

Regence

Medical Policy Manual

Transplant, Policy No. 03

Heart-Lung Transplant

Effective: May 1, 2024

Next Review: March 2025

Last Review: March 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

The heart/lung transplantation involves a coordinated triple operative procedure consisting of procurement of a donor heart-lung block, excision of the heart and lungs of the recipient, and implantation of the heart and lungs into the recipient. A heart/lung transplantation refers to the transplantation of one or both lungs and heart from a single cadaver donor.

MEDICAL POLICY CRITERIA

- I. Heart/lung *transplantation* may be considered **medically necessary** for carefully selected patients with end-stage cardiac and pulmonary disease including, but not limited to, one of the following diagnoses:
 - A. Irreversible primary pulmonary hypertension with heart failure
 - B. Nonspecific severe pulmonary fibrosis, with severe heart failure
 - C. Eisenmenger complex with irreversible pulmonary hypertension and heart failure
 - D. Cystic fibrosis with severe heart failure
 - E. Chronic obstructive pulmonary disease with heart failure
 - F. Emphysema with severe heart failure
 - G. Pulmonary fibrosis with uncontrollable pulmonary hypertension or heart failure

- II. Heart/lung transplantation is considered **not medically necessary** in patients without end-stage cardiac and pulmonary disease.
- III. Heart/lung *retransplantation* after a failed primary heart/lung transplant may be considered **medically necessary** in patients with end-stage cardiac and pulmonary disease as described in Criterion I above.
- IV. Heart/lung retransplantation is considered **not medically necessary** in patients without end-stage cardiac and pulmonary disease.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. [Ventricular Assist Devices and Total Artificial Hearts](#), Surgery, Policy No. 52
2. [Heart Transplant](#), Transplant, Policy No. 02
3. [Lung and Lobular Transplant](#), Transplant, Policy No. 08

BACKGROUND

Solid organ transplantation offers a treatment option for patients with different types of endstage organ failure that can be lifesaving or provide significant improvements to a patient's quality of life.^[1] 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 (OPTN) and United Network of Organ Sharing (UNOS).

HEART/LUNG TRANSPLANT

The majority of 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. Eventually, pulmonary hypertension may lead to a reversal of the intracardiac shunting and inadequate peripheral oxygenation, or cyanosis.^[2]

However, the total number of patients with Eisenmenger syndrome has been declining in recent years, as a result of corrective surgical techniques and improved medical management of pulmonary hypertension. Heart/lung transplants have not increased appreciably for other indications either, as 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. In these, patient survival rates are similar to lung transplant rates. Bronchiolitis obliterans syndrome is a major complication; one, five, and 10-year patient survival rates are 68%, 50%, and 40%, respectively.^[2]

In 2021, 45 individuals received heart/lung transplants in the United States. As of March 2022, there were 40 patients on the waiting list for heart/lung transplants.^[3]

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. The U.S. Food and Drug Administration 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.

EVIDENCE SUMMARY

Due to the nature of the patient population requiring heart/lung transplantation, there were no randomized controlled trials (RCTs) comparing heart/lung transplant to alternatives. Systematic reviews are based on case series and registry data. The extant RCTs compare surgical technique, infection prophylaxis, and immunosuppressive therapy and are not germane to this policy. The following is a summary of evidence based on registry data, case series, and expert opinion.

PATIENT SELECTION

Patients who are eligible for heart/lung transplantation can be listed under both the heart and lung allocation systems in the United States. In 2005, United Network for Organ Sharing (UNOS) changed the method by which lungs were allocated, from one 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 likelihood of survival.^[4] 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 on optimal therapy
- Right arterial pressure greater than 15 mm Hg
- Cardiac index less than 1.8 L/min/m².

INITIAL COMBINED HEART/LUNG TRANSPLANT

Sertic (2020) compared outcomes of bilateral lung transplantation with cardiac defect repair to combined heart/lung transplantation in adult patients with Eisenmenger's syndrome using the United Network for Organ Sharing (UNOS) database of heart/lung transplantations performed from 1987 to 2018.^[5] 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 one year (63.1% vs 68.0%, respectively), five years (38.5% vs 47.3%), and 10 years (30.2% vs 30.5%) posttransplant (p=0.6). Overall survival did not differ among

patients who received transplantation between 1987 to 1999 and those who received transplantation between 2000 to 2018 ($p=0.7$).

PEDIATRIC CONSIDERATIONS

Riggs (2020) 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.^[6] 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, five-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 ($p=0.03$) and patients who were retransplanted ($p=0.008$) 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; $p=0.04$), one to 11 year old patients (HR, 1.78; 95% CI, 1.12 to 2.8; $p=0.015$), and patients on ECMO (HR, 4.1; 95% CI, 1.3 to 12.8; $p=0.016$) had the highest risk of mortality post-transplant.

A 2014 analysis of data from the Organ Procurement and Transplantation Network (OPTN) reported on indications for pediatric heart/lung transplantation.^[7] The number of pediatric heart/lung transplants has decreased in recent years (i.e., 56 cases in 1993-1997; 21 cases in 2008-2013). The three most common indications for pediatric heart/lung transplant were primary pulmonary hypertension ($n=55$), congenital heart disease ($n=37$), and Eisenmenger syndrome ($n=30$). However, while 30 children received a heart/lung transplant for Eisenmenger syndrome through 2002, none were performed for this indication since then to the date of the analysis. Pediatric heart/lung transplants have also been performed for other indications including alpha1 antitrypsin deficiency, pulmonary vascular disease, cystic fibrosis, and dilated cardiomyopathy.

In 2012, the Registry of the International Society for Heart and Lung Transplantation (ISHLT) reported on pediatric heart/lung transplant data collected through June 2011.^[8] In recent years, the number of heart/lung transplant procedures in children has decreased, and the number of lung transplants has increased. There were no heart/lung transplants in infants between 2007 and the date of the study. Overall, survival rates after heart/lung transplants are comparable in children and adults (median half-life of 4.7 and 5.3 years, respectively). For pediatric heart/lung transplants that occurred between January 1990 and June 2010, the five-year survival rate was 49%. The two leading causes of death in the first year after transplantation were non-cytomegalovirus infection and graft failure. Beyond three years post-transplant, the major cause of death was bronchiolitis obliterans syndrome. An updated report on pediatric lung and heart-lung transplant from the same registry in 2014 did not include updated data on pediatric heart-lung transplants due to the small number of patients available.^[9]

RETRANSPLANTATION

Repeat heart-lung transplant procedures have been performed; only three published studies were identified that reported on outcomes after repeat heart-lung transplants. In 2014, the ISHLT described outcomes after retransplantation as compared with primary transplantation, including identifying risk factors leading to retransplantation and both transplant-related morbidities and mortality after retransplantation.^[10] The authors reviewed 9,248 primary transplants and 602 retransplants. After retransplantation, early time-related risk of mortality was similar to that after primary transplantation (HR 1.07; 95% CI, 0.92 to 1.25; $p=0.40$), but both late-phase time-related risk of mortality (HR 1.67; 95% CI, 1.40 to 1.99; $p<0.001$) and requirement of an additional graft (HR 1.69; 95% CI, 1.18 to 2.43; $p=0.004$) were higher. Long-term morbidities were significantly more common after retransplantation than with primary transplantation. The authors concluded that retransplantation after primary transplant in the pediatric age group, although feasible with similar early survival, is associated with decreased long-term survival and an increase in transplant-related morbidities.

Yusen (2014) reported outcomes for adult heart-lung transplants, with a focus on retransplantation, using data from the ISHLT Registry.^[11] Thirty-three participating centers reported 75 adult heart-lung transplants in 2012, a decline from the peak year for heart-lung transplants (1989) during which 226 heart-lung transplants were performed. From 1982-2012, 90 adults had a first heart–lung retransplant after a previous heart–lung transplant. These 90 patients had a median survival of 0.3 year, with an unadjusted survival rate of 52%, 43%, 36%, and 27% at three months, one year, three years, and five years, respectively. Those who survived to one year had a conditional mean survival of 7.9 years.

Shuhaiber (2008) published results from a review of data from the UNOS registry.^[12] The authors identified 799 primary heart-lung and 19 repeat heart-lung transplants. According to 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, the authors 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 four repeat transplant patients. For the 15 repeat transplant patients with primary transplant matches, survival time did not differ significantly in the two groups. Being on a ventilator was statistically significantly associated with decreased survival time. The main limitation of this analysis is the small number of repeat transplant procedures performed.

POTENTIAL CONTRAINDICATIONS

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, such as morbidity or mortality, are not expected to change due to comorbid conditions unaffected by transplantation (e.g., imminently terminal cancer or other disease). Further, consideration is given to conditions in which the necessary immunosuppression would lead to hastened demise, such as active untreated infection. However, stable chronic infections have not always been shown to reduce life expectancy in heart transplant patients.

Malignancy

Concerns regarding a potential recipient's history of cancer were based on the observation of significantly increased incidence of cancer in kidney transplant patients.^[13] In fact, carcinogenesis is two to four times more common, primarily skin cancers, in both heart transplant and lung transplant patients, likely due to the higher doses of immunosuppression necessary for the prevention of allograft rejection.^[2, 14] The incidence of *de novo* cancer in heart transplant patients approaches 26% at eight years post-transplant, the rate for lung transplant is 28% at ten years. For renal transplant patients who had a malignancy treated prior to transplant, the incidence of recurrence ranged from zero to more than 25%, depending on the tumor type.^[15, 16]

In a 2013 retrospective cohort study, *de novo* cancer-related deaths in Australian liver and cardiothoracic transplant recipients were analyzed during a median five year follow-up.^[17] *De novo* cancer-related mortality risk in liver and cardiothoracic recipients was significantly elevated compared to the matched general population (n = 171; SMR = 2.83; 95% confidence interval [95%CI], 2.43-3.27). Excess risk was observed regardless of transplanted organ, recipient age group or sex. Risk of death from *de novo* cancer was high in pediatric recipients (n = 5; SMR = 41.3; 95%CI, 13.4-96.5), four of the five deaths were non-Hodgkin lymphoma. Authors suggest that *de novo* cancer was a leading cause of late death, particularly in heart and liver transplantation.

However, it should be noted that the availability of alternate treatment strategies informs recommendations for a waiting period following high-risk malignancies: in renal transplant, a delay in transplantation is possible due to dialysis; end-stage cardiopulmonary failure patients may not have an option. A small study (n=33) of survivors of lymphoproliferative cancers who subsequently received cardiac transplant had one, five, and ten-year survival rates of 77%, 64%, and 50%, respectively.^[18] By comparison, overall one, five, and ten-year survival rates are expected to be 88%, 74%, and 55%, respectively for the general transplant candidate. 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. UNOS has not addressed malignancy in current policies.

Human Immunodeficiency Virus

Solid organ transplant for patients who are HIV-positive (HIV+) was historically controversial, due to the long-term prognosis for human immunodeficiency virus (HIV) positivity and the impact of immunosuppression on HIV disease. The availability of highly active antiretroviral therapy (HAART), has markedly changed the natural history of the disease. A 2009 retrospective case series reported favorable outcomes for seven patients with HIV who received a heart transplant.^[19] However, there is little data directly comparing outcomes for patients with and without HIV or for combined heart-lung transplants.

Current Organ Procurement and Transplantation Network (OPTN) policy permits HIV-positive transplant candidates.^[20]

OTHER

Considerations for heart transplantation and lung transplantation alone may also pertain to combined heart-lung transplantation. For example, cystic fibrosis accounts for the majority of pediatric candidates for heart-lung transplantation, and infection with *Burkholderia* species is

associated with higher mortality in these patients. Also, experience with kidney transplantation in patients infected with HIV in the era of HAART has opened discussion of transplantation of other solid organs in these patients. These topics are addressed more fully in the separate policies on heart transplantation and lung transplantation.

PRACTICE GUIDELINE SUMMARY

THE INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

In 2021, the International Society for Heart and Lung Transplantation updated their consensus-based guidelines.^[21] The guideline states:

"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)."

SUMMARY

There is enough research to show that heart/lung transplantation can improve survival for certain patients. Therefore, heart/lung transplant may be considered medically necessary in patients who meet criteria. Similarly, heart/lung retransplantation may improve survival for certain patients who have had a prior transplant. Therefore, heart/lung retransplantation may be considered medically necessary in patients with a failed prior transplant who meet the clinical criteria for heart-lung transplantation.

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CODES

Codes	Number	Description
CPT	33930	Donor cardiectomy-pneumonectomy, (including cold preparation)
	33933	Backbench standard preparation of cadaver donor heart/lung allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, and trachea for implantation
	33935	Heart-lung transplant with recipient cardiectomy-pneumonectomy
HCPCS	None	

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