Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation

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Tens of thousands of patients with advanced lung diseases may be eligible to be considered as potential candidates for lung transplant around the world each year. The timing of referral, evaluation, determination of candidacy, and listing of candidates continues to pose challenges and even ethical dilemmas. To address these challenges, the International Society for Heart and Lung Transplantation appointed an international group of members to review the literature, to consider recent advances in the management of advanced lung diseases, and to update prior consensus documents on the selection of lung transplant

candidates. The purpose of this updated consensus document is to assist providers throughout the world who are caring for patients with pulmonary disease to identify potential candidates for lung transplant, to optimize the timing of the referral of these patients to lung transplant centers, and to provide transplant centers with a framework for evaluating and selecting candidates. In addition to addressing general considerations and providing disease specific recommendations for referral and listing, this updated consensus document includes an ethical framework, a recognition of the variability in acceptance of risk between transplant centers, and establishes a system to account for how a combination of risk factors may be taken into consideration in candidate selection for lung transplantation.

Lung transplantation continues to grow as a field, with more than 4,500 transplants performed worldwide in 2019 at over 260 lung transplant centers.[1] This trend reflects the expansion of acceptable donors and candidates made possible by clinical and scientific advances. Far fewer absolute contraindications for lung transplant candidacy exist now, compared to the time of publication of prior versions of this document, making the selection of candidates even more complex.[2-4]

Goal of this consensus document

This document is intended to express a consensus of the membership of the International Society for Heart and Lung Transplantation (ISHLT) to provide guidance for timely referral, assessment, optimization, and listing of potential lung transplant candidates. The current document updates the prior three, highlighting the recognition that comorbidities and other risk factors often interact to affect post-transplant survival benefit. While lung transplantation aims to improve both survival and quality of life, the expert consensus acknowledges that when making recommendations about allocating a scare resource, survival benefit is prioritized based on the ethical framework described in this document.

Methods

This consensus document was developed in accordance with the ISHLT Standards and Guidelines committee document development policies. The consensus committee members were selected to represent the diversity of the society and were approved by the ISHLT Standards and Guidelines committee. Each member contributed to the literature searches, developed content, voted on the final consensus statements, and approved the final manuscript.

Literature searches performed in early 2020 reviewed all pertinent articles, focusing on newer peer reviewed research available since publication of the 2014 consensus document.[4] During review of the document additional pertinent newly published articles were included, but a comprehensive review of literature was not repeated. Search terms, filters, and the resultant number of articles are available in the online supplement. The recommendations reflect expert synthesis of the current literature. In areas where there was paucity of evidence, the statements reflect consensus reached by the committee with an *a priori* threshold of >80% agreement on consensus statements.

General ethical framework and allocation systems

The worldwide scarcity of donor lungs requires rationing of this lifesaving but limited societal resource. This makes the selection of transplant candidates an ethical choice as well as a medical one. The fundamental ethical principles of "utility", "justice", and "respect for persons" (see Table 1) must, therefore, provide the framework for candidate selection and organ allocation systems.[5,6]

Since lung transplant is a lifesaving procedure, the principle of utility requires that survival be maximized when choosing transplant candidates. While some national allocation systems consider utility narrowly to determine survival only at a patient level, others may apply this principle more broadly on a societal level. Candidates should be carefully selected, as an unsuccessful lung transplant affects not only the individual who was transplanted, but also a potential alternative recipient who did not have the opportunity to be transplanted due to the prevailing organ shortage. Our recommendations have the explicit goal of maximizing long-term survival in order to provide net survival gains for society as a whole.

As donor organs are obtained from society at large, equally important to utility is the principle of justice that requires all individuals with a potential survival benefit from lung transplant be given equal consideration and opportunity for transplant. Therefore, measuring an

Table 1 Ethical Principles for the Allocation of Donor Lungs[6]

Principle	Application to organ allocation
Utility	To maximize net benefit (e.g., using years of survival gained to prioritize allocation)
Justice	To distribute the benefits and burdens of organ allocation system in a fair way (e.g., using medical urgency to prioritize allocation, allowing special consideration for candidates for whom it is difficult to find a suitable organ)
Respect for persons	To treat persons as autonomous with the right for self-determination (e.g., the right to give or withhold informed consent for a lung transplant)

individual's "value" in society has no place in evaluation of transplant candidacy and this includes their contribution to society, social rank, or occupation. Similarly, group characteristics such as race, gender, or socioeconomic position should not be used to disadvantage access to transplant even if these subgroups are shown to have inferior transplant outcomes.

Finally, the principle of respect for persons authorizes a candidate's right to self-determination or autonomy. To allow candidates the opportunity to exercise this right, transplant centers must provide transparent guidelines that explain the criteria for candidate selection and organ allocation.

Timing of referral, evaluation, and listing

Referral for lung transplant is a complex process and, when possible, should begin before the need for transplant becomes urgent. Ideally, patients should be referred before they meet criteria for active waitlisting to provide an opportunity to introduce the concept of lung transplant, its requirements, and expected outcomes. Early referral may allow time for candidates to address modifiable barriers to transplant, such as obesity, malnutrition, medical comorbidities, or inadequate social support. Vaccination records should be reviewed and patients should receive vaccines as early as possible, as some vaccines require multiple injections over time, live vaccines are contraindicated after transplant, and any vaccine may be expected to have lower protective effect in the immunosuppressed. For patient referrals that are too early for full evaluation or with contraindications for transplant, specific parameters for the timing of re-referral and recommendations for ongoing optimization of candidacy should be provided.

A full evaluation includes assessment of lung disease severity, anatomy, nutritional status, degree of frailty, presence and severity of comorbidities, psychosocial circumstances, and health-related behaviors that impact recovery and long-term survival. The timing of full evaluation for transplant should be informed by transplant providers' assessment of the potentially modifiable risk factors for transplant, a patient's disease trajectory, and likelihood for prolonged wait for suitable donor organs (e.g., candidate with high level of HLA sensitization). Sometimes, a precipitous decline leads to referral under less than ideal circumstances. In these cases, every effort should be made to fully evaluate a potential candidate's eligibility in a similar manner to other candidates. Referral of patients on life sustaining interventions such as mechanical ventilation and / or extra-corporeal life support (ECLS) as a bridge to transplant (BTT), may be considered in highly selected patients at centers with expertise (see Table 2 and section on BTT below.)

Risk factors to be considered

It is essential to account for medical comorbidities, psychosocial factors, and potential for rehabilitation in the evaluation of transplant candidates. Risk factors were identified

that place potential candidates at increased risk for poor outcomes following lung transplant (Table 2). While it is important to consider the relative risk associated with a particular risk factor (e.g., increasing age or obesity), it is also relevant to think about the cumulative effect of multiple potential risk factors. Estimation of an individual's post-transplant survival based on published literature is challenging, highlighting the importance of future research to improve our ability to better predict outcomes. Further, the lung transplant community ought to consider an acceptable threshold for post-transplant survival to guide the complex task of allocation of this scarce resource in patients with high or substantially increased risk of poor post lung transplant outcomes.

Age: Consideration of an upper age limit for lung transplant candidacy remains a controversial subject. In the 2006 and 2014 guidelines, age greater than 65 years in association with low physiologic reserve and/or other relative contraindications was considered a relative contraindication.[2,4] There has been no endorsement of an upper age limit as an absolute contraindication, but older individuals have worse long-term survival following lung transplant.[7] The age of lung transplant recipients has increased over the past decade. In the United States (U.S.), candidates greater than 65 years of age now comprise more than 30% of the waiting list and are the age group with the highest transplant rate.[8] With increasing experience in older recipients, several studies have shown that carefully selected older recipients may have the same short-term survival as younger recipients.[9] However, the results are skewed by selection bias, reflecting the fact that most recipients over the age of 65 years undergoing lung transplant are highly selected with very few comorbidities such as coronary artery disease and diabetes. Despite this selection bias and acceptable short-term outcomes, lung transplant recipients over the age of 70 years have decreased longer term survival.[9]

As lung transplant centers become more comfortable with offering transplant for individuals in an older age demographic, it is important to remember the larger community has expressed preference to allocate this limited resource to younger patients first.[10] Restricting access to transplant for older adults may be ethically justified both on the basis of justice and utility. The negative effect of advanced age on post-transplant survival is significant, especially for long-term survival, limiting the net utility of lung transplant in this population both at the individual and societal level. In addition, ethical paradigms related to just distribution of scarce resources, such as the "fair-innings" perspective, require that every individual has an equal chance to live a full life and that societal resources should be expended to maximize this chance. This may justify providing preferential access to younger candidates who have a stronger claim to an organ based on this account of justice. One option to address this issue is the consideration of allocation of lungs from older donors to older recipients, as this has been demonstrated to result in comparable outcomes.[11,12] In summary, while older age is increasingly

Table 2 Risk factors for poor post-transplant outcomes

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.

accepted in lung transplant candidates, the reduced long-term survival and the relevance of ensuring a just distribution of scarce resources should be considered.

Malignancy: Age-appropriate and disease-specific cancer screening must be a part of every pre-transplant evaluation. Patients with a prior history of malignancy must undergo testing to confirm no evidence of residual or metastatic disease. Malignancy with high risk of recurrence or death is an absolute contraindication, but it is increasingly acknowledged in the context of lung transplant that not all neoplastic diseases are equal.[13,14] Certain malignancies may not be significantly affected by immunosuppression and some may be managed post-transplant with aggressive surveillance and intervention (e.g., cervical dysplasia, anal dysplasia, and cutaneous non-melanoma skin cancer). Lung transplant may be an option in circumstances where the risk of recurrence is deemed to be very low based on the type and stage of cancer and with negative metastatic evaluation. Two recent consensus statements have addressed how to consider the distinct risks associated with pre-existing malignancies prior to transplant.[13,14] Transplant centers should work closely with oncology specialists to evaluate each patient with a history of cancer to determine the stage-specific risk of recurrence or progression, which may be higher in the setting of immunosuppression, and to determine the necessary cancer-free period prior to listing.[15,16]

Renal function: Increased risk has been demonstrated in lung transplant candidates with GFR <60 ml/min/1.73m^2 by chronic kidney disease epidemiology equation (CKD-EPI) at the time of listing, especially in patients > 45 years of age.[17-21] Renal function is especially important following lung transplant as the peri-operative period is often complicated by hypotension and hypoperfusion of kidneys, and nephrotoxic calcineurin inhibitors remain the mainstay of maintenance immunosuppression. Outcomes are consistently worse for patients who develop renal failure requiring renal replacement therapy.[18] In select candidates with concomitant CKD, consideration may be given for possible simultaneous lung-kidney transplant or staged lung-kidney transplant (see multiorgan transplantation section below).

Coronary Artery Disease (CAD): A high prevalence of CAD has been demonstrated in lung transplant candidates even in those without risk factors. Thus, evaluation for CAD should remain a part of transplant candidacy assessment.[22] Consultation with a cardiologist familiar with lung transplant candidate selection should be considered for the development of protocols for pre-transplant assessment and management. Multiple retrospective studies over the past 5 years have shown that patients with mild to moderate CAD or those who have undergone revascularization for CAD may not have worse survival compared to patients without CAD.[23-26] It is important to point out that these patients have been highly selected and more often undergo single lung transplant.[27] CAD was not associated with worse survival for patients undergoing percutaneous coronary intervention with stent placement prior to lung transplant or coronary artery bypass grafting (CABG) at the time of lung transplant.[23] In those patients with a history of prior

CABG, bilateral lung transplant has been associated with inferior survival compared to those who undergo single lung transplant.[28] Considering the results of these studies, CAD should not be considered an absolute contraindication. However, CAD has been recognized as a potential marker for systemic atherosclerotic disease and patients with CAD should have additional evaluation for other underlying vascular diseases, including cerebrovascular and peripheral vascular disease.[25]

Peripheral Vascular Disease (PVD): PVD is considered a risk factor for limiting rehabilitation post-transplant and poses a risk of ischemic limb complications with peri-operative use of ECLS. PVD frequently coexists with CAD and cerebrovascular disease and may be a marker of overall medical comorbidity in a potential candidate. Although a specific threshold for PVD cannot be determined, it may be important in the evaluation of a candidate's suitability for transplant.

Heart Failure: Although patients with right heart failure can successfully undergo lung transplant, there are few data about patients with left ventricular dysfunction because the majority of centers will not transplant patients with a low left ventricular ejection fraction.

Connective Tissue Disease (CTD): Multiple studies have demonstrated that carefully selected patients with CTD have no difference in survival or allograft dysfunction compared to patients undergoing lung transplant for other indications.[29,30] Screening for extra-pulmonary systemic disease in collaboration with a multidisciplinary team, including rheumatologists, gastroenterologists, and nephrologists, is essential in these candidates as cardiovascular (including conduction abnormalities, myocarditis, heart failure, and CAD), gastrointestinal, renal, musculoskeletal, or other organ system involvement may affect post-transplant outcomes and need to be considered on a case-by-case basis. Patients with inflammatory myopathies should undergo comprehensive screening for occult neoplasm.[31]

Esophageal Dysfunction / Gastrointestinal Dysmotility/ Gastroesophageal reflux (GER): Post-transplant GER is variably associated with increased risk of acute rejection, pulmonary infection and earlier development of chronic lung allograft dysfunction (CLAD).[32,33] Anti-reflux surgery pre-transplant and early post-transplant has been associated with a decrease in the development of early allograft dysfunction.[34,35] It is important to note that conventional anti-reflux surgery may not be a suitable option in many cases due to concurrent esophageal dysmotility and/or gastroparesis. Diseases characterized by GER and esophageal dysfunction, such as scleroderma or other connective tissue disorders, may pose specific challenges for a transplant recipient due to increased risk of micro- or macro-aspiration. Despite these risks, studies of scleroderma recipients, undergoing lung transplant at centers with expertise with this patient population, have demonstrated that esophageal dysfunction does not appear to impact outcomes.[36,37]

Hematologic abnormalities: Thrombocytopenia, leukopenia, or anemia may contribute to peri-operative complications and may limit use of optimal maintenance immunosuppression and necessary antimicrobial prophylaxis following lung transplant. Untreatable hematologic disorders including bleeding diathesis, thrombophilia, or severe bone marrow dysfunction can substantially increase the risk of poor post-transplant outcomes and lung transplant should be considered only in highly selected cases. Patients with telomeropathy should undergo detailed evaluation, potentially including bone marrow biopsy, due to their concurrent risk of hematologic abnormalities including myelodysplastic syndrome.[38,39]

Body Mass Index (BMI): The preponderance of current evidence supports an increased risk of primary graft dysfunction and post-transplant mortality for obese recipients compared with normal or overweight candidates.[40-42] In one study, when stratified by degree of obesity, the risk of mortality was increased for patients with a BMI >35 and not in those with BMI 30-34.9.[42] These patients should be encouraged to lose weight as the magnitude of pre-transplant weight loss is directly correlated with improvements in post-transplant survival for candidates who are not underweight.[43,44] While low BMI has been associated with increased mortality, Cystic fibrosis (CF) recipients with BMI <17 kg/m^2 have a survival rate similar to other commonly transplanted patients.[45] Of note, the mechanisms underlying adverse effects of high or low BMI on transplant outcomes are not well understood. Recent data show that BMI is not an accurate surrogate of body composition with ongoing research efforts to better assess and risk stratify transplant candidates.

Hypoalbuminemia: Hypoalbuminemia (<3.5 g/dl) has been independently associated with decreased survival and post-operative complications.[46-48] It is also a predictor of poor survival for lung transplant candidates while on the waiting list including those who require ECLS prior to lung transplant.[49,50]

Functional Status and Frailty: Frailty, defined as a generalized vulnerability to stressors resulting from the presence of multiple physiologic deficits, is associated with an increased risk of waitlist and post-transplant mortality.[51-53] However, frailty in lung transplant candidates is often attributable to advanced lung disease and may improve following transplant.[54] When considering frailty in lung transplant candidates, it should be noted that optimal assessment tools for frailty are not yet accepted and caution is warranted in using frailty for listing decisions. Functional status remains an important predictor of post-transplant outcomes.[55,56] Pre- and post-transplant pulmonary rehabilitation should be recommended for transplant candidates and recipients.[57,58]

Human Leucocyte Antigen (HLA) Antibodies: Elevated HLA specific antibodies detected in peripheral blood may make finding a compatible donor difficult and may predict poor outcomes.[59-61] However, some centers describe successful lung transplantation despite positive cross match.[62,63] Cut-off levels for organ acceptance and the optimal methods for detection of functional donor specific antibodies have not been determined. In addition, there is significant variability among transplant centers with regards to pre-transplant

desensitization in highly sensitized candidates with insufficient evidence of effect.

Infectious disease risk factors

Multi-drug resistant organisms

Advances in diagnostic techniques, new active drugs, and efficiency in both drug and disease monitoring have improved lung transplant results in individuals colonized or infected with multi-drug resistant organisms. While these organisms are no longer universally considered an absolute contraindication, several pose substantial risk. These should be managed by centers with specialized experience and guidance by an infectious disease consultant experienced in the field of lung transplantation.

Non-tuberculous mycobacteria (NTM): *M. abscessus* subspecies *abscessus* is considered a high risk factor for lung transplant due to the intrinsic resistance to antimicrobials, tendency to relapse even after prolonged therapy, and association with CLAD after transplant.[64,65] Increasing evidence shows that intensive treatment and surveillance pre and post-lung transplant may lead to better results.[66-69] Thus, patients with *M. abscessus* should be managed at centers with expertise and protocols for managing this infection.

Non-aspergillus molds: *Scedosporium apiospermum* or *Lomentospora prolificans* may lead to severe disseminated infections after lung transplant. For *S. apiospermum*, acceptable results have been observed, while *L. prolificans* still seems to incur a substantially higher risk due to its resistance patterns. Decisions about candidacy must be individualized, considering the susceptibilities, efficacy of synergistic antifungal therapy, and potential reservoirs of infection.[70,71]

***Burkholderia cepacia* complex**: *Burkholderia cepacia* complex includes several genotypically distinct bacteria, the most common of which are *B. cenocepaci*a and *B.multivorans*. Of these, particularly *B. cenocepacia* has been associated with post-transplant infections and increased mortality especially within the first 6-12 months.[72,73] While it may be considered an absolute contraindication at many centers, patients may be candidates at specialized centers that have attained satisfactory outcomes with protocols implementing newer antibiotic combinations and intense management of sinusitis.[74-77]

Viral pathogens

Hepatitis B virus (HBV): Antivirals for HBV infection are available and safe to use post-transplant for prophylaxis and treatment. Consequently, HBV in patients without liver disease is not a barrier to lung transplant.[78]

Hepatitis C virus (HCV): Direct-acting antiviral combination therapy is widely available for HCV. Ideally, patients with HCV should be treated prior to lung transplant; however, patients with a detectable HCV viral load without significant liver fibrosis may be treated after lung transplant.[79,80]

Human immunodeficiency virus (HIV): Case series have demonstrated comparable 1-year and 5-year survival for HIV-infected lung transplant recipients with CD4+ lymphocyte counts above 200/mm^3 and HIV viral loads below 20 copies/ml.[81-85] Drug-drug interactions require expertise and careful coordination, and antiretroviral regimens free from efavirenz or ritonavir are recommended.

Psychosocial risk factors

The psychosocial evaluation of lung transplant candidates encompasses assessment of psychological function, neuropsychiatric function, social support, substance use, transplant knowledge, and behavioral adherence.[86] Despite wide recognition of the importance of psychosocial functioning for favorable lung transplant outcomes, few psychosocial contraindications are considered absolute. These include non-adherence to medical treatment, progressive cognitive impairment, and active substance use (Table 2). Importantly, psychosocial data are probabilistic by nature and therefore must not be interpreted in isolation. Transplant teams should feel empowered to use their own discretion to make informed decisions regarding patient selection with attention to the dangers of implicit bias against subsets of the population.

Non-adherence: Repeated episodes of non-adherence without evidence of improvement are considered a contraindication for adult patients. For pediatric and young adult patients, ongoing assessment of non-adherence should occur as they progress through different developmental stages.

Pre-transplant cognitive impairment may impact medical decision-making, consent, and self-management capabilities. Dementia, which has become more common as candidate age has increased, is considered a contraindication, particularly progressive forms.[4,86-89] Dementia has been associated with adverse post-operative outcomes.[90-93] Other forms of cognitive dysfunction among individuals with advanced pulmonary disease may be amplified by hypoxemia or polypharmacy, and may improve post-transplant in some cases.[94-99]

Affective and anxiety disorders may affect peri-operative outcomes and quality of life. Depressive symptoms prior to transplant have been linked to poorer transplant outcomes.[100-104] The active use of psychotropic medications among candidates should not constitute a contraindication, but careful examination of potential interactions between psychotropic and transplant-specific medications should be conducted.

Adequate support and caregiving in both the pre- and post-operative period are critical for success with lung transplant, and lack of support may increase risk of non-adherence and post-transplant mortality.[105-110] Transplant centers are encouraged to consider socioeconomic status within the broader context of the patient's support system and psychological resources in order to identify patients requiring enhanced surveillance and support. However,

socioeconomic factors should not warrant exclusion from candidacy.

Substance use disorders: Patients should be assessed for active substance use disorders and where indicated engage in treatment prior to lung transplantation. Based on medical stability, this may constitute a provision of transplant listing. At the time of evaluation and then serially during the pre-transplant period, blood and urine testing may be used to verify abstinence from substances.

Nicotine: Lung transplant candidates must demonstrate abstinence from use of all tobacco and nicotine products (including nicotine replacement therapy) prior to transplant (e.g., with serial nicotine and cotinine screening).[111] A short duration of abstinence (e.g., ≤ 6 months) and exposure to second-hand smoke confer a higher risk for relapse; duration of cessation should take into account the patient's medical acuity and stability.[86,111] Education on the importance of abstinence from all nicotine products (e.g., vaping), as well as limiting environmental or passive exposure to these products, should occur before referral for transplant and continue after transplant.[15,111-114]

Cannabis: Inhaled cannabis use must be ceased prior to lung transplant.[115-119] Orally consumed cannabis should only be used prior to transplant if recommended by a medical provider, and if approved by the lung transplant team. Orally consumed cannabinoids, including those prescribed (e.g., dronabinol), may cause positive urine drug tests, complicating routine drug screening efforts, and if continued post-transplant, cannabis has the potential to interact with immunosuppression medications.[120]

Opioids: The safety of pre-lung transplant opioid use on transplant outcomes has not been widely studied.[121,122] The risk and benefit of opioids prescribed to lung transplant candidates to palliate symptoms of pain or dyspnea should be considered on an individual basis. Medication assisted treatment (e.g., buprenorphine, naltrexone, methadone) for opioid use disorder has not been studied in advanced lung disease patients, and consultation with a psychiatrist or addictions specialist may be indicated in such cases.

Pediatric considerations

Timing of referral: Although referral for pediatric patients should rely on similar principles as for adults, the wait time for children and infants may be longer than for adults due to the challenge of acquiring suitable sized organs. For infants < 2 years, the potential opportunity to use ABO incompatible donor lungs has expanded the pool of donor lungs.[123-125] The recognition of unique and sometimes challenging aspects of pediatric recipients is crucial for their prolonged survival. Therefore, pediatric lung transplant candidates should be referred early and reviewed in detail in order to maximize their chances of having a successful transplant.

Indications for lung transplant in children: CF remains the leading indication for lung transplant in children aged 6-17 years; however, the number of candidates with idiopathic pulmonary arterial hypertension (IPAH) is increasing, and it is currently the most common indication for those 1-5 years of age.[126] For infants (<1 year) surfactant protein B deficiency and pulmonary hypertension (which is usually due to congenital heart disease, not IPAH) are the primary indications for lung transplant.[126] Other infant and childhood indications include adenosine triphosphate binding cassette protein member A3 deficiency, alveolar capillary dysplasia with misalignment of pulmonary veins, childhood interstitial lung disease, and bronchiolitis obliterans.

Consent: Children and their families require developmentally appropriate education and a child must consent/assent at the level of their understanding.

Adherence: In adolescence, nonadherence can be a significant challenge both pre- and post-transplant, potentially resulting in poor outcomes.[127-130] Therefore, non-adherence must be evaluated in detail during the referral and evaluation process to determine if it is a modifiable factor.

Transitions of care: The transition from pediatric to adult care while on the waiting list or after transplant may be problematic and careful planning is recommended.[127,131]

Growth: In the pre-transplant period optimizing growth and nutritional status in children is important, not only as preparation for the operation, but also because growth may be attenuated by medications post-transplant

Extracorporeal Membrane Oxygenation (ECMO): In the past, ECMO was considered a relative contraindication but more recently ECMO as a bridge to transplant in children has become more acceptable.[132]

Disease specific considerations in pediatric patients

CF in pediatric patients: Young adolescent females with a rapid decline in pulmonary function tests should be referred early due to their poor prognosis.[133] The US CF Foundation guidelines for lung transplant referral state patients with CF <18 years of age should be referred no later than when FEV_1 is < 50% predicted and rapidly declining (> 20% relative decline within 12 months); or FEV_1 is < 50% predicted with markers of shortened survival (low 6-minute walk, hypoxemia, hypercarbia, pulmonary hypertension); or FEV_1 is < 40% predicted.[134] Children with CF should be listed for lung transplantation when FEV_1 is <30% predicted.[134]

Pulmonary arterial hypertension (PAH) in pediatric patients: Specific guidelines for diagnosis and treatment of pediatric patients with PAH were developed in 2013.[135,136] According to the latest guidelines from the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), patients are stratified into low or high-risk categories indicating their prognosis.[137] Determinants of risk are based on clinical evidence of right ventricular dysfunction, progression of symptoms, syncope, growth, WHO functional class, serum B-type natriuretic peptide (BNP) or N-terminal (NT)-pro hormone BNP (NT-proBNP), echocardiography, and invasive measures of hemodynamics (cardiac index, mean pulmonary artery pressure, mean right atrial pressure and pulmonary vascular resistance index).[137] Patients

should be referred to a lung transplant center for evaluation when they remain in an intermediate- or high-risk category despite maximal PAH therapy (i.e., triple therapy). However, early referral is preferable especially in children with IPAH. Potts shunt or atrial septostomy (in patients with functional class III and IV and recurrent syncope) may be considered as a bridge to transplant in some centers, but this remains controversial.[136,137] Children with PAH in the high-risk category and on optimal therapy without improvement should be listed for lung transplantation.

Other diseases: Alveolar capillary dysplasia, pulmonary vein stenosis refractory to intervention, and pulmonary veno-occlusive disease (PVOD) are all rare entities with a very poor prognosis for which urgent evaluation and listing for lung transplantation should be considered.

Surgical considerations

Previous chest surgery: Previous chest surgery, particularly pleurodesis, is associated with greater blood loss and early post-operative morbidity such as renal dysfunction and primary graft dysfunction. Review of the most recent literature demonstrates that although up to 45% of lung transplant recipients have undergone previous cardiothoracic procedures, no survival difference has been observed.[138] Prior lung transplant, especially for those who have developed restrictive allograft syndrome, confers a higher risk for poor survival.[1,139,140]

Pneumothorax / Pleurodesis: When possible, management of a pneumothorax in a patient who may be a potential lung transplant candidate should be discussed with a transplant center. Although avoidance of talc pleurodesis is preferred, it is not a contraindication and the patient should be given the best immediate management.

Lobar lung transplant: Potential candidates with small chest size may be candidates for lobar lung transplant. While early complications may be higher, the 1- and 3-year survival may be comparable to conventional transplant, suggesting lobar lung transplant may be an acceptable option.[141,142]

Other considerations: Significant chest wall abnormalities, spinal deformities, or mediastinal fibrosis require individualized evaluation to determine surgical feasibility and degree of restriction anticipated post-transplant.

Bridge to transplant (BTT)/extracorporeal life support (ECLS)

With the implementation of urgency-based lung allocation systems in many countries, the use of ECLS as a BTT has become a more viable option. Technological advances have improved the efficacy of BTT devices, especially ECMO, leading to its more prevalent use in transplant centers. In general, success of BTT is dependent on center experience with ECLS and lung transplant in general.[143,144] Indications for ECLS include hypercapnic respiratory failure, hypoxic respiratory failure, and right ventricular failure.[143,144] A care plan for the use of BTT should be determined with

multidisciplinary input at the time of listing as clinical deterioration can be rapid and not all candidates may be candidates for ECLS as BTT. Extra-thoracic organ dysfunction may be a contraindication to BTT with an exception for patients with pulmonary hypertension and right ventricular dysfunction where renal and hepatic dysfunction is often reversed after ECLS initiation. Uncontrolled sepsis, older age, lack of center experience with BTT strategies, and patients who have not been considered previously for transplant, represent scenarios fraught with the likelihood of poor outcomes.

The timing for ECLS is determined by patient condition and the circumstances surrounding the likelihood for donor organ availability. The following considerations factor into the decision to initiate ECLS: oxygen saturation less than 90% with use of high flow non-invasive oxygenation devices; hemodynamic instability; use of positive pressure ventilation that could lead to further lung injury and secondary organ dysfunction; and inability of candidate to perform adequate physical therapy with current support. After initiation of ECLS, candidates should preferably be awake, carefully mobilized, and monitored continually for development of clinical characteristics that would negatively impact transplant candidacy.

Lung re-transplantation

Approximately 5% of all lung transplants performed are re-transplants.[1] The outcomes after re-transplants are inferior compared to first lung transplants, particularly if the re-transplant is done within the first year after the original transplant or for patients with restrictive allograft syndrome (RAS).[1,139,140,145-149] Several studies, however, have found acceptable results for carefully selected recipients.[140,146,150,151] In the pre-transplant evaluation of such patients, particular emphasis should be focused on understanding the possible reasons for the graft failure, such as alloimmunization, poor adherence, GER, or repeated infections.[86,152]

Multi-organ transplantation

Multi-organ transplantation is considered for patients in whom survival with isolated lung transplant is unlikely without the simultaneous transplant of another organ or in those for whom significant post-transplant organ dysfunction is anticipated in the event of lung transplant alone. Multi-organ transplant accounts for approximately 1.6% of lung transplants.[153] Multi-organ transplant candidates have a higher waiting list mortality than individuals listed for single organ transplant[154]; however, recipients who survive the difficult peri-operative period experience significant survival benefit, with favorable long-term survival.[153] The best outcomes from multi-organ transplant are achieved by specialized high-volume institutions.[155]

Heart-lung transplant: The primary indication for heart-lung transplant is pulmonary hypertension, either secondary to idiopathic pulmonary arterial hypertension or congenital heart disease (CHD).[153] Criteria for heart-lung transplant

listing described in a previous version of this document include the presence of New York Heart Association (NYHA) functional class IV symptoms despite maximal medical management, a cardiac index below 2 l/min/m², and a mean right atrial pressure above 15 mmHg[4]; however, the decision about whether to list a patient for heart-lung transplant remains difficult. Candidates free from complex CHD or left ventricular compromise can achieve comparable outcomes with isolated bilateral lung transplant.[156-159] Similarly, patients with advanced lung disease and cardiac pathology amenable to surgical repair may be candidates for lung transplant concurrent with the appropriate corrective cardiac procedure.[160]

Lung-liver transplant: Lung-liver transplant is a therapeutic option for advanced lung disease associated with cirrhosis (e.g. CF, alpha-1 antitrypsin deficiency), and end-stage liver disease with pulmonary compromise. Lung-liver transplant should be considered for patients meeting lung transplant listing criteria with biopsy proven cirrhosis and a portal gradient >10 mmHg. There is some evidence that survival is non-inferior for lung-liver transplant vs isolated lung transplant in recipients with a LAS <50; however, higher mortality amongst recipients with higher LAS and Model for End-Stage Liver Disease (MELD) scores suggests there may be a ceiling beyond which patients are too sick to achieve a survival benefit from lung-liver transplant.[161,162] Severely impaired liver synthetic function with an albumin <2.0 g/dl, INR >1.8 or the presence of severe ascites or encephalopathy should be considered contraindications.[163] In addition, one study has suggested there may be no survival advantage with lung-liver transplant when compared to matched single-organ lung transplant recipients with an equivalent degree of liver dysfunction, suggesting a need for more precise criteria to determine optimal lung-liver transplant candidates.[164]

Lung-kidney transplant: A significant and increasing proportion of potential lung transplant candidates have established renal dysfunction. Despite being sicker at baseline, patients with renal dysfunction who undergo lung-kidney transplant have similar 1-year and 5−year survival when compared to recipients of isolated lung transplant, but it is unclear whether simultaneous lung-kidney transplant can completely attenuate the increased risk of mortality in this population.[17,165]

Disease specific considerations

In addition to the general considerations and risk factors that may affect an individual's candidacy for lung transplant, there are important disease specific considerations that should guide referral and listing.

Chronic obstructive pulmonary disease (COPD)

Prognostic models that can be used to determine the appropriate timing of listing for lung transplant for COPD patients are inherently imprecise as survival is highly variable even among patients with advanced disease. In general, multidimensional models have proven to be more robust

predictors of mortality than single parameters. The most familiar of these is the BODE index [BMI, airflow limitation (forced expiratory volume in one second), dyspnea and 6-minute walk distance], which has been externally validated in at least 13 additional cohorts following the original derivation. The BODE index has been cited as the prognostic model of choice by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), and it formed the basis for listing recommendations in the 2014 ISHLT candidate selection guidelines.[4,166-168]

The calibration of the original BODE index (i.e., the degree to which the predicted mortality risk agrees with observed mortality) has been called into question by a number of subsequent studies. In particular, two studies looked specifically at the ability of the BODE index to predict mortality among lung transplant candidates with COPD.[169,170] Both found that the BODE index overestimated mortality. In the larger of the two studies, survival of 4,377 lung transplant candidates with COPD in the OPTN/UNOS database was compared to that of the cohort of COPD patients that served as the validation group in the original BODE publication.[170] Median survival of patients in the fourth quartile of BODE scores[7-10] was 59 months in the transplant candidate cohort and 37 months in the original BODE cohort. The poor calibration of the BODE index among transplant candidates likely reflects the marked differences in age, comorbidities, and active smoking in this carefully screened population compared to the general population included in the original validation cohort. BODE index has also been shown to overestimate mortality among the subset of COPD patients with alpha-1-antitrypsin deficiency, likely for similar reasons.[171]

Acknowledging the calibration issues, a fourth quartile BODE score[7-10] still appears to identify a group of transplant-eligible patients whose predicted median survival without transplant is less than the observed median survival of patients with COPD post-transplant (6.0 years).[172] It therefore stands as the best guideline for listing patients. An FEV₁ < 20% predicted is an additional consideration in listing COPD patients, as this has been identified as a threshold below which transplant is likely to confer a survival advantage.[173] Other factors associated with increased mortality that may influence listing are pulmonary hypertension, chronic hypercapnia, and severe acute exacerbations (e.g., requiring an emergency department visit or hospitalization.)[174-176]

Patients with advanced but not imminently life-threatening COPD, characterized by BODE scores in the range of 5-6 and FEV₁ 20%-25% predicted, may benefit from referral to a transplant center for initial consultation even if immediate listing is not anticipated. Additional parameters that have been identified as predictors of increased mortality (although not fully validated) that should prompt referral when present include an increase in BODE index score > 1 over past 24 months and pulmonary artery to aorta diameter > 1 on CT scan.[175,177,178] While DLCO has not been shown to be an independent predictor of mortality in COPD, a low DLCO has been associated with increased COPD symptoms, reduced exercise

performance, and severe exacerbation risk, and thus, also may prompt consideration of referral.[179,180] The patient's perception of an unacceptably poor quality of life may also be a consideration, albeit not the principal driver for referral, given the significant symptomatic benefits that transplant offers this patient population even in the face of an uncertain survival benefit.

Special considerations in COPD: Lung volume reduction (LVR), performed by either surgical or bronchoscopic approach, is an option for a subset of COPD patients with advanced emphysema who meet strict selection criteria. These procedures have been associated with improved lung function, exercise capacity, and quality of life.[181-183] Survival benefit has been demonstrated in a select group of patients with upper lobe predominant emphysema and low exercise capacity who undergo surgical LVR.[183] Notably, outcomes are not uniformly beneficial even among carefully selected candidates.[181-183]

For patients whose disease does not warrant imminent listing for lung transplant, LVR should be considered, as a successful outcome can postpone the need for transplant, and the associated improvement in functional and nutritional status can optimize the patient's suitability as a future transplant candidate.[184-187] Prior LVR surgery can lead to formation of pleural adhesions, which can pose technical challenges to the surgeon at the time of transplant. Several published series document increased operative times and peri-operative bleeding in transplant recipients who had previously undergone LVR surgery.[185,188,189] Although post-transplant survival was not impacted in some studies, one study reported that 1-, 5-, and 10-year survival was lower in individuals who had undergone LVR surgery prior to transplant when compared to individuals who had undergone transplant alone.[185,188-190]

Interstitial lung disease (ILD)

Idiopathic pulmonary fibrosis (IPF), the prototype of fibrotic ILDs, carries a prognosis of 3-5 years survival after diagnosis when untreated. Two anti-fibrotic medications (nintedanib and pirfenidone) have been shown to reduce the rate of forced vital capacity (FVC) decline and slow disease progression in patients with a definite usual interstitial pneumonia (UIP) pattern and with a probable UIP pattern on high resolution CT (HRCT).[191-193] Though the studies were not powered to show an effect on mortality, post-hoc analysis, registry data and computational models all confirm a survival benefit and likely also a decrease in the number of acute exacerbations, which are associated with a high mortality.[191,192,194] Thus, since the last version of this document, the use of these medications has become more widespread and the decision regarding the timing of listing for lung transplant has become more challenging. With the unpredictable nature of acute exacerbations, it remains advisable to refer patients with IPF early for lung transplant evaluation (Table 3).

Patients with non-IPF ILDs may also experience a disease course similar to IPF.[195-200] Recently, 3 trials have shown a response to anti-fibrotic therapy in patients with

other forms of progressive fibrotic ILD, including chronic hypersensitivity pneumonitis, autoimmune-ILD, idiopathic non-specific interstitial pneumonitis, unclassifiable idiopathic interstitial pneumonitis, and a group of other rarer fibrotic ILDs.[198,199,201,202] Importantly, in two of these trials, patients were included on the basis of disease progression despite standard management.[198,199] Combining two out of three domains (FVC decline, HRCT progression, or increased symptoms) identified patients who showed a FVC decline and a response to therapy similar to IPF.[198,203] These results may change the treatment paradigm of fibrotic ILDs, so that management decisions will be based on disease behavior as well as histological or HRCT patterns.[197] Consistent clinical predictors of survival in non-IPF ILDs include FVC and DLCO decline, hospitalization, frailty, oxygen use and symptoms; thus, timing of referral and listing for lung transplant should take these factors into account (Table 3).[204-209] In patients with concurrent emphysema, a decline in FVC is a less reliable parameter to detect progression of fibrosis, and other markers such as progression of disease on CT scan or DLCO, or development of secondary pulmonary hypertension, may be more useful.[210,211]

Predicting prognosis for individual patients with ILD remains difficult. Signs of pulmonary hypertension and right ventricular failure, or the occurrence of pneumothorax have been associated with worse outcomes in ILD.[212-215] UIP pattern on HRCT is also associated with worse outcomes in many ILDs, although for rheumatoid arthritis-ILD some debate exists on pattern versus extent of involvement on HRCT.[197,216] Promising results in novel computer-based imaging analysis need further prospective development and validation in larger data sets.[217-219] Serum and genetic biomarkers have been studied in IPF, but data are also now becoming available in other ILDs.[220-224] Whilst some biomarkers are promising, none has been validated for clinical application.[225] Different composite predictors of outcome have been developed in the past years; however, clinical uptake and external validation is limited.[226-232] At this point, no biomarker or clinical prediction algorithm has been established as a reliable predictor for disease outcome or response to therapy in ILD.[233] Therefore, early referral is still recommended to reduce the likelihood that a potentially eligible patient may miss the opportunity for lung transplant. Timing of listing should be discussed with each individual patient considering such factors as rate of progression despite standard management, expected prognosis, age, comorbidities, and transplant risks.

Patients with ILDs that may require special consideration include patients with familial fibrosis, antineutrophil cytoplasm antibody (ANCA) associated vasculitides, sarcoidosis, connective tissue disease, or Heřmanský−Pudlák syndrome.[234-237] Transplant challenges in these patients relate to potential extrapulmonary involvement which may complicate assessment and acceptance for transplant.[38,238,239] Specific transplant considerations for patients with CTD-ILD are due to be published as part of a separate ISHLT consensus document. Patients with possible familial pulmonary fibrosis should undergo assessment for

Table 3   Updated Consensus Statements

Each statement listed as a 2021 consensus statement reflects expert synthesis of the current literature with additional rationale provided in the accompanying text. The statements are all based on consensus reached by the committee (24 members) with an *a priori* threshold of >80% agreement on consensus statements.

GENERAL CONSIDERATIONS

2014 Consensus Statement	2021 Consensus Statement	Consensus N (%)
Lung transplantation should be considered for adults with chronic, end-stage lung disease who meet all the following general criteria: 1. High (>50%) risk of death from lung disease within 2 years if lung transplantation is not performed. 2. High (>80%) likelihood of surviving at least 90 days after lung transplantation. 3. High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function.	Lung transplantation should be considered for adults with chronic, end-stage lung disease who meet all the following general criteria: 1. High (>50%) risk of death from lung disease within 2 years if lung transplantation is not performed. 2. High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function.	24 (100%)
	Prior to determining that a patient is not a candidate for lung transplantation, referring providers should communicate directly with at least one lung transplant program with experience with the candidate's potential contraindication(s).	24 (100%)
	Early referral is recommended to facilitate transplant education for the patient and caregivers, an initial assessment of barriers to transplant, and determination of timing for full evaluation with specific recommendations for optimization of candidacy.	24 (100%)
	Determination of candidacy requires a detailed evaluation not only to select appropriate candidates, but also to optimize each individual's status to provide them with the best chance for a successful outcome.	24 (100%)
	Individual transplant candidacy at a particular institution depends on that center's expertise for management of patients who have risk factors posing high or substantially increased risk.	24 (100%)
	Decision making regarding timing of listing for transplant should take into consideration results of the full evaluation, including disease severity and trajectory, estimated wait time for donor organ(s) and survival time without transplant, and candidate's readiness for transplant.	24 (100%)
	Just as the decision to list is carefully considered, interval reassessment for continued listing should take place to evaluate the risks and benefits of transplant when considering any changes to the candidate's status that may impact predicted perioperative or post-transplant outcomes.	24 (100%)
	When referring for lung transplant evaluation, consider simultaneous referral to palliative care to provide decision support and treatment selection that is consistent with goals of care throughout the transplant evaluation, listing, surgery, and post-transplant.	23 (96%)

PEDIATRIC CANDIDATE RECOMMENDATIONS

2014 Consensus Statement	2021 Consensus Statement	Consensus N (%)
Timing of Referral • A progressive lung disease on maximal medical therapy. • A short predicted life expectancy • A poor quality of life. • Because the waiting times, particularly for smaller children, are longer, potential	**Timing of Referral** • In addition to general recommendations for adults, considerations for referring children for lung transplant evaluation include the following: • Patients with cystic fibrosis < 18 years of age should be referred when:	24 (100%)

Table 3 (*Continued*)

candidates should be referred to a transplant center as early as possible.

- Appropriate child and family support in place. It is essential that the child, in particular, commits to the transplant procedure and close long-term follow-up.

- ○ FEV_1 is < 50% predicted with markers of increased disease severity
- ○ FEV_1 is < 50% predicted with rapidly declining FEV_1
- ○ FEV_1 is <40% predicted

- Patients with PAH < 18 years of age should be referred when despite optimal PAH therapy:
  - ○ EPPVDN intermediate or high-risk category
  - ○ Need for IV or SC prostacyclin therapy
  - ○ Significant RV dysfunction
  - ○ WHO functional class > III
  - ○ Elevated or rising BNP or NTproBNP
  - ○ Diminished growth
  - ○ Progressive disease despite appropriate therapy or recent hospitalization for worsening of PAH
  - ○ Signs of secondary liver or kidney dysfunction due to PAH
  - ○ Potentially life-threatening complications such as recurrent hemoptysis or syncope
  - ○ Being considered for atrial septostomy or reverse Potts shunt as a palliative procedure (footnote: transplantation may be an option post procedure)

- Patients with alveolar capillary dysplasia, pulmonary vein stenosis refractory to intervention, and pulmonary veno-occlusive disease should be referred for urgent evaluation and listing.

Potential pediatric candidates should be referred to a transplant center as early as possible, to minimize waitlist mortality, especially in younger children as wait times may be longer.	24 (100%)
Ongoing assessment of non-adherence should occur for pediatric patients as they move through different stages of development.	24 (100%)
We recommend that referring physicians periodically discuss and update referral practices with their partnering transplant center.	24 (100%)

Timing of Listing

In addition to general recommendations for adults, considerations for listing children for lung transplant include the following: • Patients with CF < 18 years of age should be listed when FEV_1 < 30% predicted • Patients with PAH <18 years of age should be listed when they are in the EPPVDN high risk category and on optimal therapy without improvement	24 (100%)
Transition from pediatric to adult care while on the waiting list needs careful planning, timing, and ongoing communication	24 (100%)
In pediatric candidates, growth and nutritional status should be carefully monitored.	24 (100%)
Extracorporeal life support may be an acceptable bridge to transplant in appropriately selected pediatric candidates at centers with expertise.	24 (100%)

LUNG RE-TRANSPLANTATION

2014 Consensus Statement	2021 Consensus Statement	Consensus N (%)
	The timing of re-transplant is a complex issue and requires consideration of the rate of deterioration, time since initial transplant, the need for supportive therapies and donor lung availability, which may be limiting in some cases.	23 (95%)

Table 3 (*Continued*)

	Survival after re-transplant is inferior to that seen with the primary operation and should only be undertaken in carefully selected candidates.	24 (100%)
	In the evaluation of patients being considered for lung re-transplant, particular emphasis should be focused on understanding the possible reasons for the graft failure, such as alloimmunization, poor adherence, gastroesophageal reflux, or repeated infections.	23 (96%)

MULTI-ORGAN TRANSPLANTATION

2014 Consensus Statement	2021 Consensus Statement	Consensus N (%)
	Heart-lung and other multi-organ transplantation should be limited to centers with experience in such procedures and where specialists are available to manage each of the transplanted organs.	24 (100%)
	Candidates should meet the criteria for lung transplant listing and have significant dysfunction of one or more additional organs, or meet the listing criteria for a non-pulmonary organ transplant and have significant pulmonary dysfunction.	24 (100%)
	Waiting times are likely to be longer and the likelihood of receiving a transplant is reduced when an individual requires more than one organ. Thus, referral should occur earlier in the disease course if multi-organ transplantation may be considered.	24 (100%)

DISEASE SPECIFIC CANDIDATE RECOMMENDATIONS

Chronic Obstructive Pulmonary Disease (COPD)

2014 Consensus Statement	2021 Consensus Statement	Consensus N (%)

Timing of Referral
 	
• Disease is progressive, despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy.
• Patient is not a candidate for endoscopic or surgical LVRS. Simultaneous referral of patients with COPD for both lung transplant and LVRS evaluation is appropriate
• BODE index of 5 to 6.
• PaCO2 >50 mm Hg or 6.6 kPa and/or PaO2 <60 mm Hg or 8 kPa.
• FEV_1 <25% predicted.
	Timing of Referral
	
	• BODE score 5-6 with additional factor(s) present suggestive of increased risk of mortality:
	  ○ Frequent acute exacerbations
	  ○ Increase in BODE score >1 over past 24 months
	  ○ Pulmonary artery to aorta diameter > 1 on CT scan
	  ○ FEV_1 20-25% predicted
	
	• Clinical deterioration despite maximal treatment including medication, pulmonary rehabilitation, oxygen therapy, and, as appropriate, nocturnal non-invasive positive pressure ventilation.
	• Poor quality of life unacceptable to the patient
	• For a patient who is a candidate for bronchoscopic or surgical lung volume reduction (LVR), simultaneous referral for both lung transplant and LVR evaluation is appropriate.
		24 (100%)
		
		23 (96%)

Timing of Listing
 	
• BODE index >7.
 	
• FEV_1 <15% to 20% predicted.
• Three or more severe exacerbations during the preceding year.
• One severe exacerbation with acute hypercapnic respiratory failure.
• Moderate to severe pulmonary hypertension.
	Timing of Listing
	
	• BODE score 7-10
	
	• Additional factors that may prompt listing include:
	  ○ FEV_1 < 20% predicted
	  ○ Presence of moderate to severe pulmonary hypertension
	  ○ History of severe exacerbations
	  ○ Chronic hypercapnia
		24 (100%)

Table 3 (*Continued*)

DISEASE SPECIFIC CANDIDATE RECOMMENDATIONS		
Interstitial Lung Disease (ILD)		
2014 Consensus Statement	2021 Consensus Statement	Consensus N (%)
Timing of Referral	**Timing of Referral***	
• Histopathologic or radiographic evidence of UIP or fibrosing non-specific interstitial pneumonitis regardless of lung function.	• Referral should be made at time of diagnosis, even if a patient is being initiated on therapy, for histopathological UIP or radiographic evidence of a probable or definite UIP pattern.	22 (92%)
• Abnormal lung function: FVC <80% predicted or DLCO <40% predicted.	• Any form of pulmonary fibrosis with FVC of < 80% predicted or DLCO < 40% predicted.	24 (100%)
• Any dyspnea or functional limitation attributable to lung disease.	• Any form of pulmonary fibrosis with one of the following in the past 2 years: ○ Relative decline in FVC 10% ○ Relative decline in DLCO 15% ○ Relative decline in FVC 5% in combination with worsening of respiratory symptoms or radiographic progression	24 (100%)
• Any oxygen requirement, even if only during exertion.	• Supplemental oxygen requirement either at rest or on exertion.	24 (100%)
• For inflammatory ILD, failure to improve dyspnea, oxygen requirement, and/or lung function after a clinically indicated trial of medical therapy.	• For inflammatory ILDs, progression of disease (either on imaging or pulmonary function) despite treatment.	24 (100%)
	• For patients with connective tissue disease or familial pulmonary fibrosis, early referral is recommended as extrapulmonary manifestations may require special consideration.	24 (100%)
Timing of Listing	**Timing of Listing***	
• Decline in FVC >10% during 6 months of follow-up (note: a 5% decline is associated with a poorer prognosis and may warrant listing). • Decline in DLCO >15% during 6 months of follow-up. • Desaturation to <88% or distance <250 m on 6 minute walk test or >50 m decline in 6 minute-walk distance over a 6 month period. • Pulmonary hypertension on right heart catheterization or 2-dimensional echocardiography. • Hospitalization because of respiratory decline, pneumothorax, or acute exacerbation.	• Any form of pulmonary fibrosis with one of the following in the past 6 months despite appropriate treatment: ○ Absolute decline in FVC > 10% ○ Absolute decline in DLCO > 10% ○ Absolute decline in FVC > 5% with radiographic progression. • Desaturation to < 88% on 6 minute walk test or > 50 m decline in 6 minute walk test distance in the past 6 months • Pulmonary hypertension on right heart catheterization or 2-dimensional echocardiography (in the absence of diastolic dysfunction) • Hospitalization because of respiratory decline, pneumothorax, or acute exacerbation.	24 (100%)

*NOTE: For patients with concomitant emphysema, FVC may be a less reliable parameter.

Table 3 (*Continued*)

DISEASE SPECIFIC CANDIDATE RECOMMENDATIONS		
Cystic Fibrosis (CF)		
2014 Consensus Statement	2021 Consensus Statement	Consensus N (%)

Timing of Referral
 	
• FEV_1 that has fallen to 30% or a patient with advanced disease with a rapidly falling FEV_1 despite optimal therapy (particularly in a female patient), infected with NTM disease or *B cepacia* complex and/or with diabetes.
• A 6 minute walk distance <400 m
• Development of pulmonary hypertension in the absence of a hypoxic exacerbation (as defined by a systolic PA pressure >35 mm Hg on echocardiography or mean PA pressure >25 mm Hg measured by right heart catheterization).
• Clinical decline characterized by increasing frequency of exacerbations associated with any of the following:
  ○ An episode of acute respiratory failure requiring non-invasive ventilation.
  ○ Increasing antibiotic resistance and poor clinical recovery from exacerbations.
  ○ Worsening nutritional status despite supplementation.
  ○ Pneumothorax.
  ○ Life-threatening hemoptysis despite bronchial embolization.
	Timing of Referral
	Referral for lung transplantation should occur for an individual with CF meeting any of the following criteria despite optimal medical management including a trial of elexacaftor / tezacaftor / ivacaftor if eligible:
	• $FEV_1 < 30\%$ predicted in adults (or < 40% predicted in children)
	• $FEV_1 < 40\%$ predicted in adults (or < 50% predicted in children) and any of the following:
	  ○ Six-minute walk distance < 400 meters
	  ○ $P_aCO_2 > 50$ mmHg
	  ○ Hypoxemia at rest or with exertion
	  ○ Pulmonary hypertension (PA systolic pressure > 50 mmHg on echocardiogram or evidence of right ventricular dysfunction)
	  ○ Worsening nutritional status despite supplementation
	  ○ 2 exacerbations per year requiring intravenous antibiotics
	  ○ Massive hemoptysis (>240 mL) requiring bronchial artery embolization
	  ○ Pneumothorax
	
	• $FEV_1 < 50\%$ predicted and rapidly declining based on pulmonary function testing or progressive symptoms
	• Any exacerbation requiring positive pressure ventilation
		24 (100%)

Timing of Listing
 	
• Chronic respiratory failure.
  ○ With hypoxia alone (partial pressure of oxygen [PaO2] <8 kPa or <60 mm Hg).
  ○ With hypercapnia (partial pressure of carbon dioxide [PaCO2] >6.6 kPa or >50 mm Hg).
 	
• Long-term non-invasive ventilation therapy.
• Pulmonary hypertension.
• Frequent hospitalization.
• Rapid lung function decline.
• World Health Organization Functional Class IV.
	Timing of Listing
	Listing for lung transplantation should occur for an individual with CF meeting any of the above referral criteria in combination with any of the following:
	• $FEV_1 < 25\%$ predicted
	• Rapid decline in lung function or progressive symptoms (>30% relative decline in FEV_1 over 12 months)
	• Frequent hospitalization, particularly if > 28 days hospitalized in the preceding year
	• Any exacerbation requiring mechanical ventilation
	• Chronic respiratory failure with hypoxemia or hypercapnia, particularly for those with increasing oxygen requirements or needing long-term non-invasive ventilation therapy
	• Pulmonary hypertension (Pulmonary arterial systolic pressure > 50 mmHg on echocardiogram or evidence of right ventricular dysfunction)
	• Worsening nutritional status particularly with BMI < 18 kg/m^2 despite nutritional interventions
	• Recurrent massive hemoptysis despite bronchial artery embolization
	• World Health Organization functional class IV
		24 (100%)

Table 3 (*Continued*)

DISEASE SPECIFIC CANDIDATE RECOMMENDATIONS

Additional Recommendations Patients with CF who are referred for transplantation should be evaluated for NTM pulmonary disease. Patients with NTM disease who are being evaluated for transplantation should have the organism confirmed according to microbiology guidelines and begin treatment before transplant listing.	**Additional Recommendations** For lung transplant candidates with CF, regular communication between CF and transplant centers is encouraged (at least every six months and with major clinical changes) to review disease trajectory, proactive management of potential barriers to transplantation, along with listing status and timing including in relationship to treatment with elexacaftor / tezacaftor / ivacaftor or other novel CF medications.	24 (100%)
Treatment should be by, or in collaboration with, a physician experienced in the treatment of such patients Progressive pulmonary or extrapulmonary disease secondary to NTM despite optimal therapy or an inability to tolerate optimal therapy is a contraindication for trans-plant listing. All patients with CF referred for transplantation should be evaluated for the presence of *B cepacia*.	In individuals with CF, a lower threshold for both lung transplant referral and listing should be considered in females and those with short stature, diabetes, or increasing antibiotic resistance including infection with *Burkholderia cepacia* complex or nontuberculous mycobacteria.	24 (100%)
Patients with species other than *B cenocepacia* do not constitute an increased risk for mortality after transplantation and can be listed, provided that other criteria are met. Patients with *B cenocepacia* have an increased risk of mortality secondary to recurrent disease after trans-plantation. It is recommended that centers continuing to accept such patients should have an active research program assessing novel approaches to prevent and control recurrent disease and should be experienced in management of these patients. A full discussion with the patients of the increased risk associated with these infections should occur.	All transplant candidates with CF should be evaluated for *Burkholderia cepacia* complex, nontuberculous mycobacteria, and fungal pathogens	24 (100%)

Non-CF Bronchiectasis

2014 Consensus Statement	2021 Consensus Statement	Consensus N (%)
	For individuals with non-CF bronchiectasis, similar criteria as with CF for referral and listing for lung transplantation is reasonable, though providers should recognize that prognosis is highly variable with many patients experiencing a more stable course.	24 (100%)

Pulmonary Arterial Hypertension (PAH)

2014 Consensus Statement	2021 Consensus Statement	Consensus N (%)
Timing of Referral • NYHA Functional Class III or IV symptoms during escalating therapy. • Rapidly progressive disease (assuming weight and rehabilitation concerns not present). • Use of parenteral targeted PAH therapy regardless of symptoms or NYHA Functional Class • Known or suspected PVOD or PCH.	**Timing of Referral** • ESC/ERS intermediate or high risk or REVEAL risk score 8 despite appropriate PAH therapy • Significant RV dysfunction despite appropriate PAH therapy • Need for IV or SC prostacyclin therapy • Progressive disease despite appropriate therapy or recent hospitalization for worsening of PAH	24 (100%)

Table 3 (*Continued*)

DISEASE SPECIFIC CANDIDATE RECOMMENDATIONS

	- Known or suspected high-risk variants such as PVOD/PCH, scleroderma, large and progressive pulmonary artery aneurysms - Signs of secondary liver or kidney dysfunction due to PAH - Potentially life-threatening complications such as recurrent hemoptysis	
Timing of Listing - NYHA Functional Class III or IV despite a trial of at least 3 months of combination therapy including prostanoids. - Cardiac index of <2 liters/min/m2 - Mean right atrial pressure of >15 mm Hg 6 minute walk test of <350 m. - Development of significant hemoptysis, pericardial effusion, or signs of progressive right heart failure (renal insufficiency, increasing bilirubin, brain natriuretic peptide, or recurrent ascites).	**Timing of Listing** - ESC/ERS high risk or REVEAL risk score >10 on appropriate PAH therapy, including IV or SC prostacyclin analogues - Progressive hypoxemia, especially in patients with PVOD or PCH - Progressive, but not end-stage, liver or kidney dysfunction due to PAH - Life-threatening hemoptysis	24 (100%)

Lymphangioleiomyomatosis (LAM)

2014 Consensus Statement	2021 Consensus Statement	Consensus N (%)
	Timing of Referral Referral for lung transplantation evaluation should occur for an individual with LAM who has any of the following despite mTOR inhibitor therapy: - Severely abnormal lung function (e.g. FEV_1 < 30% predicted) - Exertional dyspnea (NYHA class III or IV) - Hypoxemia at rest - Pulmonary hypertension - Refractory pneumothorax	24 (100%)
	Timing of Listing Listing for lung transplantation should occur for an individual with LAM who meets the above referral criteria and has evidence of disease progression despite mTOR inhibitor therapy.	24 (100%)
	Cessation of mTOR inhibitor therapy should occur at the time of transplant but cessation should not be required for placement on the waiting list. It may be preferable to use everolimus and target trough levels in the lower therapeutic range for patients on the waiting list.	23 (96%)

Thoracic Malignancy

2014 Consensus Statement	2021 Consensus Statement	Consensus N (%)
- Diffuse parenchymal tumor involvement causing lung restriction and significant respiratory compromise. - Significantly reduced quality of life. - Failure of conventional medical therapies.	Lung transplant should be limited to very select cases of lung-limited adenocarcinoma in situ, minimally invasive adenocarcinoma, or lepidic predominant adenocarcinoma for patients in whom (1) surgical resection is not feasible either because of multifocal disease or significant underlying pulmonary disease; (2) multifocal disease has resulted in significant lung restriction and respiratory compromise; (3) medical oncology therapies have failed or	22 (92%)

Table 3 (*Continued*)

DISEASE SPECIFIC CANDIDATE RECOMMENDATIONS		
	are contraindicated; and (4) lung transplant is expected to be curative.	
Acute Respiratory Distress Syndrome (ARDS)		
2014 Consensus Statement	2021 Consensus Statement	Consensus N (%)
	Timing of Listing and Referral Persistent requirement for mechanical ventilatory support and /or ECLS without expectation of clinical recovery and with evidence of irreversible lung destruction.	24 (100%)

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; BMI, Body Mass Index; CF, Cystic Fibrosis; COPD, Chronic Obstructive Pulmonary Disease; DLCO, diffusion capacity of carbon monoxide; ECLS, Extracorporeal Life Support; EPPVDN, European Pediatric Pulmonary Vascular Disease Network; ESC/ ERS, European Society of Cardiology/European Respiratory Society; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ILD, Interstitial Lung Disease; LAM, Lymphangioleiomyomatosis; LVRS, Lung volume reduction surgery; NTM, Non-tuberculous mycobacteria; PA, pulmonary arterial; PCH, Pulmonary capillary hemangiomatosis; PVOD, Pulmonary veno-occlusive disease; REVEAL, Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; UIP, usual interstitial pneumonia; WHO, World Health Organization.

clinical manifestations of telemeropathy, with particular attention to evaluation for hematologic abnormalities (see above) and liver cirrhosis. Patients with sarcoidosis may need additional evaluation to examine the extent of possible cardiac involvement and to exclude malignancy as an etiology for lymphadenopathy.

For patients with ILD on the lung transplant waiting list, both nintedanib and pirfenidone may be continued until transplant. Although mechanistically anti-fibrotic medications could affect wound healing, recent case series have shown no impaired wound or anastomotic healing and no increase in bleeding risk in patients on these medications.[240,241]

Cystic fibrosis (CF)

FEV_1 has been the best individual predictor of mortality in CF, with studies from the 1990s demonstrating a median survival of 2-4 years after reaching an $FEV_1 < 30\%$ predicted.[242-244] More recent studies have shown improved outcomes in advanced CF lung disease, including an analysis demonstrating a median survival of 6.6 years in patients in the U.S. with $FEV_1 < 30\%$ predicted.[245] Moreover, while data are lacking, outcomes may further improve with highly effective CF transmembrane conductance regulator (CFTR) modulators, where early clinical experience suggests that many individuals approaching lung transplant achieve disease stabilization or even improvement with the combination of elexacaftor, tezacaftor, and ivacaftor.

Despite improved overall outcomes, many individuals with advanced CF lung disease remain at risk of short-term mortality. A 2017 study demonstrated a 10% risk of death each year after reaching an $FEV_1 < 30\%$, with many patients dying soon after reaching this threshold.[245] Adjusted predictors of death included supplemental oxygen, *Burkholderia cepacia* complex, body mass index (BMI) ≤

18 kg/m^2, female sex, insulin-requiring diabetes, and ≥ 1 exacerbation per year. Additional risk factors for mortality in those with severely compromised lung function include $FEV_1 < 25\%$ predicted, rapid decline in FEV_1, $PaCO_2 > 50$ mmHg, impaired functional status, and pulmonary hypertension.[244,246-251] Independent of FEV_1, the following factors have been associated with increasing risk of disease progression or death: frequent or severe exacerbations, massive hemoptysis requiring bronchial artery embolization, pneumothorax, malnutrition, low 6-minute walk distance, and younger age upon development of advanced disease.[247,252-260] Composite scores have also been developed including one combining FEV_1 (>60% vs 30%-60% vs <30% predicted), BMI (>18.5 vs 16-18.5 vs <16 kg/m^2), presence of *Burkholderia cepacia* complex, intravenous antibiotic courses (0, 1-2, >2 per year), history of hospitalizations, oral steroids, long-term oxygen, and need for non-invasive ventilation.[254] In this model a score of ≥ 4 was associated with a 55% risk of 3-year mortality, whereas a score of ≤ 2 carried only a 1% risk.

Transplant referral guidelines were established by the CF Foundation for use by CF centers.[134] Because of difficulties in predicting survival and late or non-referral of potential candidates, major themes in these recommendations included pre-emptive discussion of transplant in all patients with advanced lung disease, proactive recognition of risk factors for disease progression, and early referral and improved communication with transplant centers.[134,261] These goals will continue to be important even in the era of highly effective CFTR modulators, particularly in patients who are ineligible for, cannot tolerate, or do not respond to such therapy, or if adverse long-term clinical effects arise. Predictors of survival with CF may need re-evaluation in the era of highly effective CFTR modulator therapy and new data may affect thresholds for referral and listing.

Special considerations in cystic fibrosis: Several comorbidities should be considered when evaluating candidates with CF. Infection or colonization with multi-drug resistant organisms including *Burkholderia cepacia* complex, *Pseudomonas aeruginosa*, and nontuberculous mycobacteria (*M. abscessus* in particular) have been shown to increase the rate of lung function decline or death without transplant in advanced CF.[245,247,254,258,262] Implications of *B. cenocepacia, M. abscessus,* or *L. prolificans* are described above (infectious disease risk factors). Post-transplant infectious recolonization in CF is thought to be related to sinus or other upper airway reservoirs and is associated with increased risk of graft dysfunction.[263,264] Although data supporting pre-transplant sinus surgery are lacking, optimization of sino-nasal management prior to transplant should be thoroughly considered given the high incidence of sinus disease and potential post-transplant implications.[264-267]

Non-infectious comorbidities include malnutrition, which is common in CF patients approaching transplant and represents a potentially modifiable risk factor. A low BMI is associated with lung function decline and mortality in advanced CF lung disease.[245] Although low BMI has been associated with post-transplant mortality among CF patients, a recent analysis demonstrated a reasonable median post-transplant survival of 7.0 years in CF patients with pre-transplant BMI $<17 kg/m^2$, which was similar to other commonly transplanted non-CF cohorts.[45,268] Hepatobiliary disease is a less common complication that can impact candidacy and procedure choice. Cholestasis is almost universal among lung transplant candidates with CF; however, clinically important liver disease occurs in only 3%-5%, mostly before age 20 years.[269] Data are limited on the impact of CF-associated liver disease on lung transplant outcomes; however, in cases of overt portal hypertension or synthetic dysfunction, combined lung-liver transplant has had comparable outcomes to lung transplant alone, particularly over the long-term.[153,270] Finally, the risk of colorectal cancer is increased in CF compared to age-matched controls, and transplant programs should screen CF candidates with colonoscopy beginning at age 40 years based on the 2017 CF Foundation Guidelines.[271]

Non-cystic fibrosis bronchiectasis

Non-CF bronchiectasis represents 2.7% of all lung transplants reported to the ISHLT Registry between 1995and 2018.[1] Determining transplant timing is difficult due to the wide range of etiologies and demographics. Two non-CF bronchiectasis severity assessment tools were developed from the overall population (not limited to those with advanced lung disease): the FACED score [FEV_1, Age, Chronic *Pseudomonas aeruginosa*, Extension to 1-2 lobes, Dyspnea by modified Medical Research Council scale] and the bronchiectasis severity index (BSI), which adds BMI and exacerbation frequency.[272,273] The FACED score and BSI have been used to characterize prognosis and disease severity, respectively.[272,273] A high FACED score[5-7] has been associated with median survival of approximately

5.5 years. Older age and specific etiology appear to impact prognosis.

Similar to CF, $FEV_1\%$ predicted has been shown to be discriminating for mortality. One study demonstrated a 4-year mortality of 39% in non-CF bronchiectasis patients with $FEV_1 < 30\%$ predicted.[273] Outcomes between CF and non-CF bronchiectasis, however, may not be the same in advanced disease populations. In a study evaluating survival among 2,112 patients who were listed but did not undergo transplant, multivariate Cox models identified a lower risk of death (HR 0.684, CI 0.475-0.985) and 5-year mortality of only 25% in the non-CF group despite similar lung function in the CF and the non-CF groups (FEV_1 of 25.1% vs 27.1% predicted, respectively), leading the authors to propose different thresholds for transplant listing.[274]

Pulmonary arterial hypertension (PAH)

Early consideration of transplant should be emphasized for patients with PAH, as referral of patients at the onset of clinical deterioration may not provide enough time to complete the evaluation and to obtain a suitable donor organ.[275] This issue is of particular importance in countries which utilize a lung allocation score because it does not fully capture the waitlist mortality for individuals with PAH.[276-280] Notably in allocation systems that use a high priority allocation for patients with PAH who are at imminent risk of death, improved waitlist survival and an increased rate of transplant has been observed.[281]

The 2014 ISHLT consensus document on the selection of lung transplant recipients recommended referral for transplant in patients with PAH when advanced symptoms are present despite escalation of therapy or rapidly progressive disease (Table 3).[4] Listing was recommended when advanced symptoms persist despite the addition of combination therapy with prostanoids, or when there are high risk features.

Since the 2014 ISHLT consensus document, significant advances have occurred in risk stratification of PAH.[4] In particular, the 2018 World Symposium on Pulmonary Hypertension strongly recommends serial parametric risk assessment.[282] The two most frequently used risk assessment models are the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) 2.0 and the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) model.[283,284] The REVEAL equation and REVEAL subsequent score (RSS) were derived from a cohort of 2,716 patients with incident and prevalent PAH, or associated PAH, from 54 centers across the US.[283] Using a comprehensive battery of 3 non-modifiable and nine modifiable weighted variables measured at baseline, the RSS incorporates five strata to predict 1-year survival, as well as long term outcome data up to five years. An updated version of the score, REVEAL 2.0, which incorporates estimated GFR and all-cause hospitalizations within the previous six-months, has emerged as a powerful predictor of mortality

and clinical worsening.[285-287] Neither of the REVEAL scores has been validated prospectively.

The ESC/ERS model also employs the assessment of risk using a multi-parametric comprehensive analysis of clinical variables.[284] Unlike REVEAL, this model avoids use of any non-modifiable criteria, and does not "weight" the variables according to their relative importance. Several European registries have since validated the ESC/ERS risk status model; however, it is unknown if the ESC/ERS tool predicts clinical worsening or hospitalizations.[288] Finally, this approach, similar to the RSS, still needs to be validated prospectively.

The 2018 World Symposium on Pulmonary Hypertension states that the ultimate goal of therapy for patients with PAH is to achieve a low-risk status, assessed either by REVEAL or the ESC/ERS model.[282] Failure to achieve low risk status after 3-6 months mandates intensification of therapy. If low risk status is not achieved despite maximal PAH therapy within 6-months, patients should be referred for assessment of lung transplant eligibility.

Given that both models have limitations, additional clinical data also need to be taken into account during serial risk assessment and consideration of referral for transplant. These include cardiopulmonary exercise testing and right ventricular assessment by echocardiogram and/or cardiac MRI, which have been shown in various studies to add predictive power to conventional variables.[289,290] Furthermore, specific clinical scenarios known to equate to a high-risk profile need to be considered. While renal failure is a risk factor for complications after transplantation, it is important to note that renal insufficiency in PAH most frequently occurs due to cardiorenal syndrome and is reversible after lung transplant. Similarly, hepatic dysfunction can be related to right ventricular overload, which is also reversible after transplant. Other high-risk profiles include familial PAH, PVOD, CTD-PAH, CTD-PAH associated with concomitant ILD, rapidly progressive disease despite therapy, and development of hemoptysis.[282,291-293] New contemporary multimodal risk stratification tools, which outperform individual predictors of disease progression, combined with other pertinent clinical information, should be used to guide timing of referral and listing for lung transplant (Table 3).

Group 3 Pulmonary Hypertension and Congenital Heart Disease: The OPTN/UNOS registry data demonstrate that Group 3 pulmonary hypertension is common in patients with advanced CF, ILD, and COPD and is associated with increased oxygen requirements and increased mortality.[294-299] Bilateral lung transplant is preferred in the presence of Group 3 pulmonary hypertension, yet single lung transplant remains an option when the mean pulmonary artery pressure is not severely elevated (mPAP <35 mmHg).[295,300] Pulmonary hypertension can also occur in the context of congenital heart disease.[301] Patients with simple repairable defects may undergo lung transplant with cardiac repair, however, patients with complex structural heart disease should be evaluated for combined heart-lung transplant.[160,302]

Lymphangioleiomyomatosis (LAM)

Lung transplant for LAM is relatively rare; however, it is associated with better post-transplant survival compared to other advanced lung diseases.[1,303-307] Fewer patients with LAM have required lung transplant since the standardized use of mTOR inhibitors as treatment, but it remains an indication for those with severely abnormal lung function (FEV$_1$ < 30%), exertional dyspnea (NYHA class III or IV), or hypoxemia at rest.[303-306,308-315] While disease recurrence does occur post-transplant, it does not appear to limit survival.[303,304,309,311,316-318] Where organ availability allows, bilateral lung transplant may be favored given the risk of post-transplant pneumothorax in the native lung; however, single lung transplant confers similar overall survival based on limited data.[306,312,314,319]. Lung transplant for LAM may be challenging surgically due to the high prevalence of adhesions resulting from the management of pleural complications prior to transplant.[309,312-314,319] Peri-operative bleeding appears to be most associated with prior pleurectomy and use of intra-operative ECMO.[312,319] Significant hemorrhage arising from angiomyolipomas is uncommon peri-operatively and their presence should not preclude candidacy for lung transplant.[311,314]

Optimal management of mTOR inhibitors in patients with LAM listed for lung transplant remains controversial. Although exposure to mTOR inhibitors in the immediate post-transplant period has been associated with delayed bronchial anastomotic healing or anastomotic dehiscence, mTOR inhibitors are now successfully continued up until the time transplant in many centers without complications.[305,315,320] Given its shorter half-life, everolimus is usually preferred to sirolimus for listed patients.[316] While the benefit of continuing mTOR inhibitors up until transplant likely outweighs the risk, the option should be discussed with the patient.

Thoracic malignancy

Thoracic malignancy is a rare indication for lung transplant, accounting for only 0.1% of all lung transplants performed between 1995 and 2018.[1] Notably, there is an absence of current data describing outcomes of patients transplanted for thoracic malignancy, likely reflecting the abandonment of this practice in many lung transplant centers. Older data on patients undergoing lung transplant for what was previously referred to as advanced multifocal bronchioalveolar cell carcinoma (BAC) showed post-transplant survival comparable to that of patients transplanted for other lung diseases.[321-323] In contrast, the incidental finding of all but early stage lung cancer in explanted lungs has been associated with a high rate of recurrence and decreased survival.[321,324-326] Thus, lung transplant centers should establish protocols to screen candidates at higher risk for lung cancer. If a suspicious pulmonary nodule or mass is identified, the risks associated with invasive diagnostic procedures must be carefully weighed against the substantial risk associated with transplanting a patient with a thoracic malignancy.

If considered at all, lung transplant should be limited to cases of lung-limited adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma, or multifocal lung adenocarcinoma with a low invasive component and negative lymph node involvement.[327] In such cases, it may be considered for patients in whom (1) surgical resection is not feasible either because of multifocal disease or significant underlying pulmonary disease, (2) multifocal disease has resulted in significant lung restriction and respiratory compromise, (3) medical oncology therapies have failed or are contraindicated, and (4) lung transplant will be curative.[327] In lieu of a gold-standard diagnosis by resection, adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic predominant adenocarcinoma must be diagnosed based on radiographic and core biopsy results (including histology, phenotypic staining, and genotyping).[327] To exclude any extrapulmonary or lymphatic spread, staging with abdominal and chest CT, mediastinal lymph node sampling through endobronchial ultrasound-guided transbronchial needle aspiration or mediastinoscopy, brain MRI, and full-body PET should be performed prior to consideration of listing and every 3 months for patients on the waiting list.[321,327,328] At the time of transplant, mediastinoscopy or direct sampling of mediastinal lymph nodes of the recipient should be performed prior to implantation. A candidate should be informed that lung transplant may not proceed if evidence of extrapulmonary or mediastinal lymph node disease is identified intraoperatively, and a back-up recipient should be available in the event that the lung transplant is aborted for these circumstances.[327,328] Considering the 6%-9% incidence of developing lung cancer in the native lung, bilateral lung transplant is preferred.[329] The risk of disease recurrence is high.[321,322,330] Modifying the surgical approach as suggested to reduce aerogenous contamination of donor lungs at the time of implantation may mitigate the risk of relapse post-transplant.[323,331] In summary, the risk associated with lung transplant in candidates with thoracic malignancy is high, and each center therefore needs to consider whether the possible benefit outweighs this risk and balance the overall need for prioritization of transplantable organs.

Acute respiratory distress syndrome

Lung transplant for patients without underlying lung disease who have acute respiratory distress syndrome (ARDS) is rarely a feasible option given that the acuity and severity of illness often precludes full transplant assessment, or results in significant extra-pulmonary complications or death before a donor can be found.[332,333] The possibility of recovery from ARDS without lung transplant can create additional uncertainty when evaluating a potential candidate.[333] In case series and reports of successful lung transplant for ARDS, factors that favor short and long-term survival include young age, lack of comorbidities, lack of extra-pulmonary organ dysfunction, the use of ECLS as a BTT, and a pulmonary cause of ARDS.[333-340] ICU-acquired muscle weakness prior to transplant likely increases mortality in the early post-transplant period.[333] Recovery after

ARDS without transplant has been described in patients on ECMO support for greater than 3 weeks, hence lung transplant referral should be reserved for patients who have demonstrated lack of clinical improvement, persistent parenchymal infiltrates, and severely reduced lung compliance after prolonged support.[341,342] Case reports describing bilateral lung transplant for COVID-19 associated ARDS have started to emerge since January 2020. Experts in the field recommend waiting at least 4-6 weeks after the onset of respiratory failure due to COVID-19 prior to considering lung transplant.[343] While it seems likely that these cases should be evaluated like other patients with post-viral ARDS, it is too early to make conclusive recommendations at this time.

Other indications

This document attempts to address some of the most common indications for lung transplant. There are other indications for which a transplant center may be asked to evaluate lung transplant candidacy. The underlying diagnosis should be considered on a case-by-case basis, with particular attention to understanding the risk of recurrence, comorbidities, and extrapulmonary involvement.

Variability between lung transplant centers

This document reflects a consensus among lung transplant experts from around the world, however, significant differences in candidate selection practices among centers should continue to be expected. Centers need to take into consideration local circumstances and accreditation requirements. This may be due to varying governmental policies or differences in organ availability, differences in the approach towards the rationing of a scarce resource, or varying expertise. Some centers will continue to be willing to accept a greater degree of risk, accepting patients with substantially higher risk factors, particularly in centers with more organ availability. Individual centers may develop more specialized expertise in certain patient populations (e.g., scleroderma, combined cardiothoracic surgical procedures at time of lung transplant) or be better prepared to optimize specific risk factors (management of *M. abscessus* or *B. cenocepacia*). Variability in listing criteria can enhance access to lung transplant by allowing different programs to have different risk thresholds or to develop expertise in transplanting patients with certain high-risk factors, thus advancing the field by increasing the shared experience.

Because of these differences between transplant centers in candidate selection, transparency in candidate selection policies is strongly recommended. When it is determined that a patient is not a candidate, the transplant center should provide specific reasons and information about alternatives, such as seeking transplant at other programs if this is a possibility. Transplant tourism or transplantation at any center that might use an organ obtained through any form of trafficking cannot be endorsed and must be discouraged.[344]

Conclusions

Lung transplant outcomes can vary significantly depending on the clinical characteristics of candidates. This consensus statement differs from prior versions by creating categories for risk factors, acknowledging that risk factors need to be considered together in the context of the candidate as a whole, and that certain centers may choose to develop specialized expertise in addressing certain higher risk conditions. Whenever possible, all potentially modifiable risk factors should be optimized prior to lung transplant to yield the most successful long-term outcomes. Further, as transplant centers provide lung transplants for more complex candidates, research should accelerate to allow for increasingly evidence-based recommendations.

Supplementary materials

Supplementary material associated with this article, including search terms, filters, and the resultant number of articles from the literature review, can be found in the online version at https://doi.org/10.1016/j.healun.2021.07.005.

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