Heart-Lung Transplant*

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DESCRIPTION

Solid organ transplantation offers a treatment option for patients with different types of end-stage organ failure that can be lifesaving or provide significant improvements to a patient's quality of life. Many advances have been made in the last several decades to reduce perioperative complications. Available data supports improvement in long-term survival as well as improved quality of life particularly for liver, kidney, pancreas, heart, and lung transplants. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by Organ Procurement and Transplantation Network and United Network of Organ Sharing.

Most heart/lung transplant recipients have Eisenmenger syndrome (37%), followed by idiopathic pulmonary artery hypertension (28%) and cystic fibrosis (14%). Eisenmenger syndrome is a form of congenital heart disease in which systemic-to-pulmonary shunting leads to pulmonary vascular resistance. It is possible that pulmonary hypertension could lead to a reversal of the intracardiac shunting and inadequate peripheral oxygenation or cyanosis.

Heart/Lung Transplant
Combined heart/lung transplantation is intended to prolong survival and improve function in patients with end-stage cardiac and pulmonary diseases. Due to corrective surgical techniques and improved medical management of pulmonary hypertension, the total number of patients with Eisenmenger syndrome has seen a decline in recent years. Additionally, heart/lung transplants have not increased appreciably, but for other indications, it has become more common to transplant a single or double lung and maximize medical therapy for heart failure, rather than perform a combined transplant. For those indications, patient survival rates following heart/lung transplantations are similar to lung transplant rates. Bronchiolitis obliterans syndrome is a major complication. One-, 5-, and 10-year patient survival rates for heart/lung transplants performed between 1982 and 2014 were estimated at 63%, 45%, and 32%, respectively.

From January – September of 2022, 15,646 transplants were performed in the United States procured from 10,874 deceased donors and 4,772 living donors. As of October 2022, 37 patients were on the waiting list for heart/lung transplants.

Prioritization of Candidates
Patients who are eligible for heart/lung transplantation can be listed under both the heart and lung allocation systems in the U.S. In 2005, United Network for Organ Sharing (UNOS) changed the method by which lungs were allocated, from 1 based on length of time on the waiting list to a system that incorporates the severity of the patient's underlying disease, as well as the likelihood of survival, However, it has been noted that the individual systems underestimate the severity of illness in patients with both end-stage heart and lung failure, and modification of the lung allocation score can be appealed for patients with pulmonary hypertension who meet the following criteria:

- Deterioration of optimal therapy, and
- Right arterial pressure greater than 15 mm Hg or
- Cardiac index less than 1.8 L/min/m2.

Specific criteria for prioritizing donor thoracic organs for transplant are provided by the Organ Procurement and Transplantation Network (OPTN) and implemented through a contract with UNOS.

Yusen et al. (2016) analyzed data on heart/lung transplantations performed among adults between 1982 and 2015 using the registry of the International Society for Heart and Lung Transplantation (ISHLT).4, Among the 3397 heart/lung transplant recipients for whom the diagnosis was reported, 35% had congenital heart disease (CHD), 27% had pulmonary arterial hypertension, and 14% had cystic fibrosis as the primary indication. There has been a shift in indications for heart/lung transplantation over time. From 2004 to 2015, CHD (35%), pulmonary arterial hypertension (27%), and cardiomyopathy (11%) were the 3 most common indications for heart/lung transplantation. Of the 883 heart/lung transplant recipients between 2004 and 2015, 36% were 18 to 34 years old, 40% were 35 to 49 years old, and 24% were 50 years or older.

Pediatric Considerations
In an analysis of data from the OPTN, Spahr and West (2014) provided indications for pediatric heart/lung transplantation. The number of pediatric heart/lung transplants has decreased in recent years (56 cases from 1993 to 1997; 32 cases from 2008 to 2013). The 3 most common indications for pediatric heart/lung transplant were primary pulmonary hypertension (n=55), CHD (n=37), and Eisenmenger syndrome (n=30). However, while 30 children received a heart/lung transplant for Eisenmenger syndrome through 2002, no transplants for this syndrome have been performed since then. Pediatric heart/lung transplants have also been performed for other indications, including alpha 1-antitrypsin deficiency, pulmonary vascular disease, cystic fibrosis, and dilated cardiomyopathy.

Using ISHLT Registry data, Benden et al. (2012) reported on pediatric heart/lung transplant data collected through June 2011. Overall survival rates after heart/lung transplants are comparable in children (median half-life, 4.7 years) and adults (median half-life, 5.3 years). For pediatric heart/lung transplants performed between 1990 and 2010, the 5-year survival rate was 49%. The 2 leading causes of death in the first year after transplantation were a non-cytomegalovirus infection and graft failure. Beyond 3 years posttransplant, the major cause of death was bronchiolitis obliterans syndrome. An updated report by Benden et al. (2014) on pediatric lung and heart/lung transplant from the same registry did not include updated data on pediatric heart/lung transplants due to the small number of patients available.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with end-stage cardiac and pulmonary disease.

Interventions
The therapy being considered is a combined heart-lung transplant.

Comparators
The following practices are currently being used to make decisions about end-stage cardiac and pulmonary disease: medical management, double-lung transplant, and single-lung transplant.

Outcomes
The general outcomes of interest are overall survival, graft failure, improved function, and adverse events (e.g., infections). Follow-up after surgery focuses on monitoring for graft failure. Long-term follow-up can continue out to 3 to 5 years and beyond.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought

Review of Evidence

Initial Adult Transplant
(2020) Sertic et al. compared outcomes of bilateral lung transplantation with cardiac defect repair to combined heart-lung transplantation in adult patients with Eisenmenger syndrome using the UNOS database of heart-lung transplantations performed from 1987 to 2018. Among 442 patients who underwent thoracic transplantation, 316 patients underwent heart-lung transplantation, and 126 patients underwent double-lung transplantation with concomitant cardiac defect repair. Overall survival was similar between patients who underwent double-lung transplantation and those who underwent heart-lung transplantation at 1-year (63.1% vs 68.0%, respectively), 5 years (38.5% vs 47.3%), and 10 years (30.2% vs 30.5%) posttransplant (p=.6). Overall survival did not differ among patients who received transplantation between 1987 to 1999 and those who received transplantation between 2000 to 2018 (p=.7).

(2016) Yusen et al. reported on the survival of adult heart-lung transplant recipients using the ISHLT database. Among the 3775 primary heart-lung transplants performed during 1982 and 2014, the 3-month, 1-year, 3-year, 5-year, and 10-year survival rates were 71%, 63%, 52%, 45%, and 32%, respectively. The overall median survival during this period (1982 to 2014) was 3.4 years. Those who survived to 1 year had a conditional median survival of 10.3 years. Survival improved over time, with a median survival of 2.1 years for patients (n=1596) who received the transplant between 1982 and 1993, 3.9 years for patients (n=1392) between 1994 and 2003, and 5.8 years for patients between 2004 and 2014 (n=843) (p<.05 for all pairwise comparisons). Heart-lung transplant recipients in the 2004 to 2014 group had a median conditional survival beyond 10 years. Compared with lung-only transplantation (median conditional survival, 8.0 years), heart-lung transplant recipients had a better long-term survival (median conditional survival, 10.3 years).

(2015) Hill et al. compared survival following heart-lung transplantation with double-lung transplantation for idiopathic pulmonary arterial hypertension among adult transplant recipients in the Scientific Registry of Transplant Recipients database during 1987 and 2012. Among the 928 idiopathic pulmonary arterial hypertension patients, 667 underwent double-lung transplantation, and 261 underwent heart-lung transplantation. Overall, the adjusted survival was similar between double-lung transplantation and heart-lung transplant recipients. However, for recipients hospitalized in the intensive care unit, double-lung transplantation was associated with worse outcomes than heart-lung transplantation recipients (hazard ratio [HR],1.83; 95% confidence interval [CI], 1.02 to 3.28).

(2014) Jayarajan et al. compared the mortality rates (at 1 month and 5 years posttransplant) of heart-lung transplant recipients who required pretransplant ventilation (n=22) or extracorporeal membrane oxygenation (ECMO; n=15) with controls. Median survival times were 10 days, 181 days, and 1547 days among patients with pretransplant ECMO, patients with a mechanical ventilator, and the control group, respectively. Patients with pretransplant ECMO had poorer survival than the control group at 30 days (20.0% vs 83.5%) and 5 years (20.0% vs 47.4%; p<.001). Similarly, patients requiring ventilation prior to transplantation had worse survival at 1 month (77.3% vs 83.5%) and 5 years (26.5% vs 47.4%; p<.001) compared with the control group. The use of ECMO (HR, 3.82; 95% CI, 1.60 to 9.12; p=.003) or mechanical ventilation (HR, 2.01; 95% CI, 1.07 to 3.78; p=.030) as a bridge to transplantation was independently associated with mortality on multivariate analysis. The findings of the study raise concern whether combined heart-lung transplant should be carried out in patients requiring ECMO; further, the findings suggest a need for additional research to improve survival in this high-risk group of patients.

Initial Transplant: Pediatric Considerations

(2020) Riggs et al. assessed outcomes for pediatric heart-lung transplantation among children with congenital heart disease (CHD) with Eisenmenger syndrome, CHD without Eisenmenger syndrome, primary pulmonary hypertension, and "other" categories using the UNOS database of heart-lung transplantations performed from 1987 to 2018.15, Among 209 heart-lung transplantations performed during the specified time frame, 37 (17.7%) had CHD with Eisenmenger syndrome, 40 (19.1%) had CHD without Eisenmenger syndrome, 70 (33.5%) had primary pulmonary hypertension, 6 (2.9%) were retransplants, and 56 (26.8%) had another diagnosis. One-year, 5-year, and 10-year survival rates post-transplant, respectively, were 75%, 44%, and 32% for pediatric patients with CHD with Eisenmenger syndrome, 56%, 21%, and 16% for patients with CHD without Eisenmenger syndrome, 77%, 41%, and 33% for patients with primary pulmonary hypertension, 40%, 0%, and 0% for retransplanted patients, and 70%, 44%, and 20% for patients with other diagnoses. Compared to the reference group of pediatric patients with primary pulmonary hypertension, patients with CHD without Eisenmenger syndrome (p=.03) and patients who were retransplanted (p=.008) had significantly lower survival rates. Other survival comparisons were not significant. Survival rates were not different when comparing patients who received transplants between 1987 to 1999 and 2000 to 2018. Infants (HR, 2.2; 95% CI, 1.04 to 4.55; p=.04), 1- to 11-year-old patients (HR, 1.78; 95% CI, 1.12 to 2.8; p=.015), and patients on ECMO (HR, 4.1; 95% CI, 1.3 to 12.8; p=.016) had the highest risk of mortality post-transplant.

(2016) Goldfarb et al. reported on the survival of pediatric lung and heart-lung transplant recipients using the ISHLT database. Among the 698 pediatric heart-lung transplant recipients, median survival was 3.0 years, and conditional median survival was 7.8 years. There was no statistically significant difference in survival by indication, recipient age group, or time period of transplant for pediatric heart-lung transplant recipients.

Section Summary: Initial Heart-Lung Transplant
Data from transplantation registries have found longer patient survival rates after initial heart/lung transplant among adult and pediatric patients over time. The net benefit of heart transplantation compared with lung-only transplantation is also evident, especially among patients with idiopathic pulmonary arterial hypertension.

Heart/Lung Retransplantation

Clinical Context and Therapy Purpose
The purpose of combined heart/lung retransplants in patients who have had a combined heart/lung transplant complicated by graft failure or severe dysfunction of the heart/lung is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does a combined heart/lung retransplant improve the net health outcome in patients whose combined heart/lung transplant has been complicated by graft failure or severe dysfunction of the heart/lung?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with a combined heart/lung transplant complicated by graft failure or severe dysfunction of the heart/lung.

Interventions
The therapy being considered is a combined heart/lung retransplant.

Comparators
The following practices are currently being used to make decisions about a combined heart/lung transplant complicated by graft failure or severe dysfunction of the heart/lung: medical management, double-lung transplant, and single-lung transplant.

Outcomes
The general outcomes of interest are overall survival, graft failure, improved function, and adverse events (e.g., infections). Follow-up after surgery focuses on monitoring for graft failure. Long-term follow-up can continue out to 3 to 5 years and beyond.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Retransplantation
(2014) While uncommon, repeat heart-lung transplant procedures have been performed. Yusen et al. reported-on outcomes for adult heart-lung transplants, with a focus on retransplantation, using data from the ISHLT Registry. From 1982 to 2012, 90 adults had a first heart-lung retransplant after a previous heart-lung transplant. These 90 patients had a median survival of 0.3 years, with unadjusted survival rates of 52%, 43%, 36%, and 27% at 3 months, 1 year, 3 years, and 5 years, respectively. Those who survived to 1 year had a conditional median survival of 7.9 years.

(2008) A study by Shuhaiber et al. reviewed data from the UNOS registry. They identified 799 primary heart-lung transplants and 19 repeat heart-lung transplants. Using Kaplan-Meier survival analysis, the observed median survival times were 2.08 years after primary transplant and 0.34 years after repeat transplants. In addition, reviewers analyzed survival data in matched pairs of primary and repeat transplant patients who were matched on a number of potentially confounding demographic and clinical characteristics. Matches were not available for 4 repeat transplant patients. For the 15 repeat transplant patients with primary transplant matches, survival time did not differ significantly between groups. Being on a ventilator was statistically significantly associated with decreased survival time. The main limitation of this analysis was the low number of repeat transplant procedures performed.

Section Summary: Heart/Lung Retransplantation
Analysis has suggested that patients undergoing heart/lung retransplantation have a lower median survival compared with patients undergoing primary heart/lung transplantation. However, after controlling confounding variables, survival times did not differ significantly between groups. Also, the conditional mean survival of 7.9 years among those who survived to 1-year posttransplant would suggest a survival benefit of heart/lung retransplant.

Potential Contraindications to Heart-Lung Transplant (Applies to All Indications)
Individual transplant centers may differ in their guidelines, and individual patient characteristics may vary within a specific condition. In general, heart transplantation is contraindicated in patients who are not expected to survive the procedure, or in whom patient-oriented outcomes (e.g., morbidity, mortality) are not expected to change due to comorbid conditions unaffected by transplantation (e.g., imminently terminal cancer, or another disease). Further, consideration is given to conditions in which the necessary immunosuppression would lead to hastened demise (e.g., active untreated infection). However, stable chronic infections have not always been shown to reduce life expectancy in heart transplant patients.

Malignancy
Pretransplant malignancy is considered a relative contraindication for heart transplantation given that malignancy has the potential to reduce life expectancy and could prohibit immune suppression after transplantation. However, with improved cancer

survival and use of cardiotoxic chemotherapy and radiotherapy, the need for heart transplantation has increased in this population.

(2015) Mistiaen et al. conducted a systematic review to study the posttransplant outcomes for pretransplant malignancy patients. Most selected studies were small case series (median sample size, 17 patients; range, 7 to 1117 patients; mean age, 6 to 52 years).19, Hematologic malignancy and breast cancer were the most common types of pretransplant malignancies. Dilated, congestive, or idiopathic cardiomyopathy were the most common reasons for transplantation in 4 case series; chemotherapy-related cardiomyopathy was the most important reason for transplantation in the other series. Hospital mortality rates ranged between 0% and 33%, with small sample sizes potentially explaining the observed variation. A large series by Oliveira et al (2012) reported similar short- and long-term posttransplant survival rates for chemotherapy-related (n=232) and other nonischemic cardiomyopathy (n=8890) patients. The 1-, 3-, and 5-year survival rates were 86%, 79%, and 71% for patients with chemotherapy-related cardiomyopathy compared with 87%, 81%, and 74% for other transplant patients, respectively. Further, 2-, 5-, and 10-year survival rates among pretransplant malignancy patients were found to be comparable with other transplant patients. In addition to the non-malignancy-related factors such as cardiac, pulmonary, and renal dysfunction, 2 malignancy-related factors were identified as independent predictors of 5-year survival. A malignancy-free interval (the interval between treatment of cancer and heart transplantation) of less than 1 year was associated with lower 5-year survival (<60%) than with a longer interval (>75%).

Patients with prior hematologic malignancies had increased posttransplant mortality in 3 small series. For example, as reported by Sigurdardottir et al. (2012), recurrence of malignancy was more frequent among patients with a shorter disease-free interval: 63%, 26%, and 6% among patients with less than 1 year, 1 to 5 years, and more than 5 years of disease-free interval, respectively.

(2015) Yoosabai et al. conducted a retrospective review of 23,171 heart transplant recipients in the OPTN/UNOS database to identify whether pretransplant malignancy increased the risk of posttransplant malignancy. Posttransplant malignancy was diagnosed in 2673 (11.5%) recipients during the study period. A history of any pretransplant malignancy was associated with increased risk of overall posttransplant malignancy (subhazard ratio, 1.51; p<.01), skin malignancies (subhazard ratio, 1.55; p<.01), and solid organ malignancies (subhazard ratio, 1.54; p<.01) on multivariate analysis.

Recurrence Risk

The evaluation of a candidate who has a history of cancer must consider the prognosis and risk of recurrence from available information including tumor type and stage, response to therapy, and time since therapy was completed. Although evidence is limited, patients in whom cancer is thought to be cured should not be excluded from consideration for transplant. The ISHLT guidelines have recommended stratifying each patient with pretransplant malignancy as to their risk of tumor recurrence and that cardiac

transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy, and negative metastatic workup. The guidelines also recommended that the specific amount of time to wait for transplant after neoplasm remission will depend on these factors and no arbitrary time period for observation should be used.

Human Immunodeficiency Virus (HIV) Infection

(2019) Koval et al. conducted a retrospective study to assess outcomes among 29 HIV-infected patients who underwent thoracic transplant at 14 sites in the U.S. and Europe. Of the 29 patients, 21 received heart transplants, seven received lung transplants, and one received heart-lung transplant. At the time of transplantation, 2 patients had detectable HIV RNA levels and the remainder were undetectable. All patients were on a 3-drug antiretroviral regimen at the time of transplantation. One year survival did not differ for patients with HIV who received heart (90%) and lung (86%) transplants compared to control patients without HIV (p=.947 and p=.949, respectively) from the ISHLT database. Three and 5-year survival rates among patients with HIV were 73% and 64%, respectively for heart transplants, and 80% and 75%, respectively for lung transplants. Acute cellular rejection occurred in 14 (67%) heart transplant patients and 2 lung transplant patients. Infections were reported in 8 (39%) heart transplant patients and 7 (86%) lung transplant patients. Six patients (5 heart transplant and 1 lung transplant) developed malignancy; none were AIDS-defining malignancies. Suppression of HIV RNA continued for at least 1 year for all patients. One patient who had a detectable viral load at the time of (heart) transplant died after 3 years from AIDS-related complications and graft failure. However, this was due to lack of adherence and lack of appropriate follow-up. The second patient with a detectable viral load at the time of transplant lived for 10 years post-transplant. There are few data directly comparing outcomes for patients with and without HIV or for combined heart-lung transplants.

Current OPTN policy permits HIV-positive transplant candidates.

The British HIV Association and the British Transplantation Society (2017) updated their guidelines on kidney transplantation in patients with HIV disease.24, These criteria may be extrapolated to other organs:

- Adherent with treatment, particularly antiretroviral therapy
- Cluster of differentiation 4 count greater than 100 cells/mL (ideally >200 cells/mL) for at least 3 months
- Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least 6 months
- No opportunistic infections for at least 6 months
- No history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, or lymphoma.

Other Potential Contraindications

Considerations for heart transplantation and lung transplantation alone may also pertain to combined heart-lung transplantation. For example, cystic fibrosis accounts for most pediatric candidates for heart-lung transplantation, and infection with Burkholderia species is associated with higher mortality in these patients.

Section Summary: Potential Contraindications
For individuals who have end-stage cardiac and pulmonary disease who receive combined heart-lung transplant, the evidence includes case series and registry data. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related morbidity and mortality. The available literature reports on outcomes after heart-lung transplantation. Given the exceedingly poor expected survival rates without transplantation, this evidence is sufficient to demonstrate that heart-lung transplantation provides a survival benefit in appropriately selected patients. A transplant may be the only option for some patients with end-stage cardiopulmonary disease. Heart-lung transplant is contraindicated for patients in whom the procedure is expected to be futile due to comorbid disease or for whom post-transplantation care is expected to worsen comorbid conditions significantly. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Summary of Evidence
For individuals who have end-stage cardiac and pulmonary disease who receive combined heart/lung transplant, the evidence includes case series and registry data. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related morbidity and mortality. The available literature reports on outcomes after heart/lung transplantation. Given the exceedingly poor expected survival rates without transplantation, this evidence is sufficient to demonstrate that heart/lung transplantation provides a survival benefit in appropriately selected patients. A transplant may be the only option for some patients with end-stage cardiopulmonary disease. Heart/lung transplant is contraindicated for patients in whom the procedure is expected to be futile due to comorbid disease or for whom post-transplantation care is expected to worsen comorbid conditions significantly. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a combined heart/lung transplant complicated by graft failure or severe dysfunction of the heart/lung and who receive a combined heart/lung retransplant, the evidence includes case series and registry data. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related morbidity and mortality. A very limited amount of data has suggested that, after controlling for confounding variables, survival rates after primary and repeat heart/lung transplants are similar. Findings are inconclusive due to the small number of cases of repeat heart/lung transplants reported in the published literature. Repeat heart/lung transplantation is, however, likely to improve outcomes in patients with a prior failed transplant who meet the clinical criteria for heart/lung transplantation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Professional Guidelines and Position Statements

International Society for Heart and Lung Transplantation

In 2021, the International Society for Heart and Lung Transplantation updated its consensus-based guidelines on the selection of lung transplant recipients. These guidelines made the following statements about lung transplantation:

"Lung transplantation should be considered for adults with chronic, end-stage lung disease who meet all the following general criteria:

- High (>50%) risk of death from lung disease within 2 years if lung transplantation is not performed
- High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function."

For combined heart/lung transplant, the guidelines state:
"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." The guideline goes on to state: "The primary indication for heart-lung transplant is pulmonary hypertension, either secondary to idiopathic pulmonary arterial hypertension or congenital heart disease (CHD)."

The guidelines also mentioned:"... candidates free from complex CHD or left ventricular compromise can achieve comparable outcomes with isolated bilateral lung transplant. 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."

Organ Procurement and Transplantation Network (OPTN)
The Organ Procurement and Transplantation Network (OPTN) also provides a table for reasons for heart-lung transplants as seen below:

Lung and Heart/Lung Diagnosis Categories	Lung and Heart/Lung Diagnoses
Congenital Disease	Eisenmenger's Syndrome: Arterial Septal Defect Eisenmenger's Syndrome: VSD Eisenmenger's Syndrome: Multi Congenital Anomaly Eisenmenger's Syndrome: PDA Eisenmenger's Syndrome: Other Specify Congenital: Other Specify
Emphysema/COPD	Emphysema/COPD
Cystic Fibrosis	Cystic Fibrosis
Idiopathic Pulmonary Fibrosis	Idiopathic Pulmonary Fibrosis

Primary Pulmonary Hypertension	Primary Pulmonary Hypertension
Alpha -1- Antitrypsin Deficiency	Alpha-1-Antitrypsin Deficiency
Retransplant/Graft Failure	Lung Re-Tx/GF: Obliterative Bronchiolitis Lung Re-Tx/GF: Other Specify Lung Re-Tx/GF: Non-Specific Lung Re-Tx/GF: Acute Rejection Lung Re-Tx/GF: Primary Graft Failure Lung Re-Tx/GF: Restrictive
Other	Sarcoidosis Lung Disease Bronchiectasis Pulmonary Fibrosis Lymphangioleiomyomatosis Obliterative Bronchiolitis (Non-Retransplant) Pulmonary Vascular Disease Occupational Lung Disease Inhalation Burns/Trauma Rheumatoid Disease

(Accessed 10/2022)

Regulatory Status
Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration (FDA).

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation Title 21, parts 1270 and 1271. Solid organs used for transplantation are subject to these regulations.

PRIOR APPROVAL

Prior approval is required.

POLICY

See Related Medical Policy
07.03.06 Lung and Lobar Lung Transplant

Initial Transplant
Heart-lung transplantation may be considered **medically necessary** for carefully selected individuals with a diagnosis of including, but not limited to **one of the following**:

- Chronic obstructive pulmonary disease with heart failure; **or**

- Cystic fibrosis with *severe* heart failure; **or**
- Eisenmenger complex with irreversible pulmonary hypertension and heart failure; **or**
- Emphysema with *severe* heart failure; **or**
- Irreversible primary pulmonary hypertension with heart failure; **or**
- Non-specific *severe* pulmonary fibrosis with severe heart failure; **or**
- Pulmonary fibrosis with uncontrollable pulmonary hypertension or heart failure

And the individual must meet **all of the following**:

- End-stage cardiac and pulmonary disease; **and**

Retransplantation
Heart-lung retransplantation after a failed primary heart-lung transplant may be considered **medically necessary** in individuals who meet the above criteria for heart-lung transplantation.

Not Medically Necessary
Heart-lung transplantation is considered **not medically necessary** when the above criteria is not met and for all other indications.

Policy Guidelines

Solid Organ Potential Contraindications
The following potential contraindications to solid organ transplants are subject to the judgment of the transplant center:

- Known current malignancy, including metastatic cancer
- Recent malignancy with high risk of recurrence
- Untreated systemic infection making immunosuppression unsafe, including chronic infection
- Other irreversible end-stage diseases not attributed to heart or lung disease
- History of cancer with a moderate risk of recurrence
- Systemic disease that could be exacerbated by immunosuppression
- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy

The New York Heart Association (NYHA)
The New York Heart Association Functional Classification of heart failure is one of the many parameters used for selecting heart-lung recipients. It places patients in one of four categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).

III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Note: Severe heart failure is considered class III or class IV.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

For Example:

- A patient with minimal or no symptoms but a large pressure gradient across the aortic valve or severe obstruction of the left main coronary artery is classified:
  - *Function Capacity I, Objective Assessment D*
- A patient with severe anginal syndrome but angiographically normal coronary arteries is classified:
  - *Functional Capacity IV, Objective Assessment A*

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 33935 Heart-lung transplant with recipient cardiectomy-pneumonectomy

SELECTED REFERENCES

- Harringer W, Haverich A. Heart and heart-lung transplantation: standards and improvements. World J Surg 2002; 26(2):218-25.
- Reichart B, Gulbins H, Meiser BM et al. Improved results after heart-lung transplantation: a 17-year experience. Transplantation 2003; 75(1):127-32.
- United Network for Organ Sharing (UNOS). Policy 3.7. Organ Distribution: Allocation of Thoracic Organs. UNOS Policies and Bylaws. United Network for Organ Sharing, Alexandria, VA. December 2007. Available at: http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_9.pdf
- Orens JB, Estenne M, Arcasoy S et al. Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. 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(7):745-55.
- Hayes D Jr, Galantowicz M, Hoffman TM. Combined heart-lung transplantation: A perspective on the past and the future. Pediatr Cardiol. 2012 Jun 10. [Epub ahead of print].
- The ISHLT Guideline For the Care of Heart Transplant Recipients (J Heart Lung Transplant 2010;29(8);424-453
- Benden C, Edwards LB, Kucheryavaya AY, et al. The registry of the international society for heart and lung transplantation: fifteenth pediatric lung and heart-lung transplantation report-2012. J Heart Lung Transplant. Oct 2012;31(10):1087-1095. PMID 22975098
- 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (Endorsed by ISHLT)
- Aguero F, Castel MA, Cocchi S, et al. An update on heart transplantation in human immunodeficiency virus-infected patients. Am J Transplant. Jan 2016;16(1):21-28. PMID 26523614
- Yusen RD, Edwards LB, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Lung and Heart-Lung Transplant Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant. Oct 2016;35(10):1170-1184. PMID 27772669
- Le Pavec J, Hascoët S, Fadel E. Heart-lung transplantation: current indications, prognosis and specific considerations. J Thorac Dis. 2018;10(10):5946–5952. doi:10.21037/jtd.2018.09.115
- Dimopoulos K, Muthiah K, Alonso-Gonzalez R, et al Heart or heart-lung transplantation for patients with congenital heart disease in England Heart 2019;105:596-602.
- Center for Medicare & Medicaid Services (CMS). Decision Memo for TRANSPLANT Centers: Re-Evaluation of Criteria for Medicare Approval (CAG-00061N). 2000.
- Koval CE, Farr M, Krisl J, et al. Heart or lung transplant outcomes in HIV-infected recipients. J Heart Lung Transplant. Dec 2019; 38(12): 1296-1305. PMID 31636044
- Sertic F, Han J, Diagne D, et al. Not All Septal Defects Are Equal: Outcomes of Bilateral Lung Transplant With Cardiac Defect Repair vs Combined Heart-Lung Transplant in Patients With Eisenmenger Syndrome in the United States. Chest. Nov 2020; 158(5): 2097-2106. PMID 32565271
- Hill C, Maxwell B, Boulate D, et al. Heart-lung vs. double-lung transplantation for idiopathic pulmonary arterial hypertension. Clin Transplant. Dec 2015; 29(12): 1067-75. PMID 26358537
- Jayarajan SN, Taghavi S, Komaroff E, et al. Impact of extracorporeal membrane oxygenation or mechanical ventilation as bridge to combined heart-lung transplantation on short-term and long-term survival. Transplantation. Jan 15 2014; 97(1): 111-5. PMID 24056630

- Riggs KW, Chapman JL, Schecter M, et al. Pediatric heart-lung transplantation: A contemporary analysis of outcomes. Pediatr Transplant. May 2020; 24(3): e13682. PMID 32067330
- Goldfarb SB, Levvey BJ, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Lung and Heart-Lung Transplantation Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant. Oct 2016; 35(10): 1196-1205. PMID 27772671
- Yusen RD, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report--2014; focus theme: retransplantation. J Heart Lung Transplant. Oct 2014; 33(10): 1009-24. PMID 25242125
- Shuhaiber JH, Kim JB, Gibbons RD. Repeat heart-lung transplantation outcome in the United States. J Heart Lung Transplant. Oct 2008; 27(10): 1122-7. PMID 18926404
- Oliveira GH, Hardaway BW, Kucheryavaya AY, et al. Characteristics and survival of patients with chemotherapy-induced cardiomyopathy undergoing heart transplantation. J Heart Lung Transplant. Aug 2012; 31(8): 805-10. PMID 22551930
- Sigurdardottir V, Bjortuft O, Eiskjaer H, et al. Long-term follow-up of lung and heart transplant recipients with pre-transplant malignancies. J Heart Lung Transplant. Dec 2012; 31(12): 1276-80. PMID 23089300
- Yoosabai A, Mehta A, Kang W, et al. Pretransplant malignancy as a risk factor for posttransplant malignancy after heart transplantation. Transplantation. Feb 2015; 99(2): 345-50. PMID 25606783
- Koval CE, Farr M, Krisl J, et al. Heart or lung transplant outcomes in HIV-infected recipients. J Heart Lung Transplant. Dec 2019; 38(12): 1296-1305. PMID 31636044
- Organ Procurement and Transplantation Network (OPTN). Organ Procurement and Transplantation Network Policies. 2022; https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf.
- Working Party of the British Transplantation Society. Kidney and Pancreas Transplantation in Patients with HIV. Second Edition (Revised). British Transplantation Society Guidelines. Macclesfield, UK: British Transplantation Society; Published 2015. Updated 2017. https://bts.org.uk/wp-content/uploads/2017/04/02_BTS_Kidney_Pancreas_HIV.pdf
- United Network for Organ Sharing (UNOS). Transplant trends. 2021; https://unos.org/data/transplant-trends/
- United Network for Organ Sharing (UNOS). Transplant trends. About the Heart / Lung. 2021; https://unos.org/data/transplant-trends/
- Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.
- Mehra M.R., Canter, C.E, Hannan M.M., et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. Volume 35, ISSUE 1, P1-23, January 01, 2016.

https://doi.org/10.1016/j.healun.2015.10.023. Available at https://www.jhltonline.org/article/S1053-2498(15)01484-9/fulltext
- Black CK, Termanini KM, Aguirre O, et al. Solid organ transplantation in the 21 st century. Ann Transl Med. Oct 2018; 6(20): 409. PMID 30498736
- Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report--2010. J Heart Lung Transplant. Oct 2010; 29(10): 1104-18. PMID 20870165
- United Network for Organ Sharing (UNOS). Transplant trends. 2022; https://unos.org/data/transplant-trends/.
- Kalogeropoulos AP, Georgiopoulou VV, Giamouzis G, et al. Utility of the Seattle Heart Failure Model in patients with advanced heart failure. J Am Coll Cardiol. Jan 27 2009; 53(4): 334-42. PMID 19161882
- United Network for Organ Sharing (UNOS). Heart/Lung: Submitting LAS exception requests for candidates diagnosed with PH. 2022; https://unos.org/news/submitting-las-exception-requests-for-candidates-diagnosed-with-ph/.
- Spahr JE, West SC. Heart-lung transplantation: pediatric indications and outcomes. J Thorac Dis. Aug 2014; 6(8): 1129-37. PMID 25132980
- Benden C, Goldfarb SB, Edwards LB, et al. The registry of the International Society for Heart and Lung Transplantation: seventeenth official pediatric lung and heart-lung transplantation report--2014; focus theme: retransplantation. J Heart Lung Transplant. Oct 2014; 33(10): 1025-33. PMID 25242126
- Mistiaen WP. Heart transplantation in patients with previous malignancy. An overview. Acta Cardiol. Apr 2015; 70(2): 123-30. PMID 26148371
- Working Party of the British Transplantation Society. Kidney and Pancreas Transplantation in Patients with HIV. Second Edition (Revised). British Transplantation Society Guidelines. Macclesfield, UK: British Transplantation Society; Published 2015. Updated 2017. https://bts.org.uk/wp-content/uploads/2017/04/02_BTS_Kidney_Pancreas_HIV.pdf
- Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. Nov 2021; 40(11): 1349-1379. PMID 34419372
- Center for Medicare & Medicaid Services (CMS). Decision Memo for TRANSPLANT Centers: Re-Evaluation of Criteria for Medicare Approval (CAG-00061N). 2000; https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=75&ver=7&NcaName=Transplant+Centers%3A+Re-Evaluation+of+Criteria+for+Medicare+Approval&bc=BEAAAAAAEAAA&&fromdb=tru
- Organ Procurement and Transplantation Network (OPTN). Reasons for Lung Transplants. Available at: https://optn.transplant.hrsa.gov/patients/by-organ/lung/

POLICY HISTORY

Date	Reason	Action
November 2022	Annual Review	Policy Revised
November 2021	Annual Review	Policy Revised
November 2020	Annual Review	Policy Renewed
November 2019	Annual Review	Policy Renewed
November 2018	Annual Review	Policy Renewed
November 2017	Annual Review	Policy Renewed
November 2016	Annual Review	Policy Revised
November 2015	Annual Review	Policy Renewed
December 2014	Annual Review	Policy Revised
February 2014	Annual Review	Policy Renewed
March 2013	Annual Review	Policy Renewed
March 2012	Annual Review	Policy Renewed
April 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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