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Review

Lung Transplantation: Selection of Candidates

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Abstract

Lung transplantation is a last-resort treatment option for patients with end stage lung disease. The procedure is being performed more frequently and scientific advances continue to be made, but the median post-transplant survival is far shorter than other solid organ transplant recipients. Candidate selection is a resource intensive process that attempts to balance risks of the procedure with the benefits of much higher quality of life. Transplant centers must weigh disease specific considerations, medical comorbidities, and psychosocial factors with the likelihood of a successful transplantation. While the candidate selection process is exceptionally challenging, it leads to many patients undergoing successful lung transplantation.

Keywords

Lung transplantation; candidate selection; risk stratification; extracorporeal life support

1. Introduction

Lung transplantation is increasingly performed throughout the world for end stage lung diseases, with 4452 patients receiving lung transplants at 260 centers worldwide in 2017 [1], and over 2500 patients receiving lung transplants in the US alone during 2021 [2]. While survival for lung transplant recipients is not as high as that of other solid organ transplants, survival continues to improve, with the median survival of the most recent cohort (2010-2017) of lung transplant recipients being 6.7 years [1]. Lung transplantation also confers substantial health-related quality-of-life (HRQL) benefits (which vary somewhat by recipient diagnosis) [3].

As the field advances, there are fewer absolute contraindications to lung transplantation, and lung transplantation centers are becoming more comfortable with medically complex patients. The candidate selection process can be challenging, with multiple medical (disease specific and comorbid), surgical and social considerations in each potential candidate.

Donated lungs which are suitable for transplantation are far outnumbered by the patients who will benefit from lung transplantation. These scarce and lifesaving resources must be therefore allocated in an ethical way to maximize the benefit to the recipients. Various allocation systems and policies are used throughout the world, but they are all intended to maximize the ethical principles of utility, justice and respect for persons [4]. The principle of utility holds that organs should be allocated in such a way as to maximize the net overall good, while minimizing harms. As such, clinicians should aim to select patients who are sick enough to benefit from lung transplantation, but not so sick that the transplantation would lead to death. Death as a direct consequence of the lung transplant process not only harms the patient themselves, but also removes the organs from the donor pool where they would have benefited another patient.

The ethical principle of justice posits that available organs be allocated fairly to all eligible recipients; that is, all patients should be given equal consideration. According to the Organ Procurement & Transplant Network statement, the following factors should be considered when applying the principle of justice: medical urgency, likelihood of finding a suitable organ in the future, wait list time, first versus repeat transplant, age, and geographical fairness.

An important consideration is that race, gender, and socioeconomic status are excluded from utility models for organ allocation. Although there may be data that a particular group has worse post-transplantation outcomes, it is important to not withhold organs from patients in that group, so as not to add “insult to injury” by further disadvantaging a particular person or group.

The principle of respect for persons states that a patient has the right to autonomy; that is, they can exercise this right by making their own decisions. In the context of lung transplant, patients have the right to a full candidacy evaluation and education about candidate selection. They can then make their own decisions if they wish to proceed with evaluation. However, patients must understand that undergoing an evaluation does not equate with suitability for transplant.

2. Timing for Referral, Evaluation and Listing for Lung Transplantation

In general, patients with advanced progressive lung disease should be referred and evaluated for lung transplant as early in their disease course as possible. In fact, patients with idiopathic pulmonary fibrosis (IPF) should be referred for evaluation at a lung transplant center at the time of diagnosis given an unpredictable disease course [5]. Early referral allows time for the evaluation to take place and for modifiable barriers to lung transplantation, such as frailty, deconditioning,

over/underweight, and medical comorbidities such as diabetes to be addressed [6]. Patients who are referred "too early" can be monitored closely at 3-to-6-month intervals. Patients who are referred "too late," however, may have barriers that are difficult or impossible to overcome.

A full evaluation for lung transplantation includes medical and surgical evaluation, as well as assessments of nutritional, psychosocial and frailty status. Each patient's circumstances are unique, combining lung disease specific factors with age, medical comorbidities, psychosocial factors, and nutritional status. There are some risk factors that are considered absolute contraindications to lung transplantation, which include lack of patient willingness, active or recent malignancy, repeated non-adherence to medical therapy, active substance abuse, and the presence of severe medical comorbidities such as renal or hepatic failure, stroke, or acute coronary syndrome [6]. *See Figure 1 for full list of absolute contraindications as outlined by the International Society of Heart and Lung Transplantation (ISHLT).*

Risk factors can change over time and may not be a contraindication for referral, but when present at the time of listing or while listed for lung transplantation may increase risk for poor transplant outcomes. There was 100% consensus (24 committee members) for the content of the entirety of Table 2.

ABSOLUTE CONTRAINDICATIONS:

- Candidates with these conditions are considered too high risk to achieve successful outcomes post lung transplantation.
- Factor or condition that significantly increases the risk of an adverse outcome post-transplant and /or would make transplant most likely harmful for a recipient.
- Most lung transplant programs should not transplant patients with these risk factors except under very exceptional or extenuating circumstances.

1. Lack of patient willingness or acceptance of transplant
2. Malignancy with high risk of recurrence or death related to cancer
3. Glomerular filtration rate < 40 mL/min/1.73m^2 unless being considered for multi-organ transplant
4. Acute coronary syndrome or myocardial infarction within 30 days (excluding demand ischemia)
5. Stroke within 30 days
6. Liver cirrhosis with portal hypertension or synthetic dysfunction unless being considered for multi-organ transplant
7. Acute liver failure
8. Acute renal failure with rising creatinine or on dialysis and low likelihood of recovery
9. Septic shock
10. Active extrapulmonary or disseminated infection
11. Active tuberculosis infection
12. HIV infection with detectable viral load
13. Limited functional status (e.g. non-ambulatory) with poor potential for post-transplant rehabilitation
14. Progressive cognitive impairment
15. Repeated episodes of non-adherence without evidence of improvement (Note: For pediatric patients this is not an absolute contraindication and ongoing assessment of non-adherence should occur as they progress through different developmental stages.)
16. Active substance use or dependence including current tobacco use, vaping, marijuana smoking, or IV drug use
17. Other severe uncontrolled medical condition expected to limit survival after transplant

RISK FACTORS WITH HIGH OR SUBSTANTIALLY INCREASED RISK:

- Candidates with these conditions may be considered in centers with expertise specific to the condition.
- We may not have data to support transplanting patients with these risk factors or there is substantially increased risk based upon the currently available data, and further research is needed to better inform future recommendations.
- When more than one of these risk factors are present, they are thought to be possibly multiplicative in terms of increasing risk of adverse outcomes.
- Modifiable conditions should be optimized when possible.

1. Age > 70 years
2. Severe coronary artery disease that requires coronary artery bypass grafting at transplant
3. Reduced left ventricular ejection fraction < 40%
4. Significant cerebrovascular disease
5. Severe esophageal dysmotility
6. Untreatable hematologic disorders including bleeding diathesis, thrombophilia, or severe bone marrow dysfunction
7. BMI > 35 kg/m^2
8. BMI < 16 kg/m^2
9. Limited functional status with potential for post-transplant rehabilitation
10. Psychiatric, psychological or cognitive conditions with potential to interfere with medical adherence without sufficient support systems
11. Unreliable support system or caregiving plan
12. Lack of understanding of disease and / or transplant despite teaching
13. *Mycobacterium abscessus* infection
14. *Lomentospora prolificans* infection
15. *Burkholderia cenocepacia* or *gladioli* infection
16. Hepatitis B or C infection with detectable viral load and liver fibrosis
17. Chest wall or spinal deformity expected to cause restriction after transplant
18. Extracorporeal life support
19. Retransplant <1 year following initial lung transplant
20. Retransplant for restrictive CLAD
21. Retransplant for AMR as etiology for CLAD

RISK FACTORS:

- Risk factors with unfavorable implications for short and / or long-term outcomes after lung transplant.
- While acceptable for lung transplant programs to consider patients with these risk factors, multiple risk factors together may increase risk for adverse post lung transplant outcomes.

1. Age 65-70 years
2. Glomerular filtration rate 40-60 mL/min/1.73m^2
3. Mild to moderate coronary artery disease
4. Severe coronary artery disease that can be revascularized via percutaneous coronary intervention prior to transplant
5. Patients with prior coronary artery bypass grafting
6. Reduced left ventricular ejection fraction 40-50%
7. Peripheral vascular disease
8. Connective tissue diseases (scleroderma, lupus, inflammatory myopathies)
9. Severe gastroesophageal reflux disease
10. Esophageal dysmotility
11. Thrombocytopenia, leukopenia, or anemia with high likelihood of persistence after transplant
12. Osteoporosis
13. BMI 30-34.9 kg/m^2
14. BMI 16-17 kg/m^2
15. Frailty
16. Hypoalbuminemia
17. Diabetes that is poorly controlled
18. Edible marijuana use
19. *Scedosporium apiospermum* infection
20. HIV infection with undetectable viral load
21. Previous thoracic surgery
22. Prior pleurodesis
23. Mechanical ventilation
24. Retransplant >1 year for obstructive CLAD

Abbreviations: AMR, antibody mediated rejection; BMI, body mass index; CLAD, chronic lung allograft dysfunction.

Figure 1 Risk factors for poor post-transplant outcomes. (From Leard et al.) [6].

There are many other risk factors that confer varying levels of increased risk for lung transplantation. These include older age, cardiovascular disease, over/underweight, frailty, psychiatric illnesses, infections, re-transplantation, and use of ECLS at the time of transplant [6] (Figure 1). While none of these relative contraindications by themselves necessarily precludes lung transplantation, their conferred risk is additive in multiples, and centers should perform an individualized assessment in the context of that centers experience.

3. Discussion of Individual Risk Factors for Poor Post Lung Transplantation Outcomes

3.1 Age

There is no officially accepted upper age limit for selection of candidates for lung transplantation [6]. However, older age is the most significant risk factor for death following lung transplantation [7], with recipients older than 70 years of age having significantly worse survival than recipients closer to the average lung transplant recipient age of 59. Interestingly, patients under the age of 30 also have increased risk of post-transplant death, which is likely driven by psychosocial factors as well as specific medical factors such as immune responses [8].

While older age is a very important predictor of post lung transplantation mortality, there is data that suggests that short term (30-day, 3-month and 1-year) outcomes for recipients over the age of 70 have improved substantially since the year 2000, and are comparable to patients in their 60s [9]. However, long term (3- and 5-year) survival for recipients aged >70 is substantially lower than patients in their 60s. This data is almost certainly influenced by selection bias, where the older patients are very carefully selected to have minimal other medical comorbidities that would confer increased risk of mortality after lung transplantation.

As centers become more skilled at guiding older patients through the lung transplantation process leading to better perioperative and short-term outcomes, they should still consider older age as an important risk factor for increased long-term mortality. In fact, research on community preferences has shown that the general public prefers that organs preferentially go to younger recipients, in order to achieve maximum net gain in recipient survival and quality of life [10]. Therefore, it may be ethically justifiable to preferentially allocate scarce organs to younger lung transplant candidates [6]. To address this issue, it may be prudent to allocate older donor lungs to older recipients, which has been shown to be an effective approach that does not result in increased post-transplant mortality [11, 12].

3.2 Malignancy

All patients who are being evaluated for lung transplantation should undergo guideline directed age-appropriate cancer screening [6]. Post-transplantation immunosuppression is a definite risk factor for the development of new malignancy, however the effects of immunosuppression on the risk of recurrence of malignancy is less well known [13]. Active malignancy with a high risk of death is an absolute contraindication to lung transplantation. Whether patients who have a history of treated malignancy are good candidates for lung transplantation is a much more complicated question. In general, patients with a history of low-grade malignancy may be candidates for lung transplantation, whereas those with higher grades require long (i.e., 5 years) disease-free wait times after treatment before consideration for lung transplantation. Lung transplant centers should work

closely with oncology teams and follow malignancy specific guidelines [13, 14] for each patient evaluation. Newer tests that screen for a wide range of malignancies using cell free DNA having varying sensitivities and specificities [15], but more research is needed to determine their optimal role in the evaluation of lung transplant candidates.

3.3 Chronic Renal Dysfunction

Lung transplantation confers significant risk of renal injury through several mechanisms, including perioperative hypoperfusion and the use of nephrotoxic medications such as calcineurin inhibitors and antibiotics. Patients with renal dysfunction (eGFR <60 ml/min/1.73 m^2) who undergo lung transplantation have significantly worse 1- and 3-year mortality than patients who have eGFR >60 at the time of lung transplantation [16]. The optimal cutoff value for eGFR is not fully understood; other data suggest that lower values, such as 50, may be used [17]. In the lung allocation score (LAS) era, there has been a gradual increase in the incidence of post-lung transplantation hemodialysis, and these patients experience significantly worse 1- and 5-year mortality [18]. Lung transplant centers should consider each candidate's renal dysfunction in the context of their other medical comorbidities and their center's experience which such patients to determine the optimal eGFR cutoff for lung transplant candidacy.

3.4 Cardiovascular Disease

Coronary artery disease (CAD) is common in the aging population, and should be screened for in all lung transplantation candidates [19]. The optimal CAD screening modality is not known; most centers opt to perform invasive coronary angiography. Several retrospective studies have shown that in carefully selected patients, CAD does not confer increased risk for post-transplant mortality [20, 21], even in patients who undergo concurrent coronary artery bypass grafting (CABG) at the time of lung transplantation. A history of CABG was historically considered an absolute contraindication to lung transplantation, but single right lung transplantation may be a safe option for some patients with a history of CABG [22]. Patients with CAD should be carefully evaluated by transplant pulmonologists, cardiologists, and cardiothoracic surgeons to determine their candidacy for lung transplantation.

Peripheral vascular disease (PVD) is common in lung transplant candidates, but it is unclear whether it confers significant perioperative (i.e. limb ischemia related to extracorporeal life support [ECLS]) or long term mortality risk after lung transplantation [23]. If PVD results in significant claudication, post-transplant rehabilitation may be impacted. Lung transplant teams should carefully consider PVD in the individual patient's overall transplant candidacy.

Heart failure with reduced ejection fraction (HFrEF) has long been considered an absolute contraindication to lung transplantation at most centers, and there is very little data on post-lung transplantation outcomes in these patients. Patients with heart failure with preserved ejection fraction (HFpEF) have a higher risk of primary graft dysfunction after lung transplantation [24], though recent guidelines do not address HFpEF as a risk factor in lung transplantation [6]. Patients with right ventricular (RV) failure due to pulmonary arterial hypertension (PAH) or severe chronic lung disease are candidates for lung transplantation, as the right heart failure will improve with the reduction in pulmonary vascular resistance (PVR) after lung transplantation. Patients with PAH have historically had higher perioperative mortality but favorable long-term outcomes [25]. With the

increasing use of perioperative extracorporeal membrane oxygenation (ECMO) for RV support in the last 2 decades, patients with PAH have been shown to have excellent 1-year outcomes at some centers [26].

3.5 Gastrointestinal Disease

Gastroesophageal reflux disease (GERD) is associated with both early allograft injury [27] and bronchiolitis obliterans syndrome (BOS) [28]. In patients with GERD, anti-reflux surgery either before or soon after lung transplantation is associated with decreased early allograft injury [29, 30]. Esophageal dysmotility and gastroparesis are other common comorbidities in lung transplant candidates which increase the risk of aspiration, especially in patients with systemic sclerosis. However, lung transplant recipients with systemic sclerosis have similar post-transplant survival and rates of BOS to patients with non-CTD interstitial lung diseases (ILDs) [31], even in cohorts with high rates of severe esophageal dysfunction [32]. Lung transplant centers should take a careful multidisciplinary approach to candidates with significant gastrointestinal issues to mitigate post-transplant complications, with consideration of prolonged postoperative enteral feeding in patients with severe gastrointestinal issues.

Hypoalbuminemia has many causes but is often a marker of poor nutritional status in lung transplant candidates, and it is a risk factor for post-lung transplant mortality in multiple studies [33-35].

3.6 Connective Tissue Disease

Patients with connective tissue disease (CTD) related lung disease frequently have extrapulmonary manifestations, including esophageal dysmotility, renal dysfunction and cardiac abnormalities that may confer increased risk after lung transplantation. Active CTD that cannot be controlled with immunosuppression is a contraindication for lung transplantation. However, the patients with CTD who undergo lung transplantation do not appear to have worse outcomes when compared to patients with other indications, such as IPF or chronic obstructive pulmonary disease (COPD) [36, 37].

Patients with lung disease related to an idiopathic inflammatory myopathy (IIM), particularly those with anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibodies, are at high risk for rapidly progressive ILD and have a particular poor prognosis. Lung transplantation is an option for patients with lung disease related to an IIM [38], and ECMO is being increasingly used as a strategy to bridge these patients to lung transplantation [39, 40]. These patients are at high risk for malignancy [41] and should be carefully screened.

3.7 Hematology

Patients with hematological abnormalities are at increased risk for post-transplantation complications, and they are often intolerant of routine post-transplant immunosuppressive and antimicrobial therapies. Patients with bleeding disorders are at increased risk for perioperative bleeding. Patients with IPF may have a telomere mutation, which can be associated with myelosuppression and malignancy, and portend worse post-transplant outcomes [42].

3.8 Body Mass Index (BMI)

Over- and underweight patients have worse outcomes after lung transplantation, though the mechanisms for this observation are not fully understood and are likely multifactorial. Some studies suggest that both overweight (BMI >25 and <30) and obese (BMI >30) patients have increased risk for mortality and primary graft dysfunction after lung transplantation [43], while other studies suggest that it is only BMI >35 confers the significant risk of post-transplant mortality [44]. Weight loss is strongly recommended for overweight and obese lung transplant candidates, and multiple studies have shown that weight loss prior to lung transplantation results in improved post-operative survival [45, 46]. BMI >35 is an absolute contraindication for lung transplantation in most centers, with some adopting a more stringent cut-off of 32 and above.

Patients who are underweight (BMI <18.5) have consistently worse outcomes across these studies, though patients with cystic fibrosis (CF) and a BMI <17 appear to have similar outcomes to both patients with CF and normal weight and patients with COPD of all BMIs.

Patients who are either over- and underweight may achieve optimal weight with intensive multidisciplinary nutritional and exercise interventions, though this may take many months, which highlights the need for these patients to be referred for lung transplant evaluation as early as possible.

3.9 Frailty and Functional Status

Frailty is the accumulation of deficits across multiple systems that affects the body's physiologic reserve in response to stressors. While frailty is a well-established risk factor for early mortality following lung transplantation [47], frailty related to chronic lung disease can improve after transplantation [48]. There are several difference models that can be used to assess frailty prior to transplant, including phenotypic and cumulative deficit models. While these models may predict short- and long-term mortality after lung transplantation, there is poor correlation among these models [49], and clinicians should use a multimodal approach to assess frailty in lung transplant candidates.

Functional status is a patient's ability to perform their daily activities and can be measured in different ways. As measured by pre-operative 6-minute walk distance (6MWD), exercise capacity is significantly associated with both waitlist and post-transplant survival [50, 51] in patients who undergo lung transplantation. Pulmonary rehabilitation plays an essential role in preserving and improving exercise capacity in lung transplant candidates [52] and facilitating functional recovery post-transplantation [53].

3.10 Human Leukocyte Antigen (HLA) Antibodies

HLA antibodies are formed by the body against certain tissue types after pregnancy, blood transfusion and organ transplantation. The presence of HLA antibodies can significantly limit the pool of available donors for a particular lung transplant candidate, and predict a higher rate of antibody mediated rejection (AMR) [54]. The presence of preformed donor specific HLA antibodies (DSA), particularly if they are complement-fixing, is associated with poor 1-year survival [55] after lung transplantation. Lung transplant centers have approached this issue in different ways, with some centers developing protocols to accept organs with cytotoxicity crossmatch negative DSAs,

which have shown similar short- and long-term survival [56] and allograft function [57]. These protocols use virtual crossmatches to determine levels of cross reactivity between the donor and recipient, and include pre- and post-operative plasma exchange, anti-B-cell agents such as rituximab, and intravenous immunoglobulins, in addition to standard immunosuppression [58]. This is an active area of research, and protocols addressing how best to approach lung transplant candidates with DSAs are evolving.

3.11 Infectious Disease Risk Factors

There are several infectious organisms that confer increased risk after lung transplantation, due to their aggressive and fastidious nature as well as multi-drug resistance patterns. *Burkholderia cepacia* complex (BCC) represents nine gemovars, including *Burkholderia cenocepacia* and *Burkholderia multivorans*. These organisms are intrinsically multi-drug resistant and are frequently present in lung transplant candidates with CF. Pre-transplant *Burkholderia cenocepacia* infection is associated with very high 1 year mortality in lung transplant recipients with CF [59], and is considered a strict contraindication to lung transplantation at most centers. However, some centers have described treatment of post-lung transplantation *Burkholderia cenocepacia* infections with regimens that include ceftazidime/avibactam [60], with mixed results. Treatment of BCC often requires combination antibiotic therapy, and lung transplantation in patients colonized with BCC should only take place at experienced centers.

Non-tuberculous mycobacterium (NTM), specifically *Mycobacterium abscessus*, are difficult to treat infections. Some analyses suggest that *Mycobacterium abscessus* infections in lung transplant recipients confer an increased risk of death [61], whereas multiple other case series have shown that patients with pre-operative *Mycobacterium abscessus* infection can be successfully transplanted if they undergo aggressive pre- and post-operative treatment with prolonged multi-drug antibiotic regimens [62-64].

Molds including *Scedosporium apiospermum* and *Lomentospora prolificans* are multi-drug resistant organisms that can cause disseminated infections in lung transplant recipients. Some centers consider colonization with these organisms to be a contraindication to lung transplantation, while several studies demonstrated that with lifelong azole treatment, patients with CF and *Scedosporium apiospermum* colonization may be successfully transplanted [65]. Another study found that post-transplant infection with *Scedosporium apiospermum* or *Lomentospora prolificans* did not confer a survival disadvantage, so long as prolonged anti-fungal treatment was instituted [66]. In general, *Lomentospora prolificans* infection or colonization is considered a stronger contraindication to lung transplantation than *Scedosporium apiospermum*, as *Lomentospora prolificans* is resistant to virtually all available antifungals.

Lung transplant recipients with a history hepatitis B virus (HBV) infection can rarely experience HBV reactivation as a consequence of immunosuppression [67], but this does not appear to have an effect on survival. As such, HBV infection is not a contraindication to lung transplantation if the candidate does not have concomitant liver disease. Entecavir is a safe and effective HBV prophylactic option in lung transplant recipients [68].

Safe and effective treatment for hepatitis C virus (HCV) infection with direct active antivirals (DAAs) has led to a substantial decrease in patients developing HCV related liver cirrhosis and hepatocellular carcinoma requiring liver transplantation [69, 70]. Lung transplant candidates with

active HCV infection should be treated prior to lung transplantation [6], though patients with active HCV infection can be transplanted and treated with DAAs afterwards, with similar outcomes to HCV negative recipients [71].

Human immunodeficiency virus (HIV) infection has historically been considered a strict contraindication to lung transplantation, given concerns about post-transplant immunosuppression leading to significant complications. However, several centers have reported good outcomes after lung transplantation in patients with well controlled HIV infection [72-74], with close attention to concomitant infections and drug-drug interactions.

3.12 Psychosocial Considerations and Risk Factors

All patients being considered for lung transplantation should undergo a comprehensive psychosocial evaluation, with assessment of mental health history, cognitive function, social support, substance use history, treatment adherence and health behaviors [75]. Psychosocial factors that are strict contraindications to lung transplantation include active substance abuse, cognitive impairment, and medical non-adherence [6] (see Figure 1). Patients require significant social support both before and after transplant, and inadequate social support needs to be addressed and mitigated prior to listing. Severe psychiatric conditions that affect medical compliance are a contraindication to transplant. Some psychiatric conditions, such as anxiety and depression, need to be assessed for and managed aggressively to minimize their effect on post-transplant medical adherence and rehabilitation. Patients with a history of medical non-adherence may be given the opportunity to improve their behavior to become eligible for lung transplantation, especially if the patients are young or have modifiable contributors, such as transportation or social support issues.

Patients with severe or progressive cognitive issues, such as dementia, are not suitable candidates for lung transplantation [75]. However, some patients may have mild cognitive impairment from chronic lung disease and hypoxemia, which may improve or worsen after lung transplantation [76, 77].

Patients with a history of substance abuse may be considered for lung transplantation if they have been adequately treated and have a sustained period of abstinence of at least 6 months. Patients should abstain from alcohol and cannabis during the waitlist period and after transplantation. Of note, many liver transplant centers have suspended the 6 month rule for alcohol abstinence, as it does not predict outcomes or risk of relapse [78]. However, less is known about outcomes of lung transplantation in patients with shorter periods of abstinence, and most centers continue to use the 6 month rule.

Inhaled marijuana use has been associated with fungal infections in solid organ transplant recipients [79], and even oral cannabinoids can interact with immunosuppressants [80]. To be a candidate for lung transplantation, all patients must be abstinent from tobacco or nicotine products for at least 6 months. Additionally, patients should avoid exposure to secondhand smoke to minimize its effect on transplanted organs.

Opioid use in lung transplant candidates is common. Some series suggest that opioids can be safely used for dyspnea prior to transplantation [81], and these patients have similar survival to those who do not use opiates [82]. Current guidelines recommend that patients with a history of

opioid use disorder on medication assisted treatment be considered on a case-by-case basis in consultation with a psychiatrist [6].

4. Other Considerations

4.1 Surgical Considerations in the Selection of Lung Transplant Candidates

Patients who have a history of cardiothoracic surgery, including pleurodesis, may have pleural adhesions that can result in significant intraoperative bleeding and longer cardiopulmonary bypass times, which can lead to post-operative respiratory failure and renal dysfunction [83]. Despite these complications, prior cardiothoracic surgery does not appear to affect short- and long-term survival after lung transplantation [84]. Potential lung transplant candidates who develop a pneumothorax should have their management discussed with a transplant center. All pneumothorax management options should be considered, with chemical pleurodesis being used as a last resort.

Patients with significant thoracic cage abnormalities, such as spinal or chest wall deformities, present unique surgical challenges to lung transplantation, and require an individualized approach. Lobar lung transplantation may be an option for patients with small chest size, and offers similar survival to full lung transplantation [85, 86].

4.2 ECLS as a Bridge to Transplantation (BTT)

ECLS may be used to bridge critically ill patients to successful lung transplantation in highly specialized and experienced centers. Lung transplant candidates with refractory hypoxemia or hypercapnia can be managed with veno-venous (VV) ECMO, whereas patients with significant RV failure are more appropriate for veno-arterial (VA) ECMO. While significant extrapulmonary organ dysfunction is generally considered a contraindication to BTT with ECLS, patients with renal and hepatic dysfunction that is directly related to pulmonary hypertension (PH) and RV failure can improve with VA ECMO. Awake ECLS allows patients to avoid the pitfalls of mechanical ventilation and participate in medical decision making and physical therapy. In high volume centers, ECLS as a BTT results in good short- and long-term outcomes [87, 88].

4.3 Lung Re-Transplantation

The primary indication for lung re-transplantation is chronic lung allograft dysfunction (CLAD). Patients who undergo lung re-transplantation have overall worse outcomes as compared to primary lung transplantation, though this is primarily driven by the worse outcomes experienced by patients who undergo re-transplantation early (<1 year after primary lung transplantation) [89] and for the restrictive CLAD phenotype [90]. However, some centers report similar outcomes between primary and re-do lung transplantation in carefully selected patients [91]. In selecting candidates for lung re-transplantation, centers must carefully evaluate their candidates for drivers of CLAD, which include infections, acute rejection/alloimmunization, aspiration/GERD, and medical non-compliance [92].

4.4 Multiple Organ Transplantation

Multiple simultaneous organ transplant is a rare occurrence and should only be performed at high volume centers due to inherent complexity of post operative management of multiple transplanted organs. For lung transplant candidates, the simultaneous transplant of an additional organ (heart, liver, or kidney) should be considered when there is significant pre-operative organ dysfunction such that there is a low likelihood of survival with an isolated lung transplant, or if significant post-operative organ dysfunction is anticipated [6]. In the LAS era, heart-lung and lung-liver transplant candidates have higher waitlist mortality than lung-kidney and isolated lung transplant candidates [93].

Heart-lung transplant should be considered in patients with both heart and lung dysfunction, such as in PAH due to congenital heart disease and in sarcoidosis with concomitant pulmonary and cardiac disease [94]. PAH in the absence of CHD is a more controversial indication for heart-lung transplant. In retrospective studies in patients with PAH, heart-lung transplant recipients experience similar outcomes compared to isolated bilateral lung transplant recipients [95, 96], as native RV function is expected to improve after normalization of PVR. Patients with advanced lung disease and cardiac pathology amenable to surgical repair (such as intra-cardiac shunts or valvular disease) should be considered to simultaneous bilateral lung transplant and corrective surgery [97].

Indications for lung-liver transplant include advanced lung disease that meets lung transplant criteria with concomitant biopsy-proven cirrhosis and a portal gradient >10-12 mmHg [98]. Patients with advanced lung disease related to alpha-1 antitrypsin (A1AT) disease and CF have increased risk of underlying liver disease, with rates of cirrhosis between 19-43% in the former, and 22-47% in the latter [98]. For patients with LAS <50 undergoing lung-liver transplant, survival is non-inferior when compared to isolated lung transplant. However, LAS scores >50 and elevated Model for End-Stage Liver Disease (MELD) score are associated with higher post-transplant mortality [99]. Interestingly, one study showed similar survival for lung-liver recipients compared to isolated lung transplant recipients with similar levels of liver dysfunction [100]. Contraindications to lung-liver transplant include albumin <2.0, INR >1.8, severe ascites or hepatic encephalopathy [101].

Indications for lung-kidney transplant include eGFR <35, as these patients are most likely to progress to ESRD [102]. Despite having elevated disease burden with multiorgan failure, patients with underlying renal dysfunction who undergo lung-kidney transplant have similar one- and five-year survival rate when compared to matched isolated lung transplant patients [16]. However, data is limited to case series and cohort data.

5. Disease Specific Considerations

5.1 COPD

The heterogeneity of COPD, with environmental, behavioral, and genetic etiologies leads to a variable disease course which can include advanced disease. Determining which patients with advanced COPD will progress to require lung transplantation relies on validated prognostic tools such as the BODE index [94]. The BODE index includes BMI, degree of obstruction (based on forced expiratory volume in 1 second [FEV_1]), dyspnea and exercise (as graded by 6MWD); its use is recommended by the 2014 ISHLT candidate selection guidelines [94]. However, recent studies indicate that the BODE index may overestimate mortality [103, 104]. Isolated FEV_1 is another marker

for transplant consideration, and cutoffs <20% predicted demonstrate a survival advantage for lung transplant [105].

Lung transplant teams must weigh these factors to achieve optimal transplant outcomes. A BODE index of 5-6, FEV_1 percent predicted between 20-25%, or a low diffusing capacity of the lungs for carbon monoxide (DL_{CO}) should prompt referral for evaluation for lung transplantation. Trajectory of disease course also influences transplant, and patients should be referred to a lung transplant center if the BODE score increases more than 1 point in a year, if the ratio of pulmonary artery to aorta diameter on CT scan increases to greater than 1, or if patients perceive an unacceptable quality of life due to their disease [106, 107].

Prior to or concurrent with a lung transplant evaluation, providers can optimize COPD therapy through consideration of either surgical or bronchoscopic lung volume reduction (LVR) therapy. LVR therapy can improve exercise capacity, lung function, and quality of life; it may also confer a survival benefit in select patients [108, 109]. In patients undergoing a transplant evaluation, it can delay need for a transplant and optimize patient's nutritional status and exertional capacity prior to transplant [110, 111]. The downside of LVR is that it may result in pleural adhesions, which can increase operative times and bleeding [112] during lung transplantation. The modality of LVR also influences post-lung transplant outcomes, with surgical lung volume reduction associated with a higher rate of post-operative ECMO, whereas endoscopic lung volume reduction is associated with increased risk of wound infection [113]. LVR followed by bilateral lung transplant was appears to show no effect on both short term and long-term mortality at one-, three- and five-year ranges [113].

Transplant listing should occur after BODE score is elevated [7-10], if FEV_1 reaches <20% predicted, if right heart catheterization (RHC) shows moderate to severe PH, and if evidence of hypercapnia. In addition, a history of severe exacerbations, or increased frequency of exacerbations should also prompt listing for transplant [6].

Median survival for lung transplant recipients with COPD is similar to overall median survival (5.6 vs. 5.8 years) [114]. Patients with COPD experience substantial HRQL improvement after lung transplantation, and recipient age does not significantly attenuate the quality-of-life benefits [3].

5.2 Interstitial Lung Disease

The poor prognosis associated with ILD, with between a three-to-five-year median survival if untreated, necessitates lung transplant consideration at the time of diagnosis. In addition, patients with fibrotic ILD, particularly IPF, can develop acute exacerbations (AE) that are associated with high mortality [115]. Fortunately, antifibrotic therapy in IPF with either nintedanib [116] or pirfenidone [117] slows disease progression, is associated with a reduced risk of AEs, and has demonstrated a survival benefit [118]. The antifibrotics show similar response in non-IPF fibrotic interstitial lung disease such as autoimmune ILD, hypersensitivity pneumonitis, and idiopathic non-specific interstitial pneumonia [119]. Despite the benefits of antifibrotic therapy, no current therapy offers reversal of pulmonary fibrosis and therefore early lung transplant evaluation is crucial.

Lung transplantation provides a survival benefit in both IPF and non-IPF ILD for patients with a forced vital capacity (FVC) or DL_{CO} decline, need for hospitalization, evidence of frailty, oxygen requirements, or progressive symptoms [120-123]. In non-IPF ILD, early referral should occur with cases of familial fibrosis, anti-neutrophil cytoplasmic antibody (ANCA) positive pulmonary fibrosis

patients, pulmonary fibrosis due to sarcoidosis, ILD associated with connective tissue disease (CTD), or the Hermansky-Pudlak syndrome [124-126]. Familial pulmonary fibrosis patients require telemeropathy assessment, and close evaluation for hematologic abnormalities and underlying liver disease [6].

Patients should continue on antifibrotic therapy until the time of transplant, as they have not been shown to impact wound healing or outcomes [127]. Pulmonary function testing and functional evaluation can help guide transplant listing. A decline in any of the following parameters over a six-month time frame can be an indication for listing: a 10% decline in either FVC or DL_{CO}, a 5% decline in FVC with evidence of radiographic progression, or desaturation to <88% on six-minute walk testing or a decline of 50 meters or more [6]. Additional factors to weigh in transplant listing include evidence of PH on echocardiography or RHC due to decreased survival in ILD patients with PH [128], or hospitalization for acute exacerbation, pneumothorax, or respiratory decline [6].

5.3 Cystic Fibrosis

Until recently, CF was a common indication for transplant. The advent of CF modulator therapies has dramatically affected overall disease course for patients who are candidates for those therapies, with the resultant decline in the need for lung transplants for CF [129, 130]. For patients who are not candidates for CF modulator therapy, the natural disease progression and associated infectious and non-infectious complications illustrate the considerations required to optimize patients benefit from lung transplant.

The best indicator for lung transplantation remains percent predicted FEV_1, with values <30% associated with a median survival between 2-4 years [129]. In addition, providers should consider advanced disease factors such as a rapid decline in FEV_1, BMI <18, supplemental oxygen use, development of CF related diabetes mellitus requiring insulin, and more than one exacerbation per year. Other risks factors for CF mortality include resting hypercapnia ($PaCO_2$ >50), PH, massive hemoptysis requiring bronchial arterial embolization, pneumothorax, impaired functional status, and/or low six 6MWD [131-135]. Composite scores combining FEV_1, BMI, IV antibiotic use, hospitalization, steroids, oxygen or non-invasive ventilation use, or *Burkholderia cepacia* complex colonization can help prognosticate, with excellent external validity [136, 137]. Patients with more than four risk factors have 55% mortality at three years, while those with two or less risk factors had <1% risk of mortality at 3 years.

Certain complications of CF remain absolute contraindications to lung transplantation. As discussed earlier in this chapter, multidrug resistant organism (MDRO) bacterial infections such as with *Burkholderia cepacia* complex and *Mycobacterium abscessus* are contraindications at most centers [138], although recent small cohort data in *Burkholderia* shows no difference in outcomes compared to patients with no history of infection [139]. Non-infectious contraindications include malnutrition with BMI <18, hepatobiliary disease, or colorectal cancer [138]. Lung transplant candidates with CF should be screened with colonoscopy at age of 40, and routinely for hepatobiliary disease [140]. Evaluation of sinus disease is also paramount to minimize potential risk of post infectious complications and improve quality of life, although pre-transplant surgical intervention is not associated with improved survival [141-143].

5.4 Non-CF Bronchiectasis

Non-CF bronchiectasis represents 2.7% of all lung transplants between 1995-2018 [1]. Indications for transplant include the validated FACED and bronchiectasis severity index (BSI) scoring systems and FEV_1. The FACED score consists of FEV_1 (<50%), age (<70), chronic colonization (presence of *Pseudomonas*), extension (lobes affected), and dyspnea (modified medical research council [mMRC] scoring) [144]. The BSI incorporates variables of age, BMI, FEV_1, hospital admissions, exacerbations, dyspnea (mMRC score), *Pseudomonas* colonization, other bacterial colonization, and radiologic involvement [145]. A recent small observational cohort study showed no difference in scoring on survival [145]. FEV_1 is also associated with mortality in non-CF bronchiectasis with a single study showing 39% four-year mortality risk for patients with FEV_1 <30% [146]. A lung transplantation evaluation should be considered when patients reach a threshold of BSI score >9, a FACED score ≥5, or an FEV_1 <30%.

Lung transplant evaluation and prognostication for patients with non-CF bronchiectasis remain an area of ongoing study. Compared to CF-matched cohorts, non-CF bronchiectasis transplant patients appear to have a lower risk of death and five-year mortality of 25%; which illustrates the difficulty of prognostication compared to robust CF datasets [147].

5.5 Pulmonary Arterial Hypertension

Transplantation in PAH presents a clinical challenge, as the LAS system cannot fully capture both waitlist mortality and the rapid clinical deterioration that can occur. Current guidelines recommend use of serial scoring evaluation with either the REVEAL 2.0 and/or the 2015 ERS/ESC model to guide management [6, 148]. If PAH patients fail to achieve low risk status on serial scoring evaluation at three to six months, PAH therapy should be intensified. Patients who remain at a high-risk group despite optimization or therapy should be referred for lung transplant evaluation. In addition to clinical scoring systems, use of cardiopulmonary exercise testing and RV functional assessment with either trans-thoracic echocardiogram and/or cardiac MRI can further risk stratify patients [149, 150].

The decision of when to list patients with PAH is more challenging, though a new four strata risk stratification model [151] may be helpful in deciding which patients may benefit most from lung transplantation. In one retrospective study, patients who were intermediate-high risk despite receiving optimal PAH therapy were most likely to benefit from lung transplantation [152], whereas patients who achieved intermediate-low risk had a 1-year transplant-free survival of 95%, which suggests that these patients can be monitored closely without lung transplantation. Other indications for listing include REVEAL 2.0 score >10 on appropriate PAH therapy (including parenteral prostacyclin therapy), progressive hypoxemia, progressive renal or liver dysfunction, or life-threatening hemoptysis [6].

Unique considerations in PAH include multiorgan disease and the different etiologies of PAH. Renal dysfunction typically occurs secondary to cardiorenal syndrome and can improve post transplantation. Similarly, RV dysfunction in PAH heightens risk of liver dysfunction, which can also improve after lung transplantation. Familial PAH, pulmonary venous occlusive disease (PVOD), and CTD associated PAH also portend a complicated post-transplant course [148]. While some centers have had success with single lung transplantation in PAH [153], the bilateral lung transplantation provides superior outcomes in PAH [154], and is the procedure of choice at most centers.

5.6 Lymphangioleiomyomatosis (LAM)

LAM is a rare cystic lung disease that is an uncommon indication for lung transplantation. mTOR inhibitor therapy can prevent progression of disease and prevent the need for lung transplantation. Indications for transplant in LAM include FEV_1 <30%, exertional dyspnea (NYHA Class ≥III), or hypoxemia at rest (SpO_2 <88%) [155-157]. Although LAM can recur in the transplanted lung, recurrence does not appear to alter survival, and resumption of mTOR therapy can potentially eliminate recurrent disease [158]. Bilateral lung transplant is also recommended due to concern for pneumothorax in the native lung or in recurrent disease in the transplanted lung [159, 160].

Transplant considerations also include prior pleurectomy and intra-operative extracorporeal membrane oxygenation (ECMO) use, as both factors increase risk of hemorrhage [158]. Angiomyolipomas, however, do not increase bleeding risk [160, 161]. mTOR inhibitor therapy should be transitioned from long acting (sirolimus) to short acting therapies (such as everolimus) [162] prior to transplant to prevent delayed anastomotic healing and anastomotic dehiscence [163]. The risks and benefits of continuing mTOR therapy while on the lung transplant wait list should be discussed with patients prior to transplant. Any disease progression while on mTOR therapy is a strong indication for transplant evaluation.

5.7 Thoracic Malignancy

Thoracic malignancy is both a rare and declining indication for lung transplant, and accounted for less than 0.1% of transplants between 1995-2018 [1]. The major concerns with lung transplantation for malignancy include increased recurrence rates and decreased survival with the exception of incidentally detected malignancy [164, 165], and require appropriate protocols for lung cancer surveillance within transplant programs [166].

The following disease states may be appropriate for treatment with lung transplantation: adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma and/or multifocal lung adenocarcinoma with low invasive component and no evidence of lymph node involvement [167]. Transplant evaluation requires full body staging with imaging and lymph node sampling. Imaging for staging can include CT chest, abdomen, and pelvis with IV contrast, and/or a whole-body positron emission tomography scan with magnetic resonance imaging of the brain [167]. Lymph node sampling can include either endobronchial lymph node sampling or mediastinoscopy. Imaging should be repeated at three-month intervals while on the transplant waiting list [164, 168].

In patients who have isolated lung malignancy, lung transplantation may be considered if the following criteria are present: surgical resection of the malignancy is not feasible, either due to multifocal disease or if there is significant underlying pulmonary disease; the malignancy has caused significant respiratory compromise; the patient has failed or is not a candidate for medical oncologic therapy; and lung transplantation will provide a cure [6]. Furthermore, transplantation should be aborted if lymph node and/or metastatic spread is found intraoperatively during transplant [167, 168].

5.8 Acute Respiratory Distress Syndrome (ARDS)

The rapidity and severity of ARDS compound the difficulties of pre-transplant evaluation and assessment. However, given the frequency of ARDS, several criteria can assist in transplant evaluation. Prognostic factors associated with recovery post-transplant in ARDS include younger age, the absence of medical comorbidities or extra-pulmonary dysfunction, an underlying pulmonary cause of ARDS, and the use of extracorporeal life support as a bridge to transplant [169, 170]. One factor associated with increased early mortality is ICU acquired muscle weakness [171]. Patients should be considered for transplant if on ECMO for greater than three weeks without clinical improvement, with persistent parenchymal infiltrates, and severely reduced lung compliance (increased driving pressure) [172, 173].

5.9 COVID-19 Related Lung Disease

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused millions of cases of ARDS and COVID-19 related ILD. While the long-term clinical course of COVID-19 is variable, some patients develop irreversible fibrosis and may be candidates for lung transplantation [174]. As much as possible, these patients should be evaluated using all the traditional metrics detailed earlier in this chapter. Importantly, potential lung transplant candidates with COVID-19 fibrosis must clear their original infection before they are candidates for transplant and the necessary immunosuppression. Additionally, many patients with COVID-19 ARDS and fibrosis may have some gradual improvement over a period of several months, so they should be observed for an adequate amount of time (i.e., at least 4-8 weeks) to ensure that lung transplantation is their only option [175]. PH is common in patients with COVID-19 ARDS and fibrosis, but it does not appear to confer increased waitlist or post-transplant mortality [176].

6. Conclusion

Lung transplantation is being performed more commonly throughout the world and is a last resort treatment option for patients with end stage lung disease. While survival after lung transplantation appears to be increasing, it remains lower than that of all the other solid organs. As lung transplant centers gain experience, they are becoming more comfortable selecting older and more medically complex patients. The field of lung transplantation continues to evolve in exciting ways, and careful evaluation of disease specific factors, comorbid medical conditions, and other risk factors in lung transplant candidates remains crucial to successful transplantation.

Author Contributions

Christopher Thomas, Matthias Williams, and Oksana Shlobin all contributed to writing this manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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