G, et al. Heart-lung transplantation in patients with pulmonary atresia and ventricular septal defect. J Thorac Cardiovasc Surg 2009;138:738-43.

78. Wolf JH, Sulewski ME, Cassuto JR, et al. Simultaneous thoracic and abdominal transplantation: can we justify two organs for one recipient? Am J Transplant 2013;13:1806-16.

79. Couetil JP, Houssin DP, Soubrane O, et al. Combined lung and liver transplantation in patients with cystic fibrosis. A 4 1/2-year experience. J Thorac Cardiovasc Surg 1995;110:1415-22; discussion 1422-3.

80. Grannas G, Neipp M, Hoeper MM, et al. Indications for and outcomes after combined lung and liver transplantation: a single-center experience on 13 consecutive cases. Transplantation 2008;85:524-31.

81. Cassuto JR, Reese PP, Sonnad S, et al. Wait list death and survival benefit of kidney transplantation among nonrenal transplant recipients. Am J Transplant 2010;10:2502-11.

82. Lonze BE, Warren DS, Stewart ZA, et al. Kidney transplantation in previous heart or lung recipients. Am J Transplant 2009;9:578-85.

83. Arnon R, Annunziato RA, Miloh T, et al. Liver and combined lung and liver transplantation for cystic fibrosis: analysis of the UNOS database. Pediatr Transplant 2011;15:254-64.

84. Barshes NR, DiBardino DJ, McKenzie ED, et al. Combined lung and liver transplantation: the United States experience. Transplantation 2005;80:1161-7.

85. Praseedom RK, McNeil KD, Watson CJ, et al. Combined transplantation of the heart, lung, and liver. Lancet 2001;358:812-3.

86. Yi SG, Burroughs SG, Loebe M, et al. Combined lung and liver transplantation: Analysis of a single-center experience. Liver Transpl 2014;20:46-53.

87. Pirenne J, Verleden G, Nevens F, et al. Combined liver and (heart-)lung transplantation in liver transplant candidates with refractory portopulmonary hypertension. Transplantation 2002;73:140-2.

88. Saggar R, Khanna D, Furst DE, et al. Systemic sclerosis and bilateral lung transplantation: a single centre experience. Eur Respir J 2010;36:893-900.

89. Sottile PD, Iturbe D, Katsumoto TR, et al. Outcomes in systemic sclerosis- related lung disease after lung transplantation. Transplantation 2013;95:975-80.

90. de Perrot M, Chernenko S, Waddell TK, et al. Role of lung transplantation in the treatment of bronchogenic carcinomas for patients with end-stage pulmonary disease. J Clin Oncol 2004;22:4351-6.

91. Zorn GL Jr, McGiffin DC, Young KR Jr, et al. Pulmonary transplantation for advanced bronchioloalveolar carcinoma. J Thorac Cardiovasc Surg 2003;125:45-8.

92. Garver RI Jr, Zorn GL, Wu X, et al. Recurrence of bronchioloalveolar carcinoma in transplanted lungs. N Engl J Med 1999;340:1071-4.

93. Gómez-Román JJ, Del Valle CE, Zarrabeitia MT, et al. Recurrence of bronchioloalveolar carcinoma in donor lung after lung transplantation: microsatellite analysis demonstrates a recipient origin. Pathol Int 2005;55:580-4.