Published in final edited form as:

J Heart Lung Transplant. 2021 November ; 40(11): 1349–1379. doi:10.1016/j.healun.2021.07.005.

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

Lorriana E. Leard, MD[a], **Are M. Holm, MD, PhD**[b], **Maryam Valapour, MD, MPP**[c], **Allan R. Glanville, MBBS, MD**[d], **Sandeep Attawar, MBBS, MS, MCh**[e], **Meghan Aversa, MD**[f], **Silvia V. Campos, MD**[g], **Lillian M. Christon, PhD**[h], **Marcelo Cypel, MD, MSc**[f], **Göran Dellgren, MD, PhD**[i], **Matthew G. Hartwig, MD, MHS**[j], **Siddhartha G. Kapnadak, MD**[k], **Nicholas A. Kolaitis, MD, MAS**[a], **Robert M. Kotloff, MD**[l], **Caroline M. Patterson, MD**[m], **Oksana A Shlobin, MD**[n], **Patrick J. Smith, PhD, MPH**[j], **Amparo Solé, MD, PhD**[o], **Melinda Solomon, MD**[p], **David Weill, MD**[q], **Marlies S. Wijsenbeek, MD, PhD**[r], **Brigitte W.M. Willemse, MD, PhD**[s], **Selim M. Arcasoy, MD MPH**[t], **Kathleen J. Ramos, MD, MSc**[k]

[a]University of California San Francisco, California, USA

[b]Oslo University Hospital, Oslo, Norway

[c]Cleveland Clinic, Ohio, USA

[d]St. Vincent's Hospital, New South Wales, Australia

[e]Krishna Institute of Medical Sciences Institute for Heart and Lung Transplantation, Hyderabad, India

[f]University of Toronto, Ontario, Canada

[g]Heart Institute (InCor) University of Sao Paulo Medical School, Sao Paulo, Brazil

[h]Medical University of South Carolina, South Carolina, USA

[i]Sahlgrenska University Hospital and University of Gothenburg, Sweden

[j]Duke University, North Carolina, USA

[k]University of Washington, Washington, USA

[l]University of Pennsylvania, Pennsylvania, USA

[m]Royal Papworth Hospital, Cambridge, UK

[n]Inova Fairfax Hospital, Virginia, USA

[o]University Hospital La Fe, Valencia, Spain

[p]Hospital for Sick Children, University of Toronto, Ontario, Canada

Corresponding Author: Lorriana Leard, M.D., Professor of Clinical Medicine, Vice Chief, Clinical Operations, Division of Pulmonary, Critical Care, Allergy, & Sleep Medicine, University of California San Francisco, 505 Parnassus Ave. HSE-1308, San Francisco, CA 94143-0111, Phone:415-476-8287, Fax: 415-476-5712, Lorriana.Leard@ucsf.edu, Twitter: @LorrianaLeard.

Note: The manuscript has been approved by the ISHLT Board of Directors, Publications Oversight Committee, and Standards and Guidelines Committee.

[q]Weill Consulting Group, New Orleans, Louisiana, USA

[r]Erasmus MC, University Medical Center Rotterdam, The Netherlands

[s]Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[t]Columbia University, New York, USA

Keywords

consensus; lung transplant; emphysema; chronic obstructive pulmonary disease; interstitial lung disease; pulmonary hypertension; cystic fibrosis; ethics; risk factor

INTRODUCTION:

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 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 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 perioperative 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 perioperative 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 peripheral vascular disease 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 perioperative 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, CF recipients with BMI <17 kg/m^2 have a survival 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 postoperative 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 high 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 postoperative 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 perioperative 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,) 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 compliance, 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/m^2, 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. cystic fibrosis, 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 >10mmHg. There is some evidence that survival is non-inferior for lung-liver transplant versus 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-min 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 FEV_1 < 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 perioperative 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, three 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 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

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 regulator (CFTR) modulators, where early clinical experience suggests that many individuals approaching lung transplant achieve disease stabilization or even improvement with 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, $PaCO_2$ > 50mmHg, 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 six-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 preemptive 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 <17kg/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 1995–2018.(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 where a lung allocation system utilizes a score that 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 three non-modifiable and nine modifiable weighted variables measured at baseline, the RSS incorporates five strata to predict one-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 six-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<35mmHg).(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– 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 intra-operatively, 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 Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Chambers DC, Cherikh WS, Harhay MO, et al. : The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult lung and heart–lung transplantation Report—2019; Focus theme: Donor and recipient size match. J Heart Lung Transplant 2019;38:1042–55. [PubMed: 31548030]
2. Orens JB, Estenne M, Arcasoy S, et al. : International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:745–55. [PubMed: 16818116]
3. Maurer JR, Frost AE, Estenne M, Higenbottam T, Glanville AR: International guidelines for the selection of lung transplant candidates. Transplantation 1998;66:951–6. [PubMed: 9798716]
4. Weill D, Benden C, Corris PA, et al. : A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2015.
5. Beauchamp T, Childress J: Principles of Biomedical Ethics. 7th edition: New York: Oxford University Press; 2012.
6. Ethical Principles in the Allocation of Human Organs. Organ Procurement and Transplant Network. Accessed August 12, 2021. https://optn.transplant.hrsa.gov/resources/ethics/ethical-principles-in-the-allocation-of-human-organs/
7. Lehr CJ, Blackstone EH, McCurry KR, Thuita L, Tsuang WM, Valapour M: Extremes of age decrease survival in adults after lung transplant. Chest 2020;157:907–15. [PubMed: 31419403]
8. Valapour M, Lehr CJ, Skeans MA, et al. : OPTN/SRTR 2019 Annual Data Report: Lung. Am J Transplant 2021;21 Suppl 2:441–520. [PubMed: 33595190]
9. Hayanga AJ, Aboagye JK, Hayanga HE, et al. : Contemporary analysis of early outcomes after lung transplantation in the elderly using a national registry. J Heart Lung Transplant 2015;34:182–8. [PubMed: 25447584]

10. Tong A, Howard K, Jan S, et al. : Community preferences for the allocation of solid organs for transplantation: a systematic review. Transplantation 2010;89:796–805. [PubMed: 20090570]
11. Hall DJ, Jeng EI, Gregg JA, et al. : The impact of donor and recipient age: older lung transplant recipients do not require younger lungs. Ann Thorac Surg 2019;107:868–76. [PubMed: 30444994]
12. Katsnelson J, Whitson BA, Tumin D, et al. : Lung transplantation with lungs from older donors: an analysis of survival in elderly recipients. J Surg Res 2017;214:109–16. [PubMed: 28624031]
13. Al-Adra DP, Hammel L, Roberts J, et al. : Pretransplant solid organ malignancy and organ transplant candidacy: A consensus expert opinion statement. Am J Transplant 2021;21:460–74. [PubMed: 32969590]
14. Al-Adra DP, Hammel L, Roberts J, et al. : Preexisting melanoma and hematological malignancies, prognosis, and timing to solid organ transplantation: A consensus expert opinion statement. Am J Transplant 2021;21:475–83. [PubMed: 32976703]
15. Berastegui C, LaPorta R, López-Meseguer M, et al. : Epidemiology and risk factors for cancer after lung transplantation. Transplantation Proceedings: Elsevier; 2017. p. 2285–91.
16. Acuna SA, Huang JW, Daly C, Shah PS, Kim SJ, Baxter NN: Outcomes of solid organ transplant recipients with preexisting malignancies in remission: a systematic review and meta-analysis. Transplantation 2017;101:471–81. [PubMed: 27101077]
17. Woll F, Mohanka M, Bollineni S, et al. : Characteristics and Outcomes of Lung Transplant Candidates With Preexisting Renal Dysfunction. Transplantation proceedings: Elsevier; 2020. p. 302–8.
18. Banga A, Mohanka M, Mullins J, et al. : Characteristics and outcomes among patients with need for early dialysis after lung transplantation surgery. Clin Transplant 2017;31:e13106.
19. Degen DA, Janardan J, Barraclough KA, et al. : Predictive performance of different kidney function estimation equations in lung transplant patients. Clin Biochem 2017;50:385–93. [PubMed: 28108166]
20. Osho AA, Castleberry AW, Snyder LD, et al. : The Chronic Kidney Disease Epidemiology Collaboration (CKDEPI) equation best characterizes kidney function in patients being considered for lung transplantation. J Heart Lung Transplant 2014;33:1248–54. [PubMed: 25107351]
21. Osho AA, Castleberry AW, Snyder LD, et al. : Assessment of different threshold preoperative glomerular filtration rates as markers of outcomes in lung transplantation. Ann Thorac Surg 2014;98:283–90. [PubMed: 24793682]
22. Manoushagian S, Meshkov A: Evaluation of solid organ transplant candidates for coronary artery disease. Am J Transplant 2014;14:2228–34. [PubMed: 25220486]
23. Halloran K, Hirji A, Li D, et al. : Coronary artery disease and coronary artery bypass grafting at the time of lung transplantation do not impact overall survival. Transplantation 2019;103:2190–5. [PubMed: 30801514]
24. Khandhar SJ, Althouse AD, Mulukutla S, et al. : Postoperative outcomes and management strategies for coronary artery disease in patients in need of a lung transplantation. Clin Transplant 2017;31:e13026.
25. Chaikriangkrai K, Jyothula S, Jhun HY, et al. : Impact of pre-operative coronary artery disease on cardiovascular events following lung transplantation. J Heart Lung Transplant 2016;35:115–21. [PubMed: 26452997]
26. Koprivanac M, Budev MM, Yun JJ, et al. : How important is coronary artery disease when considering lung transplant candidates? J Heart Lung Transplant 2016;35:1453–61. [PubMed: 27266805]
27. Makey IA, Sui JW, Huynh C, Das NA, Thomas M, Johnson S: Lung transplant patients with coronary artery disease rarely die of cardiac causes. Clin Transplant 2018;32:e13354.
28. McKellar SH, Bowen ME, Baird BC, Raman S, Cahill BC, Selzman CH: Lung transplantation following coronary artery bypass surgery—improved outcomes following single-lung transplant. J Heart Lung Transplant 2016;35:1289–94. [PubMed: 27381675]
29. Courtwright AM, El-Chemaly S, Dellaripa PF, Goldberg HJ: Survival and outcomes after lung transplantation for non-scleroderma connective tissue–related interstitial lung disease. J Heart Lung Transplant 2017;36:763–9. [PubMed: 28131664]

30. Takagishi T, Ostrowski R, Alex C, Rychlik K, Pelletiere K, Tehrani R: Survival and extrapulmonary course of connective tissue disease after lung transplantation. JCR: Journal of Clinical Rheumatology 2012;18:283–9. [PubMed: 22955476]
31. Ameye H, Ruttens D, Benveniste O, Verleden G, Wuyts W: Is lung transplantation a valuable therapeutic option for patients with pulmonary polymyositis? Experiences from the Leuven transplant cohort. Transplantation proceedings: Elsevier; 2014. p. 3147–53.
32. Lo WK, Burakoff R, Goldberg HJ, Feldman N, Chan WW: Pre-transplant impedance measures of reflux are associated with early allograft injury after lung transplantation. J Heart Lung Transplant 2015;34:26–35. [PubMed: 25444368]
33. King BJ, Iyer H, Leidi AA, Carby MR: Gastroesophageal reflux in bronchiolitis obliterans syndrome: a new perspective. J Heart Lung Transplant 2009;28:870–5. [PubMed: 19716037]
34. Lo WK, Goldberg HJ, Wee J, Fisichella PM, Chan WW: Both Pre-Transplant and Early Post-Transplant Antireflux Surgery Prevent Development of Early Allograft Injury After Lung Transplantation. J Gastrointest Surg 2016;20:111–8; discussion 8. [PubMed: 26493975]
35. Hartwig MG, Anderson DJ, Onaitis MW, et al. : Fundoplication after lung transplantation prevents the allograft dysfunction associated with reflux. Ann Thorac Surg 2011;92:462–8; discussion; 8–9. [PubMed: 21801907]
36. Sottile PD, Iturbe D, Katsumoto TR, et al. : Outcomes in systemic sclerosis-related lung disease after lung transplantation. Transplantation 2013;95:975–80. [PubMed: 23545509]
37. Miele CH, Schwab K, Saggar R, et al. : Lung Transplant Outcomes in Systemic Sclerosis with Significant Esophageal Dysfunction. A Comprehensive Single-Center Experience. Ann Am Thorac Soc 2016;13:793–802. [PubMed: 27078625]
38. Tokman S, Singer J, Devine M, et al. : Clinical outcomes of lung transplantation in patients with telomerase complex mutations. J Heart Lung Transplant 2015;34:S139–S40.
39. Swaminathan AC, Neely ML, Frankel CW, et al. : Lung transplant outcomes in patients with pulmonary fibrosis with telomere-related gene variants. Chest 2019;156:477–85. [PubMed: 30978332]
40. Upala S, Panichsillapakit T, Wijarnpreecha K, Jaruvongvanich V, Sanguankeo A: Underweight and obesity increase the risk of mortality after lung transplantation: a systematic review and meta-analysis. Transpl Int 2016;29:285–96. [PubMed: 26613209]
41. Jomphe V, Mailhot G, Damphousse V, et al. : The impact of waiting list BMI changes on the short-term outcomes of lung transplantation. Transplantation 2018;102:318–25. [PubMed: 28825952]
42. Singer JP, Peterson ER, Snyder ME, et al. : Body composition and mortality after adult lung transplantation in the United States. Am J Respir Crit Care Med 2014;190:1012–21. [PubMed: 25233138]
43. Chandrashekaran S, Keller CA, Kremers WK, Peters SG, Hathcock MA, Kennedy CC: Weight loss prior to lung transplantation is associated with improved survival. J Heart Lung Transplant 2015;34:651–7. [PubMed: 25578626]
44. Clausen ES, Frankel C, Palmer SM, Snyder LD, Smith PJ: Pre-transplant weight loss and clinical outcomes after lung transplantation. J Heart Lung Transplant 2018;37:1443–7. [PubMed: 30228085]
45. Ramos KJ, Kapnadak SG, Bradford MC, et al. : Underweight patients with cystic fibrosis have acceptable survival following lung transplantation: a united network for organ sharing registry study. Chest 2020.
46. Halpern AL, Boshier PR, White AM, et al. : A Comparison of frailty measures at listing to predict outcomes after lung transplantation. Ann Thorac Surg 2020;109:233–40. [PubMed: 31479636]
47. Chamogeorgakis T, Mason DP, Murthy SC, et al. : Impact of nutritional state on lung transplant outcomes. J Heart Lung Transplant 2013;32:693–700. [PubMed: 23664761]
48. Baldwin M, Arcasoy S, Shah A, et al. : Hypoalbuminemia and early mortality after lung transplantation: a cohort study. Am J Transplant 2012;12:1256–67. [PubMed: 22335491]
49. Komatsu T, Oshima A, Chen-Yoshikawa TF, et al. : Physical activity level significantly affects the survival of patients with end-stage lung disease on a waiting list for lung transplantation. Surg Today 2017;47:1526–32. [PubMed: 28540430]

50. Banga A, Batchelor E, Mohanka M, et al. : Predictors of outcome among patients on extracorporeal membrane oxygenation as a bridge to lung transplantation. Clin Transplant 2017;31.
51. Baldwin MR, Singer JP, Huang D, et al. : Refining low physical activity measurement improves frailty assessment in advanced lung disease and survivors of critical illness. Ann Am Thorac Soc 2017;14:1270–9. [PubMed: 28398076]
52. Singer JP, Diamond JM, Anderson MR, et al. : Frailty phenotypes and mortality after lung transplantation: A prospective cohort study. Am J Transplant 2018;18:1995–2004. [PubMed: 29667786]
53. Singer JP, Diamond JM, Gries CJ, et al. : Frailty Phenotypes, Disability, and Outcomes in Adult Candidates for Lung Transplantation. Am J Respir Crit Care Med 2015;192:1325–34. [PubMed: 26258797]
54. Venado A, McCulloch C, Greenland JR, et al. : Frailty trajectories in adult lung transplantation: A cohort study. J Heart Lung Transplant 2019;38:699–707. [PubMed: 31005571]
55. Freiberger D, Gould Delaney A, Forbes P, Manley D, Visner GA: Pediatric lung transplant: Correlation of pretransplant condition with post-transplant outcomes. Pediatr Transplant 2020:e13889.
56. Armstrong HF, Garber CE, Bartels MN: Exercise testing parameters associated with post lung transplant mortality. Respir Physiol Neurobiol 2012;181:118–22. [PubMed: 22503816]
57. Li M, Mathur S, Chowdhury NA, Helm D, Singer LG: Pulmonary rehabilitation in lung transplant candidates. J Heart Lung Transplant 2013;32:626–32. [PubMed: 23701852]
58. Wickerson L, Rozenberg D, Janaudis-Ferreira T, et al. : Physical rehabilitation for lung transplant candidates and recipients: An evidence-informed clinical approach. World J Transplant 2016;6:517. [PubMed: 27683630]
59. Courtwright AM, Cao S, Wood I, et al. : Clinical Outcomes of Lung Transplantation in the Presence of Donor-Specific Antibodies. Ann Am Thorac Soc 2019;16:1131–7. [PubMed: 31026404]
60. Kim M, Townsend KR, Wood IG, et al. : Impact of pretransplant anti-HLA antibodies on outcomes in lung transplant candidates. Am J Respir Crit Care Med 2014;189:1234–9. [PubMed: 24749479]
61. Smith JD, Ibrahim MW, Newell H, et al. : Pre-transplant donor HLA-specific antibodies: characteristics causing detrimental effects on survival after lung transplantation. J Heart Lung Transplant 2014;33:1074–82. [PubMed: 24954882]
62. Bosanquet JP, Witt CA, Bemiss BC, et al. : The impact of pre-transplant allosensitization on outcomes after lung transplantation. J Heart Lung Transplant 2015;34:1415–22. [PubMed: 26169666]
63. Tinckam K, Keshavjee S, Chaparro C, et al. : Survival in sensitized lung transplant recipients with perioperative desensitization. Am J Transplant 2015;15:417–26. [PubMed: 25612494]
64. Smibert O, Snell GI, Bills H, Westall GP, Morrissey CO: Mycobacterium abscessus Complex - a Particular Challenge in the Setting of Lung Transplantation. Expert Rev Anti Infect Ther 2016;14:325–33. [PubMed: 26732819]
65. Friedman DZP, Cervera C, Halloran K, Tyrrell G, Doucette K: Non-tuberculous mycobacteria in lung transplant recipients: Prevalence, risk factors, and impact on survival and chronic lung allograft dysfunction. Transpl Infect Dis 2020;22:e13229.
66. Raats D, Lorent N, Saegeman V, et al. : Successful lung transplantation for chronic Mycobacterium abscessus infection in advanced cystic fibrosis, a case series. Transpl Infect Dis 2019;21:e13046.
67. Perez AA, Singer JP, Schwartz BS, et al. : Management and clinical outcomes after lung transplantation in patients with pre-transplant Mycobacterium abscessus infection: A single center experience. Transpl Infect Dis 2019;21:e13084.
68. Qvist T, Pressler T, Thomsen VO, Skov M, Iversen M, Katzenstein TL: Nontuberculous mycobacterial disease is not a contraindication to lung transplantation in patients with cystic fibrosis: a retrospective analysis in a Danish patient population. Transplant Proc 2013;45:342–5. [PubMed: 23267788]
69. Lobo LJ, Chang LC, Esther CR Jr., Gilligan PH, Tulu Z, Noone PG: Lung transplant outcomes in cystic fibrosis patients with pre-operative Mycobacterium abscessus respiratory infections. Clin Transplant 2013;27:523–9. [PubMed: 23710571]

70. Solé A, García-Robles AA, Jordá C, et al. : Salvage therapy with topical posaconazole in lung transplant recipients with invasive Scedosporium infection. Am J Transplant 2018;18:504–9. [PubMed: 29116676]
71. Parize P, Boussaud V, Poinsignon V, et al. : Clinical outcome of cystic fibrosis patients colonized by Scedosporium species following lung transplantation: A single-center 15-year experience. Transpl Infect Dis 2017;19.
72. Alexander BD, Petzold EW, Reller LB, et al. : Survival after lung transplantation of cystic fibrosis patients infected with Burkholderia cepacia complex. Am J Transplant 2008;8:1025–30. [PubMed: 18318775]
73. Murray S, Charbeneau J, Marshall BC, LiPuma JJ: Impact of burkholderia infection on lung transplantation in cystic fibrosis. Am J Respir Crit Care Med 2008;178:363–71. [PubMed: 18535253]
74. Daccò V, Claut L, Piconi S, et al. : Successful ceftazidime-avibactam treatment of post-surgery Burkholderia multivorans genomovar II bacteremia and brain abscesses in a young lung transplanted woman with cystic fibrosis. Transpl Infect Dis 2019;21:e13082.
75. Los-Arcos I, Len O, Martín-Gómez MT, et al. : Lung transplantation in two cystic fibrosis patients infected with previously pandrug-resistant Burkholderia cepacia complex treated with ceftazidime-avibactam. Infection 2019;47:289–92. [PubMed: 30565008]
76. Cantón-Bulnes ML, Hurtado Martínez Á, López-Cerero L, Arenzana Seisdedos Á, Merino-Bohorquez V, Garnacho-Montero J: A case of pan-resistant Burkholderia cepacia complex bacteremic pneumonia, after lung transplantation treated with a targeted combination therapy. Transpl Infect Dis 2019;21:e13034.
77. Goodlet KJ, Nailor MD, Omar A, et al. : Successful Lung Re-transplant in a Patient with Cepacia Syndrome due to Burkholderia ambifaria. J Cyst Fibros 2019;18:e1–e4. [PubMed: 30224331]
78. Álvarez-López P, Riveiro-Barciela M, Oleas-Vega D, et al. : Anti-HBc impacts on the risk of hepatitis B reactivation but not on survival of solid-organ transplant recipients. Medicine (Baltimore) 2020;99:e19407.
79. Belli LS, Perricone G, Adam R, et al. : Impact of DAAs on liver transplantation: Major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. J Hepatol 2018;69:810–7. [PubMed: 29940268]
80. Arora SS, Axley P, Ahmed Z, et al. : Decreasing frequency and improved outcomes of hepatitis C-related liver transplantation in the era of direct-acting antivirals - a retrospective cohort study. Transpl Int 2019;32:854–64. [PubMed: 30866110]
81. Kern RM, Seethamraju H, Blanc PD, et al. : The feasibility of lung transplantation in HIV-seropositive patients. Ann Am Thorac Soc 2014;11:882–9. [PubMed: 24964265]
82. Morabito V, Grossi P, Lombardini L, et al. : Solid Organ Transplantation in HIV+ Recipients: Italian Experience. Transplant Proc 2016;48:424–30. [PubMed: 27109970]
83. Ong S, Levy RD, Yee J, et al. : Successful lung transplantation in an HIV seropositive patient with desquamative interstitial pneumonia: a case report. BMC Pulm Med 2018;18:162. [PubMed: 30326889]
84. Ambaraghassi G, Ferraro P, Poirier C, Rouleau D, Fortin C: Double lung transplantation in an HIV-positive patient with Mycobacterium kansasii infection. Transpl Infect Dis 2019;21:e12999.
85. Koval CE, Farr M, Krisl J, et al. : Heart or lung transplant outcomes in HIV-infected recipients. J Heart Lung Transplant 2019;38:1296–305. [PubMed: 31636044]
86. Dew MA, DiMartini AF, Dobbels F, et al. : The 2018 ISHLT/APM/AST/ICCAC/STSW recommendations for the psychosocial evaluation of adult cardiothoracic transplant candidates and candidates for long-term mechanical circulatory support. J Heart Lung Transplant 2018;37:803–23. [PubMed: 29709440]
87. Stilley CS, Bender CM, Dunbar-Jacob J, Sereika S, Ryan CM: The impact of cognitive function on medication management: three studies. Health Psychol 2010;29:50–5. [PubMed: 20063935]
88. Kuntz K, Weinland SR, Butt Z: Psychosocial Challenges in Solid Organ Transplantation. J Clin Psychol Med Settings 2015;22:122–35. [PubMed: 26370201]
89. Barbour KA, Blumenthal JA, Palmer SM: Psychosocial issues in the assessment and management of patients undergoing lung transplantation. Chest 2006;129:1367–74. [PubMed: 16685030]

90. Smith PJ, Stonerock GL, Ingle KK, et al. : Neurological Sequelae and Clinical Outcomes After Lung Transplantation. Transplant Direct 2018;4:e353.
91. Sher Y, Mooney J, Dhillon G, Lee R, Maldonado JR: Delirium after lung transplantation: Association with recipient characteristics, hospital resource utilization, and mortality. Clin Transplant 2017;31.
92. Smith PJ, Blumenthal JA, Hoffman BM, et al. : Reduced Cerebral Perfusion Pressure during Lung Transplant Surgery Is Associated with Risk, Duration, and Severity of Postoperative Delirium. Ann Am Thorac Soc 2016;13:180–7. [PubMed: 26731642]
93. Smith PJ, Rivelli SK, Waters AM, et al. : Delirium affects length of hospital stay after lung transplantation. J Crit Care 2015;30:126–9. [PubMed: 25307975]
94. van Beers M, Janssen DJA, Gosker HR, Schols A: Cognitive impairment in chronic obstructive pulmonary disease: disease burden, determinants and possible future interventions. Expert Rev Respir Med 2018;12:1061–74. [PubMed: 30296384]
95. Kakkera K, Padala KP, Kodali M, Padala PR: Association of chronic obstructive pulmonary disease with mild cognitive impairment and dementia. Curr Opin Pulm Med 2018;24:173–8. [PubMed: 29232279]
96. Parekh PI, Blumenthal JA, Babyak MA, et al. : Gas exchange and exercise capacity affect neurocognitive performance in patients with lung disease. Psychosom Med 2005;67:425–32. [PubMed: 15911906]
97. Dodd JW: Lung disease as a determinant of cognitive decline and dementia. Alzheimers Res Ther 2015;7:32. [PubMed: 25798202]
98. Smith PJ, Rivelli S, Waters A, et al. : Neurocognitive changes after lung transplantation. Ann Am Thorac Soc 2014;11:1520–7. [PubMed: 25375275]
99. Hoffman BM, Blumenthal JA, Carney RC, et al. : Changes in neurocognitive functioning following lung transplantation. Am J Transplant 2012;12:2519–25. [PubMed: 22548872]
100. Dew MA, Rosenberger EM, Myaskovsky L, et al. : Depression and Anxiety as Risk Factors for Morbidity and Mortality After Organ Transplantation: A Systematic Review and Meta-Analysis. Transplantation 2015;100:988–1003. [PubMed: 26492128]
101. Trumper A, Appleby L: Psychiatric morbidity in patients undergoing heart, heart and lung, or lung transplantation. J Psychosom Res 2001;50:103–5. [PubMed: 11274667]
102. Stilley CS, Dew MA, Stukas AA, et al. : Psychological symptom levels and their correlates in lung and heart-lung transplant recipients. Psychosomatics 1999;40:503–9. [PubMed: 10581979]
103. Rosenberger EM, DiMartini AF, DeVito Dabbs AJ, et al. : Psychiatric Predictors of Long-term Transplant-Related Outcomes in Lung Transplant Recipients. Transplantation 2016;100:239–47. [PubMed: 26177087]
104. Rosenberger EM, Dew MA, Crone C, DiMartini AF: Psychiatric disorders as risk factors for adverse medical outcomes after solid organ transplantation. Curr Opin Organ Transplant 2012;17:188–92. [PubMed: 22277955]
105. Dobbels F, Vanhaecke J, Desmyttere A, Dupont L, Nevens F, De Geest S: Prevalence and correlates of self-reported pretransplant nonadherence with medication in heart, liver, and lung transplant candidates. Transplantation 2005;79:1588–95. [PubMed: 15940050]
106. Teichman BJ, Burker EJ, Weiner M, Egan TM: Factors associated with adherence to treatment regimens after lung transplantation. Prog Transplant 2000;10:113–21. [PubMed: 10933765]
107. Smith PJ, Blumenthal JA, Trulock EP, et al. : Psychosocial Predictors of Mortality Following Lung Transplantation. Am J Transplant 2016;16:271–7. [PubMed: 26366639]
108. Dew MA, DiMartini AF, Dabbs ADV, et al. : Adherence to the medical regimen during the first two years after lung transplantation. Transplantation 2008;85:193. [PubMed: 18212623]
109. Smith PJ, Snyder LD, Palmer SM, et al. : Depression, social support, and clinical outcomes following lung transplantation: a single-center cohort study. Transpl Int 2018;31:495–502. [PubMed: 29130541]
110. Phillips KM, Burker EJ, White HC: The roles of social support and psychological distress in lung transplant candidacy. Prog Transplant 2011;21:200–6. [PubMed: 21977880]

111. Hofmann P, Benden C, Kohler M, Schuurmans MM: Smoking resumption after heart or lung transplantation: a systematic review and suggestions for screening and management. J Thorac Dis 2018;10:4609–18. [PubMed: 30174913]
112. Bauldoff GS, Holloman CH, Carter S, Pope-Harman AL, Nunley DR: Cigarette smoking following lung transplantation: effects on allograft function and recipient functional performance. J Cardiopulm Rehabil Prev 2015;35:147–53. [PubMed: 25412223]
113. Anis KH, Weinrauch LA, D'Elia JA: Effects of smoking on solid organ transplantation outcomes. Am J Med 2019;132:413–9. [PubMed: 30452885]
114. Hellemons ME, Agarwal PK, Van der Bij W, et al. : Former smoking is a risk factor for chronic kidney disease after lung transplantation. Am J Transplant 2011;11:2490–8. [PubMed: 21883906]
115. National Academies of Sciences E, Medicine, Health, et al.: The National Academies Collection: Reports funded by National Institutes of Health. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington (DC): National Academies Press (US) Copyright 2017 by the National Academy of Sciences. All rights reserved.; 2017.
116. Marks WH, Florence L, Lieberman J, et al. : Successfully treated invasive pulmonary aspergillosis associated with smoking marijuana in a renal transplant recipient. Transplantation 1996;61:1771–4. [PubMed: 8685958]
117. Hamadeh R, Ardehali A, Locksley RM, York MK: Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient. Chest 1988;94:432–3. [PubMed: 3293934]
118. Levi ME, Montague BT, Thurstone C, Kumar D, Huprikar SS, Kotton CN: Marijuana use in transplantation: A call for clarity. Clin Transplant 2019;33:e13456.
119. Kulig K: Interpretation of Workplace Tests for Cannabinoids. J Med Toxicol 2017;13:106–10. [PubMed: 27686239]
120. Kulig K: Interpretation of workplace tests for cannabinoids. J Med Toxicol 2017;13:106–10. [PubMed: 27686239]
121. Vahidy S, Li D, Hirji A, et al. : Pretransplant opiod use and survival after lung transplantation Transplantation 2019.
122. Colman R, Singer LG, Barua R, Downar J: Outcomes of lung transplant candidates referred for co-management by palliative care: A retrospective case series. Palliat Med 2015;29:429–35. [PubMed: 25634636]
123. Lancaster TS, Miller JR, Epstein DJ, DuPont NC, Sweet SC, Eghtesady P: Improved waitlist and transplant outcomes for pediatric lung transplantation after implementation of the lung allocation score. J Heart Lung Transplant 2017;36:520–8. [PubMed: 27866928]
124. Andrews WS, Kane BJ, Hendrickson RJ: Organ allocation and utilization in pediatric transplantation. Semin Pediatr Surg 2017;26:186–92. [PubMed: 28964472]
125. Grasemann H, de Perrot M, Bendiak GN, et al. : ABO-incompatible lung transplantation in an infant. Am J Transplant 2012;12:779–81. [PubMed: 22152044]
126. Hayes D Jr., Cherikh WS, Chambers DC, et al. : The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Twenty-second pediatric lung and heart-lung transplantation report-2019; Focus theme: Donor and recipient size match. J Heart Lung Transplant 2019;38:1015–27. [PubMed: 31548028]
127. Paraskeva MA, Edwards LB, Levvey B, et al. : Outcomes of adolescent recipients after lung transplantation: An analysis of the International Society for Heart and Lung Transplantation Registry. J Heart Lung Transplant 2018;37:323–31. [PubMed: 28320631]
128. Killian MO: Psychosocial predictors of medication adherence in pediatric heart and lung organ transplantation. Pediatr Transplant 2017;21.
129. Killian MO, Schuman DL, Mayersohn GS, Triplett KN: Psychosocial predictors of medication non-adherence in pediatric organ transplantation: A systematic review. Pediatr Transplant 2018;22:e13188.
130. Lefkowitz DS, Fitzgerald CJ, Zelikovsky N, Barlow K, Wray J: Best practices in the pediatric pretransplant psychosocial evaluation. Pediatr Transplant 2014;18:327–35. [PubMed: 24802341]

131. Putschoegl A, Dipchand AI, Ross H, Chaparro C, Johnson JN: Transitioning from pediatric to adult care after thoracic transplantation. J Heart Lung Transplant 2017;36:823–9. [PubMed: 28342709]

132. Casswell GK, Pilcher DV, Martin RS, et al. : Buying time: The use of extracorporeal membrane oxygenation as a bridge to lung transplantation in pediatric patients. Pediatr Transplant 2013;17:E182–8. [PubMed: 24164831]

133. Benden C: Specific aspects of children and adolescents undergoing lung transplantation. Curr Opin Organ Transplant 2012;17:509–14. [PubMed: 22941318]

134. Ramos KJ, Smith PJ, McKone EF, et al. : Lung transplant referral for individuals with cystic fibrosis: Cystic Fibrosis Foundation consensus guidelines. J Cyst Fibros 2019;18:321–33. [PubMed: 30926322]

135. Ivy DD, Abman SH, Barst RJ, et al. : Pediatric pulmonary hypertension. J Am Coll Cardiol 2013;62:D117–26. [PubMed: 24355636]

136. Rosenzweig EB, Abman SH, Adatia I, et al. : Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J 2019;53.

137. Hansmann G, Koestenberger M, Alastalo TP, et al. : 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant 2019;38:879–901. [PubMed: 31495407]

138. Omara M, Okamoto T, Arafat A, Thuita L, Blackstone EH, McCurry KR: Lung transplantation in patients who have undergone prior cardiothoracic procedures. J Heart Lung Transplant 2016;35:1462–70. [PubMed: 27773457]

139. Verleden SE, Todd JL, Sato M, et al. : Impact of CLAD Phenotype on Survival After Lung Retransplantation: A Multicenter Study. Am J Transplant 2015;15:2223–30. [PubMed: 25940517]

140. Halloran K, Aversa M, Tinckam K, et al. : Comprehensive outcomes after lung retransplantation: A single-center review. Clin Transplant 2018;32:e13281.

141. Mitilian D, Sage E, Puyo P, et al. : Techniques and results of lobar lung transplantations. Eur J Cardiothorac Surg 2014;45:365–9; discussion 9–70. [PubMed: 23900745]

142. Date H, Sato M, Aoyama A, et al. : Living-donor lobar lung transplantation provides similar survival to cadaveric lung transplantation even for very ill patients†. Eur J Cardiothorac Surg 2015;47:967–72; discussion 72–3. [PubMed: 25228745]

143. Benazzo A, Schwarz S, Frommlet F, et al. : Twenty-year experience with extracorporeal life support as bridge to lung transplantation. J Thorac Cardiovasc Surg 2019;157:2515–25. e10. [PubMed: 30922636]

144. Hoetzenecker K, Donahoe L, Yeung JC, et al. : Extracorporeal life support as a bridge to lung transplantation–experience of a high-volume transplant center. J Thorac Cardiovasc Surg 2018;155:1316–28. e1. [PubMed: 29248282]

145. Wallinder A, Danielsson C, Magnusson J, Riise GC, Dellgren G: Outcomes and Long-term Survival After Pulmonary Retransplantation: A Single-Center Experience. Ann Thorac Surg 2019;108:1037–44. [PubMed: 31121129]

146. Doyle S, Hayes D Jr., Stewart WCL, Whitson BA, Tobias JD, Tumin D: Predictive Utility of Lung Allocation Score for Retransplantation Outcomes. Ann Thorac Surg 2018;106:1525–32. [PubMed: 30369429]

147. Cerón Navarro JA, Peñafiel Guzman S, Baquero Velandia D, et al. : Lung retransplant. Experience of a referral centre. Med Clin (Barc) 2021;156:1–6. [PubMed: 32430205]

148. Ren D, Kaleekal TS, Graviss EA, et al. : Retransplantation Outcomes at a Large Lung Transplantation Program. Transplant Direct 2018;4:e404.

149. Revilla-López E, Berastegui C, Sáez-Giménez B, et al. : Lung Retransplantation Due to Chronic Lung Allograph Dysfunction: Results From a Spanish Transplant Unit. Arch Bronconeumol 2019;55:134–8. [PubMed: 30131203]

150. Biswas Roy S, Panchanathan R, Walia R, et al. : Lung Retransplantation for Chronic Rejection: A Single-Center Experience. Ann Thorac Surg 2018;105:221–7. [PubMed: 29100649]

151. Waseda R, Benazzo A, Hoetzenecker K, et al. : The influence of retransplantation on survival for pediatric lung transplant recipients. J Thorac Cardiovasc Surg 2018;156:2025–34.e2. [PubMed: 30343700]
152. Verleden SE, Vanaudenaerde BM, Emonds MP, et al. : Donor-specific and -nonspecific HLA antibodies and outcome post lung transplantation. Eur Respir J 2017;50.
153. Chambers DC, Cherikh WS, Goldfarb SB, et al. : The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth adult lung and heart-lung transplant report-2018; Focus theme: Multiorgan Transplantation. J Heart Lung Transplant 2018;37:1169–83. [PubMed: 30293613]
154. Wolf JH, Sulewski ME, Cassuto JR, et al. : Simultaneous thoracic and abdominal transplantation: can we justify two organs for one recipient? Am J Transplant 2013;13:1806–16. [PubMed: 23718142]
155. Shudo Y, Wang H, Lingala B, et al. : Evaluation of Risk Factors for Heart-Lung Transplant Recipient Outcome: An Analysis of the United Network for Organ Sharing Database. Circulation 2019;140:1261–72. [PubMed: 31589491]
156. Fadel E, Mercier O, Mussot S, et al. : Long-term outcome of double-lung and heart-lung transplantation for pulmonary hypertension: a comparative retrospective study of 219 patients. Eur J Cardiothorac Surg 2010;38:277–84. [PubMed: 20371187]
157. de Perrot M, Granton JT, McRae K, et al. : Outcome of patients with pulmonary arterial hypertension referred for lung transplantation: a 14-year single-center experience. J Thorac Cardiovasc Surg 2012;143:910–8. [PubMed: 22306224]
158. Hill C, Maxwell B, Boulate D, et al. : Heart-lung vs. double-lung transplantation for idiopathic pulmonary arterial hypertension. Clin Transplant 2015;29:1067–75. [PubMed: 26358537]
159. Brouckaert J, Verleden SE, Verbelen T, et al. : Double-lung versus heart-lung transplantation for precapillary pulmonary arterial hypertension: a 24-year single-center retrospective study. Transpl Int 2019;32:717–29. [PubMed: 30735591]
160. Choong CK, Sweet SC, Guthrie TJ, et al. : Repair of congenital heart lesions combined with lung transplantation for the treatment of severe pulmonary hypertension: a 13-year experience. J Thorac Cardiovasc Surg 2005;129:661–9. [PubMed: 15746752]
161. Yi SG, Burroughs SG, Loebe M, et al. : Combined lung and liver transplantation: analysis of a single-center experience. Liver Transpl 2014;20:46–53. [PubMed: 24136814]
162. Yi SG, Lunsford KE, Bruce C, Ghobrial RM: Conquering combined thoracic organ and liver transplantation: indications and outcomes for heart-liver and lung-liver transplantation. Curr Opin Organ Transplant 2018;23:180–6. [PubMed: 29389820]
163. Weill D: Lung transplantation: indications and contraindications. J Thorac Dis 2018;10:4574–87. [PubMed: 30174910]
164. Freischlag K, Ezekian B, Schroder PM, et al. : A Propensity-matched Survival Analysis: Do Simultaneous Liver-lung Transplant Recipients Need a Liver? Transplantation 2019;103:1675–82. [PubMed: 30444805]
165. Reich HJ, Chan JL, Czer LS, et al. : Combined Lung-Kidney Transplantation: An Analysis of the UNOS/OPTN Database. Am Surg 2015;81:1047–52. [PubMed: 26463306]
166. Celli BR, Cote CG, Marin JM, et al. : The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350:1005–12. [PubMed: 14999112]
167. Bellou V, Belbasis L, Konstantinidis AK, Tzoulaki I, Evangelou E: Prognostic models for outcome prediction in patients with chronic obstructive pulmonary disease: systematic review and critical appraisal. BMJ 2019;367:l5358. [PubMed: 31585960]
168. Disease GIfCOL: Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease: 2020 Report. 2020.
169. Pirard L, Marchand E: Reassessing the BODE score as a criterion for listing COPD patients for lung transplantation. Int J Chron Obstruct Pulmon Dis 2018;13:3963–70. [PubMed: 30573956]
170. Reed RM, Cabral HJ, Dransfield MT, et al. : Survival of Lung Transplant Candidates With COPD: BODE Score Reconsidered. Chest 2018;153:697–701. [PubMed: 29054348]

171. Thabut G, Mornex JF, Pison C, et al. : Performance of the BODE index in patients with alpha1-antitrypsin deficiency-related COPD. Eur Respir J 2014;44:78–86. [PubMed: 24525449]

172. International Society for Heart and Lung Transplantation Registry. Adult Lung Transplantation Statistics. 2019.

173. Thabut G, Ravaud P, Christie JD, et al. : Determinants of the survival benefit of lung transplantation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2008;177:1156–63. [PubMed: 18310481]

174. Oswald-Mammosser M, Weitzenblum E, Quoix E, et al. : Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. Chest 1995;107:1193–8. [PubMed: 7750305]

175. LaFon DC, Bhatt SP, Labaki WW, et al. : Pulmonary artery enlargement and mortality risk in moderate to severe COPD: results from COPDGene. Eur Respir J 2020;55.

176. Yang H, Xiang P, Zhang E, et al. : Is hypercapnia associated with poor prognosis in chronic obstructive pulmonary disease? A long-term follow-up cohort study. BMJ Open 2015;5:e008909.

177. Martinez FJ, Han MK, Andrei AC, et al. : Longitudinal change in the BODE index predicts mortality in severe emphysema. Am J Respir Crit Care Med 2008;178:491–9. [PubMed: 18535255]

178. de-Torres JP, Ezponda A, Alcaide AB, et al. : Pulmonary arterial enlargement predicts long-term survival in COPD patients. PLoS One 2018;13:e0195640.

179. Balasubramanian A, MacIntyre NR, Henderson RJ, et al. : Diffusing capacity of carbon monoxide in assessment of COPD. Chest 2019;156:1111–9. [PubMed: 31352035]

180. Martinez FJ, Foster G, Curtis JL, et al. : Predictors of mortality in patients with emphysema and severe airflow obstruction. Am J Respir Crit Care Med 2006;173:1326–34. [PubMed: 16543549]

181. Criner GJ, Delage A, Voelker K, et al. : Improving Lung Function in Severe Heterogenous Emphysema with the Spiration Valve System (EMPROVE). A Multicenter, Open-Label Randomized Controlled Clinical Trial. Am J Respir Crit Care Med 2019;200:1354–62. [PubMed: 31365298]

182. Criner GJ, Sue R, Wright S, et al. : A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE). Am J Respir Crit Care Med 2018;198:1151–64. [PubMed: 29787288]

183. Fishman A, Martinez F, Naunheim K, et al. : A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348:2059–73. [PubMed: 12759479]

184. Bavaria JE, Pochettino A, Kotloff RM, et al. : Effect of volume reduction on lung transplant timing and selection for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg 1998;115:9–17; discussion −8. [PubMed: 9451040]

185. Burns KE, Keenan RJ, Grgurich WF, Manzetti JD, Zenati MA: Outcomes of lung volume reduction surgery followed by lung transplantation: a matched cohort study. Ann Thorac Surg 2002;73:1587–93. [PubMed: 12022555]

186. Meyers BF, Yusen RD, Guthrie TJ, et al. : Outcome of bilateral lung volume reduction in patients with emphysema potentially eligible for lung transplantation. J Thorac Cardiovasc Surg 2001;122:10–7. [PubMed: 11436031]

187. Senbaklavaci O, Wisser W, Ozpeker C, et al. : Successful lung volume reduction surgery brings patients into better condition for later lung transplantation. Eur J Cardiothorac Surg 2002;22:363–7. [PubMed: 12204724]

188. Backhus L, Sargent J, Cheng A, Zeliadt S, Wood D, Mulligan M: Outcomes in lung transplantation after previous lung volume reduction surgery in a contemporary cohort. J Thorac Cardiovasc Surg 2014;147:1678–83 e1. [PubMed: 24589202]

189. Shigemura N, Gilbert S, Bhama JK, et al. : Lung transplantation after lung volume reduction surgery. Transplantation 2013;96:421–5. [PubMed: 23736352]

190. Inci I, Iskender I, Ehrsam J, et al. : Previous lung volume reduction surgery does not negatively affect survival after lung transplantation. Eur J Cardiothorac Surg 2018;53:596–602. [PubMed: 28957998]

191. King TE, Bradford WZ, Castro-Bernardini S, et al. : A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. New England journal of medicine 2014;370:2083–92.
192. Richeldi L, du Bois RM, Raghu G, et al. : Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New England journal of medicine 2014;370:2071–82.
193. Raghu G, Wells AU, Nicholson AG, et al. : Effect of nintedanib in subgroups of idiopathic pulmonary fibrosis by diagnostic criteria. Am J Respir Crit Care Med 2017;195:78–85. [PubMed: 27331880]
194. Lederer DJ, Martinez FJ: Idiopathic pulmonary fibrosis. N Engl J Med 2018;378:1811–23. [PubMed: 29742380]
195. Wijsenbeek M, Kreuter M, Olson A, et al. : Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. Curr Med Res Opin 2019;35:2015–24. [PubMed: 31328965]
196. Cottin V, Hirani NA, Hotchkin DL, et al. : Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2018;27.
197. Wijsenbeek M, Cottin V: Spectrum of fibrotic lung diseases. N Engl J Med 2020;383:958–68. [PubMed: 32877584]
198. Flaherty KR, Wells AU, Cottin V, et al. : Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019;381:1718–27. [PubMed: 31566307]
199. Maher TM, Corte TJ, Fischer A, et al. : Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir Med 2020;8:147–57. [PubMed: 31578169]
200. Nasser M, Larrieu S, Si-Mohamed S, et al. : Progressive fibrosing interstitial lung disease: a clinical cohort (the PROGRESS study). Eur Respir J 2021;57.
201. Behr J, Neuser P, Prasse A, et al. : Exploring efficacy and safety of oral Pirfenidone for progressive, non-IPF lung fibrosis (RELIEF) - a randomized, double-blind, placebo-controlled, parallel group, multi-center, phase II trial. BMC Pulm Med 2017;17.
202. Distler O, Highland KB, Gahlemann M, et al. : Nintedanib reduces lung function decline in patients with systemic sclerosis-associated interstitial lung disease: results of the SENSCIS trial. American journal of respiratory and critical care medicine 2019;199.
203. Wells AU, Flaherty KR, Brown KK, et al. : Nintedanib in patients with progressive fibrosing interstitial lung diseases—subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med 2020.
204. Raghu G, Ley B, Brown KK, et al. : Risk factors for disease progression in idiopathic pulmonary fibrosis. Thorax 2020;75:78–80. [PubMed: 31611341]
205. Montgomery E, Macdonald PS, Newton PJ, et al. : Frailty as a Predictor of Mortality in Patients With Interstitial Lung Disease Referred for Lung Transplantation. Transplantation 2020;104:864–72. [PubMed: 31397799]
206. Guler SA, Kwan JM, Leung JM, Khalil N, Wilcox PG, Ryerson CJ: Functional ageing in fibrotic interstitial lung disease: the impact of frailty on adverse health outcomes. Eur Respir J 2020;55.
207. Snyder L, Neely ML, Hellkamp AS, et al. : Predictors of death or lung transplant after a diagnosis of idiopathic pulmonary fibrosis: Insights from the IPF-PRO Registry. Respir Res 2019;20.
208. Ratwani AP, Ahmad KI, Barnett SD, Nathan SD, Brown AW: Connective tissue disease-associated interstitial lung disease and outcomes after hospitalization: A cohort study. Respir Med 2019;154:1–5. [PubMed: 31176795]
209. Khadawardi H, Mura M: A simple dyspnoea scale as part of the assessment to predict outcome across chronic interstitial lung disease. Respirology 2017;22:501–7. [PubMed: 27862639]
210. Yoon HY, Kim TH, Seo JB, et al. : Effects of emphysema on physiological and prognostic characteristics of lung function in idiopathic pulmonary fibrosis. Respirology 2019;24:55–62. [PubMed: 30136753]
211. Cottin V, Hansell DM, Sverzellati N, et al. : Differences in FVC decline by extent of emphysema in patients with combined pulmonary fibrosis and emphysema (CPFE) syndrome. European respiratory journal. (var.pagings) 2015;46.

212. Amano M, Izumi C, Baba M, et al. : Progression of right ventricular dysfunction and predictors of mortality in patients with idiopathic interstitial pneumonias. J Cardiol 2020;75:242–9. [PubMed: 31547948]
213. Kirkil G, Lower EE, Baughman RP: Predictors of Mortality in Pulmonary Sarcoidosis. Chest 2018;153:105–13. [PubMed: 28728933]
214. Hayes D, Black SM, Tobias JD, Kirkby S, Mansour HM, Whitson BA: Influence of pulmonary hypertension on patients with idiopathic pulmonary fibrosis awaiting lung transplantation. Ann Thorac Surg 2016;101:246–52. [PubMed: 26319484]
215. Nishimoto K, Fujisawa T, Yoshimura K, et al. : The prognostic significance of pneumothorax in patients with idiopathic pulmonary fibrosis. Respirology 2018;23:519–25. [PubMed: 29130562]
216. Singh N, Varghese J, England BR, et al. : Impact of the pattern of interstitial lung disease on mortality in rheumatoid arthritis: A systematic literature review and meta-analysis. Semin Arthritis Rheum 2019;49:358–65. [PubMed: 31153706]
217. Walsh SLF: Imaging biomarkers and staging in IPF. Curr Opin Pulm Med 2018;24:445–52. [PubMed: 30015679]
218. Jacob J, Bartholmai BJ, Rajagopalan S, et al. : Predicting outcomes in idiopathic pulmonary fibrosis using automated computed tomographic analysis. Am J Respir Crit Care Med 2018;198:767–76. [PubMed: 29684284]
219. Jacob J, Bartholmai BJ, Rajagopalan S, et al. : Unclassifiable-interstitial lung disease: Outcome prediction using CT and functional indices. Respir Med 2017;130:43–51. [PubMed: 29206632]
220. Scott MKD, Quinn K, Li Q, et al. : Increased monocyte count as a cellular biomarker for poor outcomes in fibrotic diseases: a retrospective, multicentre cohort study. Lancet Respir Med 2019;7:497–508. [PubMed: 30935881]
221. Maher T, Jenkins G, Cottin V, et al. : Blood biomarkers predicting disease progression in patients with IPF: data from the INMARK trial. European respiratory journal 2019;54.
222. Maher TM, Oballa E, Simpson JK, et al. : An epithelial biomarker signature for idiopathic pulmonary fibrosis: an analysis from the multicentre PROFILE cohort study. Lancet Respir Med 2017;5:946–55. [PubMed: 29150411]
223. Raghu G, Richeldi L, Jagerschmidt A, et al. : Idiopathic Pulmonary Fibrosis: Prospective, Case-Controlled Study of Natural History and Circulating Biomarkers. Chest 2018;154:1359–70. [PubMed: 30526970]
224. Newton CA, Oldham JM, Ley B, et al. : Telomere length and genetic variant associations with interstitial lung disease progression and survival. Eur Respir J 2019;53.
225. Inoue Y, Kaner RJ, Guiot J, et al. : Diagnostic and Prognostic Biomarkers for Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype. Chest 2020.
226. Torrisi SE, Ley B, Kreuter M, et al. : The added value of comorbidities in predicting survival in idiopathic pulmonary fibrosis: A multicentre observational study. Eur Respir J 2019;53.
227. Moua T, Lee AS, Ryu JH: Comparing effectiveness of prognostic tests in idiopathic pulmonary fibrosis. Expert Rev Respir Med 2019;13:993–1004. [PubMed: 31405303]
228. Ryerson CJ, Vittinghoff E, Ley B, et al. : Predicting survival across chronic interstitial lung disease: The ILD-GAP model. Chest 2014;145:723–8. [PubMed: 24114524]
229. Morisset J, Vittinghoff E, Elicker BM, et al. : Mortality Risk Prediction in Scleroderma-Related Interstitial Lung Disease: The SADL Model. Chest 2017;152:999–1007. [PubMed: 28629914]
230. Morisset J, Vittinghoff E, Lee BY, et al. : The performance of the GAP model in patients with rheumatoid arthritis associated interstitial lung disease. Respir Med 2017;127:51–6. [PubMed: 28502419]
231. Sharp C, Adamali HI, Millar AB: A comparison of published multidimensional indices to predict outcome in idiopathic pulmonary fibrosis. ERJ Open Res 2017;3.
232. George PM, Spagnolo P, Kreuter M, et al. : Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. Lancet Respir Med 2020;8:925–34. [PubMed: 32890499]
233. Brown KK, Martinez FJ, Walsh SLF, et al. : The natural history of progressive fibrosing interstitial lung diseases. Eur Respir J 2020.

234. Newton CA, Batra K, Torrealba J, et al. : Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive. Eur Respir J 2016;48:1710–20. [PubMed: 27540018]

235. Sato S, Masui K, Nishina N, et al. : Initial predictors of poor survival in myositisassociated interstitial lung disease: A multicentre cohort of 497 patients. Rheumatology 2018;57:1212–21. [PubMed: 29596687]

236. Kishaba T, McGill R, Nei Y, et al. : Clinical characteristics of dermatomyosits/polymyositis associated interstitial lung disease according to the autoantibody. J Med Invest 2018;65:251–7. [PubMed: 30282869]

237. Moghadam-Kia S, Oddis CV, Sato S, Kuwana M, Aggarwal R: Anti-Melanoma Differentiation-Associated Gene 5 Is Associated with Rapidly Progressive Lung Disease and Poor Survival in US Patients with Amyopathic and Myopathic Dermatomyositis. Arthritis Care Res 2016;68:689–94.

238. Newton CA, Kozlitina J, Lines JR, Kaza V, Torres F, Garcia CK: Telomere length in patients with pulmonary fibrosis associated with chronic lung allograft dysfunction and post–lung transplantation survival. J Heart Lung Transplant 2017;36:845–53. [PubMed: 28262440]

239. Ribeiro Neto ML, Jellis CL, Joyce E, Callahan TD, Hachamovitch R, Culver DA: Update in cardiac sarcoidosis. Ann Am Thorac Soc 2019;16:1341–50. [PubMed: 31322914]

240. Delanote I, Wuyts WA, Yserbyt J, Verbeken EK, Verleden GM, Vos R: Safety and efficacy of bridging to lung transplantation with antifibrotic drugs in idiopathic pulmonary fibrosis: A case series. BMC Pulm Med 2016;16.

241. Leuschner G, Stocker F, Veit T, et al. : Outcome of lung transplantation in idiopathic pulmonary fibrosis with previous anti-fibrotic therapy. J Heart Lung Transplant 2017.

242. Mayer-Hamblett N, Rosenfeld M, Emerson J, Goss CH, Aitken ML: Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. Am J Respir Crit Care Med 2002;166:1550–5. [PubMed: 12406843]

243. Kerem E, Reisman J, Corey M, Canny GJ, Levison H: Prediction of mortality in patients with cystic fibrosis. N Engl J Med 1992;326:1187–91. [PubMed: 1285737]

244. Milla CE, Warwick WJ: Risk of death in cystic fibrosis patients with severely compromised lung function. Chest 1998;113:1230–4. [PubMed: 9596299]

245. Ramos KJ, Quon BS, Heltshe SL, et al. : Heterogeneity in Survival in Adult Patients With Cystic Fibrosis With FEV1 < 30% of Predicted in the United States. Chest 2017;151:1320–8. [PubMed: 28115168]

246. Hayes D Jr., Kirkby S, Whitson BA, et al. : Mortality Risk and Pulmonary Function in Adults With Cystic Fibrosis at Time of Wait Listing for Lung Transplantation. Ann Thorac Surg 2015;100:474–9. [PubMed: 26138770]

247. Lehr CJ, Skeans M, Dasenbrook E, et al. : Effect of Including Important Clinical Variables on Accuracy of the Lung Allocation Score for Cystic Fibrosis and Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2019;200:1013–21. [PubMed: 31199166]

248. Belkin RA, Henig NR, Singer LG, et al. : Risk factors for death of patients with cystic fibrosis awaiting lung transplantation. Am J Respir Crit Care Med 2006;173:659–66. [PubMed: 16387803]

249. Sole A, Perez I, Vazquez I, et al. : Patient-reported symptoms and functioning as indicators of mortality in advanced cystic fibrosis: A new tool for referral and selection for lung transplantation. J Heart Lung Transplant 2016;35:789–94. [PubMed: 27021279]

250. Hayes D Jr., Tobias JD, Mansour HM, et al. : Pulmonary hypertension in cystic fibrosis with advanced lung disease. Am J Respir Crit Care Med 2014;190:898–905. [PubMed: 25222938]

251. Hayes D Jr., Tumin D, Daniels CJ, et al. : Pulmonary Artery Pressure and Benefit of Lung Transplantation in Adult Cystic Fibrosis Patients. Ann Thorac Surg 2016;101:1104–9. [PubMed: 26687141]

252. Flume PA, Strange C, Ye X, Ebeling M, Hulsey T, Clark LL: Pneumothorax in cystic fibrosis. Chest 2005;128:720–8. [PubMed: 16100160]

253. de Boer K, Vandemheen KL, Tullis E, et al. : Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis. Thorax 2011;66:680–5. [PubMed: 21680566]

254. Nkam L, Lambert J, Latouche A, Bellis G, Burgel PR, Hocine MN: A 3-year prognostic score for adults with cystic fibrosis. J Cyst Fibros 2017;16:702–8. [PubMed: 28330773]
255. Flight WG, Barry PJ, Bright-Thomas RJ, Butterfield S, Ashleigh R, Jones AM: Outcomes Following Bronchial Artery Embolisation for Haemoptysis in Cystic Fibrosis. Cardiovasc Intervent Radiol 2017;40:1164–8. [PubMed: 28289842]
256. Flume PA, Yankaskas JR, Ebeling M, Hulsey T, Clark LL: Massive hemoptysis in cystic fibrosis. Chest 2005;128:729–38. [PubMed: 16100161]
257. Town JA, Monroe EJ, Aitken ML: Deaths Related to Bronchial Arterial Embolization in Patients With Cystic Fibrosis: Three Cases and an Institutional Review. Chest 2016;150:e93–e8. [PubMed: 27719829]
258. Kerem E, Viviani L, Zolin A, et al. : Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient registry. Eur Respir J 2014;43:125–33. [PubMed: 23598952]
259. Martin C, Chapron J, Hubert D, et al. : Prognostic value of six minute walk test in cystic fibrosis adults. Respir Med 2013;107:1881–7. [PubMed: 24157200]
260. Robinson W, Waltz DA: FEV(1) as a guide to lung transplant referral in young patients with cystic fibrosis. Pediatr Pulmonol 2000;30:198–202. [PubMed: 10973037]
261. Martin C, Hamard C, Kanaan R, et al. : Causes of death in French cystic fibrosis patients: The need for improvement in transplantation referral strategies! J Cyst Fibros 2016;15:204–12. [PubMed: 26391389]
262. Esther CR Jr., Esserman DA, Gilligan P, Kerr A, Noone PG: Chronic Mycobacterium abscessus infection and lung function decline in cystic fibrosis. J Cyst Fibros 2010;9:117–23. [PubMed: 20071249]
263. Morlacchi LC, Greer M, Tudorache I, et al. : The burden of sinus disease in cystic fibrosis lung transplant recipients. Transpl Infect Dis 2018;20:e12924.
264. Vital D, Hofer M, Benden C, Holzmann D, Boehler A: Impact of sinus surgery on pseudomonal airway colonization, bronchiolitis obliterans syndrome and survival in cystic fibrosis lung transplant recipients. Respiration 2013;86:25–31. [PubMed: 22922656]
265. Leung MK, Rachakonda L, Weill D, Hwang PH: Effects of sinus surgery on lung transplantation outcomes in cystic fibrosis. Am J Rhinol 2008;22:192–6. [PubMed: 18416979]
266. Holzmann D, Speich R, Kaufmann T, et al. : Effects of sinus surgery in patients with cystic fibrosis after lung transplantation: a 10-year experience. Transplantation 2004;77:134–6. [PubMed: 14724449]
267. Luparello P, Lazio MS, Voltolini L, Borchi B, Taccetti G, Maggiore G: Outcomes of endoscopic sinus surgery in adult lung transplant patients with cystic fibrosis. Eur Arch Otorhinolaryngol 2019;276:1341–7. [PubMed: 30689038]
268. Lederer DJ, Wilt JS, D'Ovidio F, et al. : Obesity and underweight are associated with an increased risk of death after lung transplantation. Am J Respir Crit Care Med 2009;180:887–95. [PubMed: 19608717]
269. Nash EF, Volling C, Gutierrez CA, et al. : Outcomes of patients with cystic fibrosis undergoing lung transplantation with and without cystic fibrosis-associated liver cirrhosis. Clin Transplant 2012;26:34–41. [PubMed: 21272072]
270. Freischlag KW, Messina J, Ezekian B, et al. : Single-Center Long-Term Analysis of Combined Liver-Lung Transplant Outcomes. Transplant Direct 2018;4:e349.
271. Hadjiliadis D, Khoruts A, Zauber AG, Hempstead SE, Maisonneuve P, Lowenfels AB: Cystic Fibrosis Colorectal Cancer Screening Consensus Recommendations. Gastroenterology 2018;154:736–45.e14. [PubMed: 29289528]
272. Martinez-Garcia MA, de Gracia J, Vendrell Relat M, et al. : Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. Eur Respir J 2014;43:1357–67. [PubMed: 24232697]
273. Chalmers JD, Goeminne P, Aliberti S, et al. : The bronchiectasis severity index. An international derivation and validation study. Am J Respir Crit Care Med 2014;189:576–85. [PubMed: 24328736]

274. Hayes D Jr., Kopp BT, Tobias JD, et al. : Survival in Patients with Advanced Non-cystic Fibrosis Bronchiectasis Versus Cystic Fibrosis on the Waitlist for Lung Transplantation. Lung 2015;193:933–8. [PubMed: 26429393]

275. Hoeper MM, Benza RL, Corris P, et al. : Intensive care, right ventricular support and lung transplantation in patients with pulmonary hypertension. Eur Respir J 2019;53.

276. Chen H, Shiboski SC, Golden JA, et al. : Impact of the lung allocation score on lung transplantation for pulmonary arterial hypertension. Am J Respir Crit Care Med 2009;180:468–74. [PubMed: 19520906]

277. Schaffer JM, Singh SK, Joyce DL, et al. : Transplantation for idiopathic pulmonary arterial hypertension: improvement in the lung allocation score era. Circulation 2013;127:2503–13. [PubMed: 23697910]

278. Gomberg-Maitland M, Glassner-Kolmin C, Watson S, et al. : Survival in pulmonary arterial hypertension patients awaiting lung transplantation. J Heart Lung Transplant 2013;32:1179–86. [PubMed: 24074527]

279. Benza RL, Miller DP, Frost A, Barst RJ, Krichman AM, McGoon MD: Analysis of the lung allocation score estimation of risk of death in patients with pulmonary arterial hypertension using data from the REVEAL Registry. Transplantation 2010;90:298–305. [PubMed: 20559158]

280. Wille KM, Edwards LB, Callahan LR, McKoy AR, Chan KM: Characteristics of lung allocation score exception requests submitted to the national Lung Review Board. J Heart Lung Transplant 2017;36:812–4. [PubMed: 28372950]

281. Savale L, Le Pavec J, Mercier O, et al. : Impact of High-Priority Allocation on Lung and Heart-Lung Transplantation for Pulmonary Hypertension. Ann Thorac Surg 2017;104:404–11. [PubMed: 28527964]

282. Galiè N, Channick RN, Frantz RP, et al. : Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J 2019;53.

283. Benza RL, Miller DP, Gomberg-Maitland M, et al. : Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164–72. [PubMed: 20585012]

284. Galiè N, Humbert M, Vachiery JL, et al. : 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119. [PubMed: 26320113]

285. Benza RL, Gomberg-Maitland M, Elliott CG, et al. : Predicting survival in patients with pulmonary arterial hypertension: The REVEAL Risk Score Calculator 2.0 and comparison with ESC/ERS-Based risk assessment strategies. Chest 2019;156:323–37. [PubMed: 30772387]

286. Chakinala MM, Coyne DW, Benza RL, et al. : Impact of declining renal function on outcomes in pulmonary arterial hypertension: A REVEAL registry analysis. J Heart Lung Transplant 2018;37:696–705. [PubMed: 29174533]

287. Frost AE, Badesch DB, Miller DP, Benza RL, Meltzer LA, McGoon MD: Evaluation of the predictive value of a clinical worsening definition using 2-year outcomes in patients with pulmonary arterial hypertension: a REVEAL Registry analysis. Chest 2013;144:1521–9. [PubMed: 23907471]

288. Hoeper MM, Kramer T, Pan Z, et al. : Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J 2017;50.

289. van de Veerdonk MC, Kind T, Marcus JT, et al. : Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol 2011;58:2511–9. [PubMed: 22133851]

290. Badagliacca R, Papa S, Poscia R, et al. : The added value of cardiopulmonary exercise testing in the follow-up of pulmonary arterial hypertension. J Heart Lung Transplant 2019;38:306–14. [PubMed: 30581051]

291. Montani D, O'Callaghan DS, Savale L, et al. : Pulmonary veno-occlusive disease: recent progress and current challenges. Respir Med 2010;104 Suppl 1:S23–32. [PubMed: 20456932]
292. Launay D, Humbert M, Berezne A, et al. : Clinical characteristics and survival in systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease. Chest 2011;140:1016–24. [PubMed: 21474572]
293. Young A, Vummidi D, Visovatti S, et al. : Prevalence, Treatment, and Outcomes of Coexistent Pulmonary Hypertension and Interstitial Lung Disease in Systemic Sclerosis. Arthritis Rheumatol 2019;71:1339–49. [PubMed: 30762947]
294. Nathan SD, Barbera JA, Gaine SP, et al. : Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J 2019;53.
295. Hayes D Jr., Black SM, Tobias JD, Mansour HM, Whitson BA: Prevalence of Pulmonary Hypertension and its Influence on Survival in Patients With Advanced Chronic Obstructive Pulmonary Disease Prior to Lung Transplantation. Copd 2016;13:50–6. [PubMed: 26366936]
296. Hayes D Jr., Higgins RS, Black SM, et al. : Effect of pulmonary hypertension on survival in patients with idiopathic pulmonary fibrosis after lung transplantation: an analysis of the United Network of Organ Sharing registry. J Heart Lung Transplant 2015;34:430–7. [PubMed: 25444371]
297. Hayes D Jr., Higgins RS, Kirkby S, et al. : Impact of pulmonary hypertension on survival in patients with cystic fibrosis undergoing lung transplantation: an analysis of the UNOS registry. J Cyst Fibros 2014;13:416–23. [PubMed: 24388063]
298. Hayes D Jr., Tumin D, Budev MM, Tobias JD, St John RC, Kukreja J: Adverse outcomes associated with pulmonary hypertension in chronic obstructive pulmonary disease after bilateral lung transplantation. Respir Med 2017;128:102–8. [PubMed: 28476472]
299. Hayes D Jr., Black SM, Tobias JD, Mansour HM, Whitson BA: Influence of pulmonary hypertension on survival in advanced lung disease. Lung 2015;193:213–21. [PubMed: 25787084]
300. Villavicencio MA, Axtell AL, Osho A, et al. : Single- Versus Double-Lung Transplantation in Pulmonary Fibrosis: Impact of Age and Pulmonary Hypertension. Ann Thorac Surg 2018;106:856–63. [PubMed: 29803692]
301. Simonneau G, Montani D, Celermajer DS, et al. : Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53.
302. Wong K, Tecson K, Cedars A: Outcomes of Multi-Organ Transplant in Adult Patients With Congenital Heart Disease. J Am Heart Assoc 2019;8:e014088.
303. Ando K, Okada Y, Akiba M, et al. : Lung Transplantation for lymphangioleiomyomatosis in Japan. PLoS One 2016;11:e0146749.
304. Khawar MU, Yazdani D, Zhu Z, Jandarov R, Dilling DF, Gupta N: Clinical outcomes and survival following lung transplantation in patients with lymphangioleiomyomatosis. J Heart Lung Transplant 2019;38:949–55. [PubMed: 31303421]
305. Baldi BG, Samano MN, Campos SV, et al. : Experience of lung transplantation in patients with lymphangioleiomyomatosis at a Brazilian reference centre. Lung 2017;195:699–705. [PubMed: 28823029]
306. Kurosaki T, Otani S, Miyoshi K, et al. : Favorable survival even with high disease-specific complication rates in lymphangioleiomyomatosis after lung transplantation-long-term follow-up of a Japanese center. Clin Respir J 2020;14:116–23. [PubMed: 31729820]
307. Kpodonu J, Massad MG, Chaer RA, et al. : The US experience with lung transplantation for pulmonary lymphangioleiomyomatosis. J Heart Lung Transplant 2005;24:1247–53. [PubMed: 16143241]
308. Salman J, Ius F, Sommer W, et al. : Long-Term Results of Bilateral Lung Transplantation in Patients With End-Stage Pulmonary Lymphangioleiomyomatosis. Prog Transplant 2019;29:115–21. [PubMed: 31084354]
309. Pechet TT, Meyers BF, Guthrie TJ, et al. : Lung transplantation for lymphangioleiomyomatosis. J Heart Lung Transplant 2004;23:301–8. [PubMed: 15019639]
310. Johnson SR, Cordier JF, Lazor R, et al. : European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. Eur Respir J 2010;35:14–26. [PubMed: 20044458]

311. Reynaud-Gaubert M, Mornex JF, Mal H, et al. : Lung transplantation for lymphangioleiomyomatosis: the French experience. Transplantation 2008;86:515–20. [PubMed: 18724219]

312. Machuca TN, Losso MJ, Camargo SM, et al. : Lung transplantation for lymphangioleiomyomatosis: single-center Brazilian experience with no chylothorax. Transplant Proc 2011;43:236–8. [PubMed: 21335196]

313. Ussavarungsi K, Hu X, Scott JP, et al. : Mayo clinic experience of lung transplantation in pulmonary lymphangioleiomyomatosis. Respir Med 2015;109:1354–9. [PubMed: 26321137]

314. Benden C, Rea F, Behr J, et al. : Lung transplantation for lymphangioleiomyomatosis: the European experience. J Heart Lung Transplant 2009;28:1–7. [PubMed: 19134523]

315. McCormack FX, Inoue Y, Moss J, et al. : Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med 2011;364:1595–606. [PubMed: 21410393]

316. El-Chemaly S, Goldberg HJ, Glanville AR: Should mammalian target of rapamycin inhibitors be stopped in women with lymphangioleiomyomatosis awaiting lung transplantation? Expert Rev Respir Med 2014;8:657–60. [PubMed: 25199529]

317. Zaki KS, Aryan Z, Mehta AC, Akindipe O, Budev M: Recurrence of lymphangioleiomyomatosis: Nine years after a bilateral lung transplantation. World J Transplant 2016;6:249–54. [PubMed: 27011924]

318. Nakagiri T, Shintani Y, Minami M, et al. : Lung Transplantation for Lymphangioleiomyomatosis in a Single Japanese Institute, With a Focus on Late-onset Complications. Transplant Proc 2015;47:1977–82. [PubMed: 26293084]

319. Oishi H, Watanabe T, Matsuda Y, et al. : Single lung transplantation for lymphangioleiomyomatosis: a single-center experience in Japan. Surg Today 2018;48:944–50. [PubMed: 29808303]

320. Ando K, Kurihara M, Kataoka H, et al. : Efficacy and safety of low-dose sirolimus for treatment of lymphangioleiomyomatosis. Respir Investig 2013;51:175–83.

321. Ahmad U, Wang Z, Bryant AS, et al. : Outcomes for lung transplantation for lung cancer in the United Network for Organ Sharing Registry. Ann Thorac Surg 2012;94:935–40; discussion 40–1. [PubMed: 22835555]

322. Zorn GL Jr., McGiffin DC, Young KR Jr., Alexander CB, Weill D, Kirklin JK: Pulmonary transplantation for advanced bronchioloalveolar carcinoma. J Thorac Cardiovasc Surg 2003;125:45–8. [PubMed: 12538984]

323. Paloyan EB, Swinnen LJ, Montoya A, Lonchyna V, Sullivan HJ, Garrity E: Lung transplantation for advanced bronchioloalveolar carcinoma confined to the lungs. Transplantation 2000;69:2446–8. [PubMed: 10868657]

324. de Perrot M, Chernenko S, Waddell TK, et al. : Role of lung transplantation in the treatment of bronchogenic carcinomas for patients with end-stage pulmonary disease. J Clin Oncol 2004;22:4351–6. [PubMed: 15514376]

325. Ahmad U, Hakim AH, Tang A, et al. : Patterns of recurrence and overall survival in incidental lung cancer in explanted lungs. Ann Thorac Surg 2019;107:891–6. [PubMed: 30391248]

326. Nakajima T, Cypel M, de Perrot M, et al. : Retrospective analysis of lung transplant recipients found to have unexpected lung cancer in explanted lungs. Seminars in thoracic and cardiovascular surgery: Elsevier; 2015. p. 9–14.

327. Glanville AR, Wilson BE: Lung transplantation for non-small cell lung cancer and multifocal bronchioalveolar cell carcinoma. Lancet Oncol 2018;19:e351–e8. [PubMed: 30084382]

328. Machuca TN, Keshavjee S: Transplantation for lung cancer. Curr Opin Organ Transplant 2012;17:479–84. [PubMed: 22907541]

329. Van Raemdonck D, Vos R, Yserbyt J, Decaluwe H, De Leyn P, Verleden GM: Lung cancer: a rare indication for, but frequent complication after lung transplantation. J Thorac Dis 2016;8:S915–s24. [PubMed: 27942415]

330. Garver RI Jr., Zorn GL, Wu X, McGiffin DC, Young KR Jr., Pinkard NB: Recurrence of bronchioloalveolar carcinoma in transplanted lungs. N Engl J Med 1999;340:1071–4. [PubMed: 10194236]

331. Gómez-Román JJ, Del Valle CE, Zarrabeitia MT, et al. : Recurrence of bronchioloalveolar carcinoma in donor lung after lung transplantation: microsatellite analysis demonstrates a recipient origin. Pathol Int 2005;55:580–4. [PubMed: 16143034]

332. Ranieri VM, Rubenfeld GD, Thompson BT, et al. : Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526–33. [PubMed: 22797452]

333. Chang Y, Lee SO, Shim TS, et al. : Lung Transplantation as a Therapeutic Option in Acute Respiratory Distress Syndrome. Transplantation 2018;102:829–37. [PubMed: 29189633]

334. Turner DA, Rehder KJ, Bonadonna D, et al. : Ambulatory ECMO as a bridge to lung transplant in a previously well pediatric patient with ARDS. Pediatrics 2014;134:e583–5. [PubMed: 25049344]

335. Kon ZN, Wehman PB, Gibber M, et al. : Venovenous extracorporeal membrane oxygenation as a bridge to lung transplantation: successful transplantation after 155 days of support. Ann Thorac Surg 2015;99:704–7. [PubMed: 25639416]

336. Jackson A, Cropper J, Pye R, Junius F, Malouf M, Glanville A: Use of extracorporeal membrane oxygenation as a bridge to primary lung transplant: 3 consecutive, successful cases and a review of the literature. J Heart Lung Transplant 2008;27:348–52. [PubMed: 18342760]

337. Barrio J, Sánchez C, Vicente R, et al. : Successful sequential double-lung transplantation for adult respiratory distress syndrome after long-term mechanical ventilation. Eur J Anaesthesiol 2004;21:326–7. [PubMed: 15109200]

338. Pipeling MR, Fan E: Therapies for refractory hypoxemia in acute respiratory distress syndrome. JAMA 2010;304:2521–7. [PubMed: 21139113]

339. Salam S, Kotloff R, Garcha P, et al. : Lung Transplantation After 125 Days on ECMO for Severe Refractory Hypoxemia With No Prior Lung Disease. ASAIO J 2017;63:e66–e8. [PubMed: 28857906]

340. Iacono A, Groves S, Garcia J, Griffith B: Lung transplantation following 107 days of extracorporeal membrane oxygenation. Eur J Cardiothorac Surg 2010;37:969–71. [PubMed: 19896387]

341. Kon ZN, Dahi S, Evans CF, et al. : Long-Term Venovenous Extracorporeal Membrane Oxygenation Support for Acute Respiratory Distress Syndrome. Ann Thorac Surg 2015;100:2059–63. [PubMed: 26296269]

342. Rosenberg AA, Haft JW, Bartlett R, et al. : Prolonged duration ECMO for ARDS: futility, native lung recovery, or transplantation? ASAIO J 2013;59:642–50. [PubMed: 24172270]

343. Cypel M, Keshavjee S: When to consider lung transplantation for COVID-19. Lancet Respir Med 2020;8:944–6. [PubMed: 32857989]

344. The Declaration of Istanbul on organ trafficking and transplant tourism (2018 Edition). Transplantation 2019;103:218–9. [PubMed: 30681644]

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)

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/1.73m2 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 (FOOTNOTE: 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 over 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 greater than or equal to 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 on insulin 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

Table 3:

Updated consensus statements:

Each statement listed as a 2020 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.

2014 Consensus statement	2020 Consensus statement	Consensus N (%)
General Considerations		
Lung transplantation should be considered for adults with chronic, end-stage lung disease who meet all the following general criteria: 1. High (>50%) risk of death from lung disease within 2 years if lung transplantation is not performed. 2. High (>80%) likelihood of surviving at least 90 days after lung transplantation. 3. High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function.	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		
Timing of referral	**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 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.
	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:
	  • 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
		24 (100%)

2014 Consensus statement	2020 Consensus statement	Consensus N (%)
	• 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	**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		
	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%)
	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 (95%)
Multi-Organ Transplantation		
	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		

2014 Consensus statement	2020 Consensus statement	Consensus N (%)
Chronic Obstructive Pulmonary Disease (COPD)		
Timing of Referral	**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. · FEV1 <25% predicted.	• 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 (95%)
Timing of Listing	**Timing of Listing**	
· BODE index >7. · FEV1 <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.	• 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%)
Interstitial Lung Disease		
Timing of Referral	**Timing of Referral**	
• Histopathologic or radiographic evidence of usual interstitial pneumonitis (UIP) or fibrosing non-specific interstitial pneumonitis (NSIP), regardless of lung function. • Abnormal lung function: forced vital capacity (FVC) <80% predicted or diffusion capacity of the lung for carbon monoxide (DLCO) <40% predicted. • Any dyspnea or functional limitation attributable to lung disease. • Any oxygen requirement, even if only during exertion. • For inflammatory interstitial lung disease (ILD), failure to improve dyspnea, oxygen requirement, and/or lung function after a clinically indicated trial of medical therapy.	• Referral should be made at time of diagnosis, even if a patient is being initiated on therapy, for histopathological usual interstitial pneumonia (UIP) or radiographic evidence of a probable or definite UIP pattern. • Any form of pulmonary fibrosis with forced vital capacity (FVC) of < 80% predicted or diffusion capacity of carbon monoxide (DLCO) < 40% predicted. • 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 • Supplemental oxygen requirement either at rest or on exertion. • For inflammatory ILDs, progression of disease (either on imaging or pulmonary function) despite treatment. • For patients with connective tissue disease or familial pulmonary fibrosis, early referral is recommended as extrapulmonary manifestations may require special consideration. FOOTNOTE: For patients with concomitant emphysema, FVC may be a less reliable parameter.	22 (92%) 24 (100%) 24 (100%) 24 (100%) 24 (100%) 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 MWT or > 50 m decline in 6 MWT 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. FOOTNOTE: For patients with concomitant emphysema, FVC may be a less reliable parameter.	24 (100%)
Cystic Fibrosis		

2014 Consensus statement	2020 Consensus statement	Consensus N (%)
Timing of Referral	**Timing of Referral**	

· FEV1 that has fallen to 30% or a patient with advanced disease with a rapidly falling FEV1 despite optimal therapy (particularly in a female patient), infected with non-tuberculous mycobacterial (NTM) disease or B cepacia complex (see previous comment on B cenocepacia and subsequently) and/or with diabetes.
· A 6-minute walk distance <400 m
· Development of pulmonary hypertension in the absence of a hypoxic exacerbation (as defined by a systolic pulmonary arterial pressure (PAP) >35 mm Hg on echocardiography or mean PAP >25 mm Hg measured by right heart catheterization).
Clinical decline characterized by increasing frequency of exacerbations associated with any of the following:
• An episode of acute respiratory failure requiring non-invasive ventilation.
• Increasing antibiotic resistance and poor clinical recovery from exacerbations.
• Worsening nutritional status despite supplementation.
• Pneumothorax.
• Life-threatening hemoptysis despite bronchial embolization.
	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:
	• FEV1 < 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%)

	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%)
Timing of Listing	**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.	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 (PA 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%)
	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%)
All patients with CF who are referred for transplantation should be evaluated for NTM pulmonary disease. Patients with NTM disease who are being evaluated for transplantation should have the organism confirmed according to microbiology guidelines and begin treatment before transplant listing. Treatment should be by, or in collaboration with, a physician experienced in the treatment	All transplant candidates with CF should be evaluated for *Burkholderia cepacia* complex, nontuberculous mycobacteria, and fungal pathogens.	24 (100%)

2014 Consensus statement	2020 Consensus statement	Consensus N (%)
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. 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.		
Non-CF Bronchiectasis		
	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		
Timing of Referral	**Timing of Referral**	
· NYHA Functional Class III or IV symptoms during escalating therapy. · Rapidly progressive disease (assuming weight and rehabilitation concerns not present). · Use of parenteral targeted pulmonary arterial hyper-tension (PAH) therapy regardless of symptoms or NYHA Functional Class · Known or suspected pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis.	• 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 • 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	24 (100%)
Timing of Listing	**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 pep-tide, or recurrent ascites).	• 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)		
	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. FEV1 < 30% predicted) • Exertional dyspnea (NYHA class III or IV) • Hypoxemia at rest • Pulmonary hypertension • Refractory pneumothorax	24 (100%)

2014 Consensus statement	2020 Consensus statement	Consensus N (%)
	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%)
Adenocarcinoma In Situ and Minimally Invasive Adenocarcinoma		
Timing of Referral and Listing	**Timing of Referral and Listing**	
· 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 are contraindicated; and (4) lung transplant is expected to be curative.	22 (92%)
Acute Respiratory Distress Syndrome		
	Timing of Referral	
	Persistent requirement for mechanical ventilatory support and /or ECLS without expectation of clinical recovery and with evidence of irreversible lung destruction.	24 (100%)