

Heart Transplant

Effective: May 1, 2019

Next Review: March 2020

Last Review: April 2019

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

A heart transplant consists of replacing a diseased heart with a healthy donor heart. Transplantation is used for patients with refractory end-stage cardiac disease.

MEDICAL POLICY CRITERIA

I. Adult Patients

- A. Human heart transplantation may be considered **medically necessary** for adults with end-stage heart failure (see Policy Guidelines) when one or more of the following accepted or probable indications is met:

Accepted Indications^[1]

1. Hemodynamic compromise due to heart failure demonstrated by any one of the following:
 - a. Maximal VO₂ (oxygen consumption) <10 mL/kg/min with achievement of anaerobic metabolism
 - b. Refractory cardiogenic shock
 - c. Documented dependence on intravenous inotropic support to maintain adequate organ perfusion

2. Severe ischemia consistently limiting routine activity not amenable to bypass surgery or angioplasty, or
3. Recurrent symptomatic ventricular arrhythmias refractory to ALL accepted therapeutic modalities.

Probable indications^[1]

4. Maximal VO₂ <14 mL/kg/min and major limitation of the patient's activities, or
5. Recurrent unstable ischemia not amenable to bypass surgery or angioplasty, or
6. Instability of fluid balance/renal function not due to patient noncompliance with regimen of weight monitoring, flexible use of diuretic drugs, and salt restriction

II. Pediatric Patients

- A. Human heart transplantation may be considered **medically necessary** in pediatric patients (see Policy Guidelines) when one of the following criteria (1 or 2) are met:

1. There is a diagnosis of heart failure with persistent symptoms at rest and any one or more of the following criteria below (a-c) are met:
 - a. Continuous infusion of intravenous inotropic agents; or
 - b. Mechanical ventilatory support; or
 - c. Mechanical circulatory support.

OR

2. There is a diagnosis of pediatric heart disease with symptoms of heart failure in patients who do not meet the criteria above but any one of the following criteria is met:
 - a. Severe limitation of exercise and activity (if measurable, such patients would have a peak maximum oxygen consumption <50% predicted for age and sex); or
 - b. Cardiomyopathies or previously repaired or palliated congenital heart disease, and significant growth failure attributable to the heart disease; or
 - c. Near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator; or
 - d. Restrictive cardiomyopathy with reactive pulmonary hypertension; or
 - e. Reactive pulmonary hypertension and potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future; or
 - f. Anatomical and physiological conditions likely to worsen the natural history of congenital heart disease in infants with a functional single ventricle; or
 - g. Anatomical and physiological conditions that may lead to consideration for heart transplantation without systemic ventricular dysfunction.

- III. Human heart retransplantation after a failed primary heart transplant may be considered **medically necessary** in patients who meet criteria for heart transplantation.
- IV. Human heart transplantation is considered **not medically necessary** when Criteria I or Criteria II is not met.

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

POLICY GUIDELINES

Adults with histories of congenital heart disease may be considered under applicable criteria for either Adult Patients (Criteria I) or Pediatric Patients (Criteria II).

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/Lung Transplant](#), Transplant, Policy No. 03

BACKGROUND

In the United States, approximately 6.5 million people have heart failure and 309,000 die each year from this condition.^[2] The reduction of cardiac output is considered to be severe when systemic circulation cannot meet the body's needs under minimal exertion. Heart transplantation can potentially improve both survival and quality of life in patients with end-stage heart failure.

Heart failure may be the consequence of a number of differing etiologies, including ischemic heart disease, cardiomyopathy, or congenital heart defects. The leading indication for heart transplant has shifted over time from ischemic to non-ischemic cardiomyopathy. During the period 2009 to 2014, nonischemic cardiomyopathy was the dominant underlying primary diagnosis among patients 18-39 years (64%) and 40-59 years (51%) undergoing transplant operations. Ischemic cardiomyopathy was the dominant underlying primary diagnosis among the heart transplant recipients 60-69 years and 70 years and older, 50% and 55% respectively.^[3] Overall, ischemic cardiomyopathy is the underlying heart failure diagnosis in approximately 40% of men and 20% of women who receive a transplant. Approximately 3% of the heart transplants during this time period were in adults with congenital heart disease.^[4] The reduction of cardiac output is considered to be severe when systemic circulation cannot meet the body's needs under minimal exertion. Heart transplantation can potentially improve both survival and quality of life. According to the Organ Procurement and Transplant Network (OPTN), patient survival rate at one year is 87.5% in males and 85.6% in females and at five years is 72.4% in males and 67.4% in females.^[5]

The demand for heart transplants far exceeds the availability of donor organs, and the length of time patients are on the waiting list for transplants has increased.

According to data from the Organ Procurement and Transplantation Network, in 2016, a total of 3191 heart transplants were performed in the United States. As of July 16, 2017, there were 3996 patients on the waiting list for a heart transplant.^[6] Also in recent years, advances in medical and device therapy for patients with advanced heart failure has improved the survival of patients awaiting heart transplantation. Due to the variable natural history of heart failure, functional and hemodynamic parameters have been utilized to estimate prognosis.

From 2008 to 2015, approximately 4% of heart transplants were repeat transplantations.^[4] Heart retransplantation raises ethical issues due to the lack of sufficient donor hearts for initial transplants. The United Network for Organ Sharing (UNOS) does not have separate organ allocation criteria for repeat heart transplant recipients.

EVIDENCE SUMMARY

PRIORITIZATION OF CANDIDATES

The majority of heart transplant recipients are now hospitalized Status 1 patients at the time of transplant. This shift has occurred due to the increasing demand on the scarce resource of donor organs resulting in an increased waiting time for donor organs. Patients initially listed as a Status 2 candidates may deteriorate to a Status 1 candidate before a donor organ becomes available. At the same time, as medical and device therapy for advanced heart failure has improved, some patients on the transplant list will recover enough function to become delisted.

Johnson (2010) reported on waiting list trends in the U.S. between 1999 and 2008.^[7] They noted an increasing trend of adult patients with congenital heart disease and retransplantation. The proportion of patients listed as Status 1 continued to increase, even as waiting list and post-transplant mortality for this group decreased. Meanwhile, Status 2 patients have decreased as a proportion of all candidates. Completed transplants have trended toward the extremes of age, with more infants and patients older than age 65 years having transplants in recent years. This is an update to what Lietz and Miller published in 2007, where they reported on patient survival on the heart transplant waiting list, comparing the era between 1990 and 1994 to the era of 2000 to 2005.^[8] One year survival for UNOS Status 1 candidates improved from 49.5% to 69.0%. Status 2 candidates fared even better, with 89.4% surviving 1 year compared to 81.8% in the earlier time period.

As a consequence, aggressive treatment of heart failure has been emphasized in recent guidelines. Prognostic criteria have been investigated to identify patients who have truly exhausted medical therapy and thus are likely to derive the maximum benefit for heart transplantation. Maximal oxygen consumption (VO₂), which is measured during maximal exercise, is one measure that has been suggested as a critical objective criterion of the functional reserve of the heart. The American College of Cardiology (ACC) has adopted maximal VO₂ as one criterion for patient selection.^[1] Studies have suggested that transplantation can be safely deferred in those patients with a maximal VO₂ of greater than 14 mL/kg/min. The importance of the maximal VO₂ has also been emphasized by an American Heart Association Scientific Statement addressing heart transplant candidacy.^[9] In past years, a left ventricular ejection fraction (LVEF) of less than 20% or a New York Heart Association (NYHA) Class III or IV status may have been used to determine transplant

candidacy. However, as indicated by the ACC criteria, these measurements are no longer considered adequate to identify transplant candidates. These measurements may be used to identify patients for further cardiovascular workup but should not be the sole criteria for transplant.

Methods other than maximal VO₂ have been proposed as predictive models in adults.^[10-13] The Heart Failure Survival Scale (HFSS) and Seattle Heart Failure Model (SHFM) are two examples. In particular, the SHFM provides an estimate of 1-, 2-, and 3-year survival with the use of routinely obtained clinical and laboratory data. Information regarding pharmacologic and device usage is incorporated into the model, permitting some estimation of effects of current, more aggressive heart failure treatment strategies. In 2006, Levy and colleagues^[14] introduced the model using multivariate analysis of data from the PRAISE1 heart failure trial (n=1,125). Applied to the data of five other heart failure trials, the SHFM correlated well with actual survival (r: 0.98, standard error of the estimate=±3). The SHFM has been validated in both ambulatory and hospitalized heart failure populations^[15-17] but with a noted underestimation of mortality risk, particularly in blacks and device recipients.^[18,19] None of these models have been universally adopted by transplant centers.

INITIAL HEART TRANSPLANT

Survival after heart transplant

Nguyen (2017) investigated the benefit of heart transplantation compared with waiting list while accounting for the estimated risk of a given donor-recipient match among 28,548 heart transplant candidates in the OPTN between July 2006 and December 2015.^[20] Net benefit from heart transplantation was evident across all estimates of donor-recipient status 1A and 1B candidates: status 1A (lowest-risk quartile hazard ratio [HR], 0.37; 95% CI, 0.31 to 0.43; highest-risk quartile HR=0.52; 95% CI, 0.44 to 0.61) and status 1B candidates (lowest-risk quartile HR=0.41; 95% CI, 0.36 to 0.47; highest-risk quartile HR=0.66; 95% CI, 0.58 to 0.74). Status 2 candidates showed a benefit from heart transplantation; however, survival benefit was delayed. For the highest-risk donor-recipient matches, a net benefit of transplantation occurred immediately for status 1A candidates, after 12 months for status 1B candidates, and after 3 years for status 2 candidates.

Lund (2016) examined the risk factors associated with 10-year posttransplant mortality among patients undergoing heart transplantation during 2000-2005 using the International Society for Heart and Lung Transplantation (ISHLT) Registry.^[3] Markers of pretransplant severity of illness, such as pretransplant ventilator use (HR=1.35; 95% CI, 1.17 to 1.56; n=338), dialysis use (HR=1.51; 95% CI, 1.28 to 1.78; n=332), underlying diagnoses of ischemic (HR=1.16; 95% CI: 1.10 to 1.23; n=7822), congenital (HR=1.21; 95% CI, 1.04 to 1.42; n=456) or restrictive (HR=1.33; 95% CI, 1.13 to 1.58; n=315) heart disease (vs non-ischemic cardiomyopathy), and retransplant (HR=1.18; 95% CI, 1.02 to 1.35; n=489) were associated with post-transplant mortality risk at 10 years.

Ting (2016) published a report that retrospectively evaluated outcomes of 134 patients one month to 78 years old (average 28) who received mechanical circulatory support for acute myocarditis with cardiogenic shock, between 1994 and 2014.^[21] Patients recovering without a transplant were compared to those who received a transplant under mechanical circulatory support. 54% of patients survived on mechanical circulatory support, without transplant. Only 5% of the patients underwent transplant. The authors concluded transplant survival under mechanical circulatory support had favorable mid- and long-term outcomes.

Starling (2016) and Svobodova (2016) published studies evaluating transplant outcomes based on biomarkers and/or antibodies. Starling published a one year observational, multicenter, cohort study in which 200 heart transplant patients were evaluated for biomarkers that could predict heart transplant outcomes.^[22] Laboratory tests included anti-AHL antibody analysis, ELISPOT Panel of reactive T cell (PRT) assays, plasma angiogenesis-related proteins, peripheral blood and tissue gene expression profiling. Svobodova published a single-center retrospective study that evaluated antibody-mediated rejection (AMR).^[23] Data was analyzed for pre- and post-transplant antibodies and antigens in transplant recipients and/or donors. Median follow-up was 39 months. Starling concluded it is still difficult to find reliable biomarkers that can determine heart transplant outcomes. Svobodova stated monitoring pre- and post-transplant antigens and antibodies may predict rejection.

According to the Organ Procurement and Transplantation Network (OPTN), Kaplan-Meier survival rates for heart transplants performed during 2008-2015 based on available U.S. data as of July 10, 2017, the 1-year survival after heart transplant was 90.5% (95% confidence interval [CI], 89.9% to 91.2%) and 91.1% (95% CI, 90.1% to 92.1%) for men and women, respectively. Three-year survival rates were 85.1% (95% CI, 84.3% to 86.0%) and 85.2% (95% CI, 83.8% to 86.4%) for men and women, respectively, and 5-year survival rates were 78.4% (95% CI, 77.3% to 79.3%) and 77.7% (95% CI, 76.0% to 79.2%), respectively.^[5] Rana (2015) conducted a retrospective analysis of solid organ transplant recipients registered in the UNOS database from 1987 to 2012, including 54,746 patients who underwent a heart transplant.^[24] Transplant recipients were compared with patients listed for transplant, but who did not receive a transplant after propensity score matching based on a variety of clinical characteristics. After matching, the median survival was 9.5 years in transplant recipients compared with 2.1 years in waiting list patients.

A 2013 study examined characteristics of patients who survived longer than 20 years after heart transplantation at a single center.^[25] Thirty-nine heart transplant recipients who survived over 20 years post-transplant were compared to 98 patients who died between one and 20-years post-transplant. Independent factors associated with long-term survival were younger recipient age i.e., <45 years versus 45 years and older (OR: 3.9, 95% CI: 1.6-9.7) and idiopathic cardiomyopathy i.e. versus other etiologies (OR: 3.3, 95% CI: 1.4-7.8).

Bhama (2013) published results from study that reported on survival outcomes for heart transplantation in a cohort of adults with congenital heart disease (CHD) and identified risk factors for mortality that would help guide recipient and donor selection.^[26] A retrospective analysis identified 19 patients that had transplantation for CHD and compared to 428 transplant patients that underwent transplantation for conditions other than CHD. There was no significant difference in survival (CHD vs control) at 30 days (89% vs 92%, $p = 0.5567$), one year (84% vs 86%, $p = 0.6976$), or five years (70% vs 72%, $p = 0.8478$). The only significant predictor of death in the CHD group was donor organ ischemic time >four hours (HR 13.26, 95% CI 1.3 to 132.2, $p = 0.028$). Authors suggested that adults with CHD have excellent early and mid-term survival after heart transplantation.

A 2012 study by Kalic analyzed prospectively collected data from the United Network for Organ Sharing (UNOS) registry.^[27] The analysis included 9,404 individuals who had survived 10 years after heart transplant and 10,373 individuals who had died before 10 years. Among individuals who had died, mean survival was 3.7 years post-transplant. In multivariate analysis, statistically significant predictors of surviving at least 10 years after heart transplant included:

- Age younger than 55 years (odds ratio [OR]: 1.24, 95% confidence interval [CI]: 1.10 to 1.38),
- Younger donor age (OR: 1.01, 95% CI: 1.01 to 1.02),
- Shorter ischemic time (OR: 1.11, 95% CI: 1.05 to 1.18),
- White race (OR: 1.35, 95% CI: 1.17 to 1.56), and
- Annual center volume of nine or more heart transplants (OR: 1.31, 95% CI: 1.17 to 1.47).

Factors that significantly decreased the likelihood of 10-year survival in multivariate analysis included:

- Mechanical ventilation (OR: 0.53, 95% CI: 0.36 to 0.78), and
- Diabetes (OR: 0.67, 95% CI: 0.57 to 0.78).

Jalowiec (2011) compared clinical outcomes in sex-matched and sex-mismatched heart transplant recipients.^[28] They retrospectively reviewed data from 347 heart transplant recipients; 237 (78.7%) received a heart from a same-sex donor, 40 (11.5%) cases involved a female donor and male recipient, and 34 (9.8%) cases involved a male donor and female recipient. There was not a statistically significant difference in the mortality rate during the first month post-transplant between the sex-matched and either sex-mismatched group. In adjusted analyses, two of the other nine study outcomes differed significantly among the three groups. The male donor-female recipient group had significantly more treated rejection episodes during the first year post-transplant and significantly more days of rehospitalization after the initial discharge than either of the other two groups. The incidence of steroid-induced diabetes, cardiac allograft vasculopathy, non-skin cancers, number of intravenous (IV)-treated infections post-transplant, and initial hospital length of stay were not significantly different among groups.

Pediatric considerations

The highest 1- and 3- year survival rate among pediatric patients undergoing heart transplant in the US, during 2008-2015, were 11-17 year old patients according to OPTN.^[5] Patients younger than 1-year-olds had the lowest 1-, 3-, and 5-year survival among pediatric patients.

Rossano (2016) examined survival among pediatric heart transplant recipients using the ISHLT Registry. Among 12,091 pediatric patients undergoing heart transplantation during 1982-2014, the overall median survival was 20.7 years for infants, 18.2 years for children ages 1 to 5 years, 14.0 years for those ages 6 to 10 years, and 12.7 years for those ages 11 to 17 years. As the first year posttransplant represents the greatest risk for mortality, survival conditional on survival to 1 year was longer.^[29]

Authors conducted a multivariable analysis of pediatric patients undergoing heart transplant during 2003-2013 to identify the factors associated with 1-year mortality. Infection requiring intravenous drug therapy within 2 weeks of transplant (HR=1.36; 95% CI, 1.10 to 1.68), ventilator use (HR=1.41; 95% CI, 1.13 to 1.76), donor cause of death (cerebrovascular accident vs head trauma) (HR=1.59; 95% CI, 1.20 to 2.09), diagnosis (congenital heart disease [CHD] vs cardiomyopathy (HR=1.91; 95% CI, 1.46 to 2.52), and retransplant vs cardiomyopathy (HR=2.23; 95% CI, 1.53 to 3.25), recipient dialysis (HR=2.36; 95% CI, 1.57 to 3.57), ECMO with a diagnosis of CHD vs no ECMO (HR=2.42; 95% CI, 1.74 to 3.35), ischemic time (p<0.001), donor weight (p<0.001), estimated glomerular filtration rate (eGFR; p=0.002), and pediatric center volume (p<0.001) were risk factors for 1-year mortality. Earlier era (1999-

2000 vs 2007-2009), CHD (vs DCM), use of ECMO (vs no device), and pediatric center volume were risk factors for 5-, 10-, and 15-year mortality. A panel-reactive antibody (PRA) greater than 10% was associated with worse 5- and 10-year survival and eGFR was associated with 5- and 10-year mortality.

Kulkarni (2016) published an evaluation of a multicenter prospective single ventricle reconstruction trial to determine outcomes of infant patients with a single ventricle who were listed for transplant after the Norwood procedure.^[30] A public database was used to compare infants while on the waiting list and after transplant. Risk factors were also evaluated for those patients put on the waiting list for a transplant and for those who survived without a transplant. Of 555 patients 33 were listed and underwent transplant. One-year survival after being put on the waiting list, including those that died after transplant was 48%. Diagnosis for being put on the transplant list after the Norwood procedure, included worsening right ventricular function, non-hypoplastic left heart syndrome, and a complex intensive care unit stay. The authors determined patients having heart transplant as a rescue procedure within a year of the Norwood procedure had a higher risk of complications and mortality.

Garberner (2016) published a study that evaluated transplant outcomes for pediatric patients with myocarditis versus dilated cardiomyopathy (DCM).^[31] During the study 137 children with myocarditis and 1,249 children with DCM underwent heart transplant. Data was taken from the Organ Procurement and Transplant Network (OPTN) database. The data for children with myocarditis was evaluated for a higher risk of mortality pre-transplant. The authors noted several study limitations including that they could not confirm data accuracy, but stated after the adjustment for severity of illness, children with myocarditis were not at a higher risk of mortality pre- and post-transplant than patients with DCM.

According to OPTN data, in 2015, 423 heart transplants were performed in children younger than 18 years of age.^[6] Five-year survival rates by age group were: less than one year: 68.6% (95% CI, 62.0% to 75.1%); one to five years: 69.4% (95% CI, 64.1% to 74.7%); six to ten years: 73.1% (95% CI, 66.7% to 79.5%); and 11-17 years: 75.1% (95% CI, 72.6% to 77.5%).

A retrospective analysis of OPTN data focusing on the adolescent population was published by Savia in 2014.^[32] From 1987 to 2011, 99 adolescents (age, 13-18) heart transplants were performed with myocarditis and 456 adolescents with coronary heart disease (CHD). Among adolescent transplant recipients with myocarditis, median graft survival was 6.9 years (95% CI, 5.6 to 9.6 years), which was significantly less than other age groups (i.e., 11.8 years and 12.0 years in younger and older adults, respectively). However, adolescents with CHD had a graft survival rate of 7.4 years (95% CI, 6.8 to 8.6 years), similar to that of other age groups.

According to the International Society for Heart and Lung Transplantation, 532 heart transplants in children younger than 18 years-old were reported worldwide in 2010.^[33] This number compares to 543 reported in 2009. Among the pediatric transplants, about 25% were in infants younger than age one year, 37% were in children between the ages of one and 10 years, and 38% were in adolescents between the ages of 11 to 17 years. In infants, the most common indications for heart transplant were congenital heart disease (56%) and cardiomyopathy (40%). For children older than 10 years of age, the most common indication was cardiomyopathy (63%). Median survival has varied with age of the transplant recipient. Median survival was 19.2 years for infants, 15.6 years for one to 10 year-olds, and 11.9 years for 11-17 year-olds.

In 2011, a retrospective review of pediatric cardiac transplantation patients was published by Auerbach.^[34] A total of 191 patients who underwent primary heart transplantation at a single center in the United States were included; their mean age was 9.7 years (range, 0 to 23.6 years). Overall graft survival was 82% at one year and 68% at five years; the most common causes of graft loss were acute rejection and graft vasculopathy. Overall patient survival was 82% at one year and 72% at five years. In multivariate analysis, the authors found that congenital heart disease (HR: 1.6, 95% CI: 1.02-2.64) and requiring mechanical ventilation at the time of transplantation (HR: 1.6, 95% CI: 1.13-3.10) were both significantly independently associated with an increased risk of graft loss. Renal dysfunction was a significant risk factor in univariate analysis but was not included in the multivariate model due to the small study group. Limitations of the study include that it was retrospective and conducted in only one center.

Patel (2010) presented a retrospective review of echocardiography and serum markers as a predictor of death or need for transplantation in newborns, children, and young adults with heart failure.^[35] A total of 99 children with 139 admissions were evaluated on LVEF and tricuspid regurgitation, as well as on various serum markers for their predictive ability of death or need for transplantation in a stepwise multivariate Cox regression model. While brain natriuretic peptide (BNP) and tricuspid regurgitation were not predictive of need for transplantation, ejection fraction and lymphocytosis were predictive (ejection fraction odds ratio [OR]: 0.94, 95% CI: 0.90-0.98; for lymphocytosis, OR 5.40, 95% CI: 1.67–17.4). Serum levels of creatinine and sodium were also predictive. Clinical prediction rules based on these findings have not been compared to current strategies and await clinical validation.

Noting that children listed for heart transplantation have the highest waiting list mortality of all solid organ transplant patients, Almond analyzed data from the U.S. Scientific Registry of Transplant Recipients to determine if the pediatric heart allocation system, as revised in 1999, prioritizes patients optimally and to identify high-risk populations that may benefit from pediatric cardiac assist devices.^[36] Of 3,098 children (younger than 18 years of age) listed between 1999 and 2006, a total of 1,874 (60%) were listed as Status 1A. Of those, 30% were placed on ventilation and 18% were receiving extracorporeal membrane oxygenation. Overall, 533 (17%) died, 1,943 (63%) received transplants, 252 (8%) recovered, and 370 (12%) remained listed. The authors found that Status 1A patients are a heterogeneous population with large variation in mortality based on patient-specific factors. Predictors of waiting list mortality included extracorporeal membrane oxygenation support (hazard ratio [HR]: 3.1), ventilator support (HR: 1.9), listing status 1A (HR: 2.2), congenital heart disease (HR: 2.2), dialysis support (HR: 1.9), and non-white race/ethnicity (HR: 1.7). The authors concluded that the pediatric heart allocation system captures medical urgency poorly, specific high-risk subgroups can be identified, and further research is needed to better define the optimal organ allocation system for pediatric heart transplantation.

HEART RETRANSPLANTATION

An analysis of OPTN data from 2008 to 2015 reported that 724 retransplants were performed (of 18,676 heart transplants, 3.9% of all transplants). Kaplan-Meier patient survival rates at 1, 3, and 5 years were lower among the retransplant recipients compared with primary transplant recipients.^[5] An analysis of OPTN data from 1995 to 2012 reported that 987 retransplants were performed (of 28,464 heart transplants, 3.5% of all transplants).^[37] Median survival among retransplant recipients was 8 years. The estimated survival at 1, 5, 10, and 15 years following retransplant was 80%, 64%, 47% and 30%, respectively. Compared with primary transplant

recipients, retransplant patients had a somewhat higher risk of death (risk ratio [RR]=1.27, 95% CI, 1.13 to 1.42).

A number of studies have reviewed clinical experience with heart retransplantation in adults. In 2013, Saito published a retrospective review of data on 593 heart transplants performed at their institution; 22 of these (4%) were repeat transplantations.^[38] The mean interval between initial and repeat transplant was 5.1 years. The indications for a repeat transplant were acute rejection in seven patients (32%), graft vascular disease in 10 patients (45%), and primary graft failure in five patients (23%). Thirty-day mortality after cardiac retransplantation was 32% (7 of 22 patients). Among patients who survived the first 30 days (n=15), 1-, 5- and 10-year survival rates were 93.3%, 79% and 59%, respectively. Comparable survival rates for patients undergoing primary cardiac transplants at the same institution (n=448) were 93%, 82% and 63%, respectively. An interval of one year or less between the primary and repeat transplantation significantly increased the risk of mortality. Three of nine patients (33.3%) with less than a year between the primary and retransplantation survived to 30 days. In comparison 12 of 13 patents (92%) with at least one year between primary and retransplantation were alive at 30 days after surgery.

Tjang (2008) published a systematic review of this literature that identified 22 studies reporting clinical outcomes of heart retransplantation in patients over 18 years old.^[39] The most common indications for retransplantation were cardiac allograft vasculopathy (55%), acute rejection (19%) and primary graft failure (17%). The early mortality rate in individual studies was 16% (range: 5% to 38%). Some of the factors associated with poorer outcome after retransplantation were shorter transplant interval, refractory acute rejection, primary graft failure and an initial diagnosis of ischemic cardiomyopathy.

Topkara (2005) reviewed data on 766 adult patients who underwent heart transplantation between 1992 and 2002.^[40] Forty-one (5%) of patients underwent repeat transplants; the indication for retransplantation was transplant-related coronary artery disease in 37 of 41 (90%) of these patients. Due to early experience with retransplantation, criteria at this institution were changed in 1993 so that patients with intractable acute rejection within 6 months of the initial transplant were ineligible for repeat transplants. One and five-year survival rates were 85.1% and 72.9%, respectively after primary transplantation and 72.2% and 47.5%, respectively after retransplantation. Survival rates were significantly lower in the retransplantation group, $p < 0.001$. The authors did not report survival rates stratified by the length of time between initial and repeat transplantations.

Pediatric Considerations

As with initial heart transplants, children waiting for heart retransplantation have high waitlist mortality. Alsoufi (2015) published results from a retrospective analysis (1988 to 2013) that examined their experience with heart transplantations in pediatric patients with underlying congenital heart disease.^[41] The study included sixteen patients who underwent primary heart transplantation. Participants were predominately male, and had a median age of 3.8 years. Competing risks analysis showed that at 10 years after heart transplantation, 13% of patients had undergone retransplantation, 43% of patients had died without retransplantation, and 44% of patients were alive without retransplantation. After retransplantation, 52% of patients were alive and 18% of patients had undergone a second retransplantation. Overall 15-year survival after initial heart transplantation was 41%. It is important to note this study has methodological

considerations, which include but are not limited to, a small sample size; therefore, generalizability of results is limited.

Bock (2014) evaluated data on 632 pediatric patients who were listed for a heart retransplant at least one year (median, 7.3 years) after the primary transplant.^[42] Patients' median age was four years at the time of the primary transplant and 14 years when they were relisted. Median waiting time was 75.3 days and mortality was 25.2% (159 of 632). However, waitlist mortality decreased significantly after 2006 (31% before 2006 and 17% after 2006, $p < 0.01$).

Copeland (2014) published results from a retrospective chart review ($n=183$) and evaluated late survival among pediatric heart transplant patients, living for more than 15 years after transplant.^[43] A total of 32 deaths were reported due to the following conditions: cardiac allograft vasculopathy (CAV); 11 (34.3%); posttransplant lymphoproliferative disease, 18.8%; acute rejection, 12.5%; sepsis, 6.3%; multiorgan failure, 3.1%; and unknown reasons, 25%. A total of 30 patients required cardiac retransplantation due to CAV. The authors concluded that heart transplantation in pediatric patients results in acceptable long-term survival. In patients who develop CAV and renal dysfunction, heart retransplantation is an acceptable form of palliative treatment.

Friedland-Little (2014) published results from a retrospective analysis (1985-2011) of pediatric and young adult survivors who had undergone repeat heart transplantations.^[44] Patients were included in the review who had a primary heart transplant before the age of 21, and had undergone a third transplant. Patients were matched 1:3 with a control group of second heart transplant patients by age, era and re-transplant indication. The authors found no difference between third heart transplant patients ($n=27$) and the control second heart transplantation patients ($n=79$) with respect to survival (76% vs 80% at one year, 62% vs 58% at five years and 53% vs 34% at 10 years, $p = 0.75$). However, generalizability of the study's results may be limited due to methodological limitations, such as small sample size.

Mahle (2005) reviewed data from the United Network for Organ Sharing (UNOS) on heart retransplantation in patients less than 18 years old.^[45] A total of 219 retransplantations occurring 1987 to 2004 were identified. The median age at initial transplant was 3 years old and the median age at retransplantation was nine years old. The median interval between initial procedure and retransplantation was 4.7 years. The most common indications for retransplantation were coronary allograft vasculopathy ($n=111$, 51%), non-specific graft failure ($n=34$, 18%) and acute rejection ($n=19$, 9%). Retransplantation was associated with worse overall survival than initial transplantation. One and five and ten year survival rates were 83%, 70% and 58%, respectively after primary transplantation and 79%, 53% and 44%, respectively after retransplantation. The most common causes of death after retransplantation were acute rejection (14%), coronary allograft vasculopathy (14%) and infections (13%).

In both the adult and pediatric studies, poorer survival after retransplantation than initial transplantation is not surprising given that patients undergoing retransplantation experienced additional clinical disease or adverse events. The increased mortality from retransplantation appears to be mainly from increased short-term mortality. Longer-term survival rates after retransplantation seem reasonable, especially when patients with a higher risk of poor outcomes (e.g., those with a shorter interval between primary and repeat transplantation) are excluded. Also, patients with failed initial transplant have no other options besides a retransplantation.

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.

Pretransplant malignancy is considered a relative contraindication for heart transplantation considering this has the potential to reduce life expectancy and could prohibit immune suppression after transplantation. However, with improved cancer survival over the years and use of cardiotoxic chemotherapy and radiotherapy, the need for heart transplantation has increased in this population,

Mistiaen (2015) conducted a systematic review to study the posttransplant outcome of pretransplant malignancy patients.^[46] Most selected studies were small case series. Mean patient age varied from 6 years to 52 years. Hematologic malignancy and breast cancer were the most common type of pretransplant malignancies. Dilated, congestive, or idiopathic cardiomyopathy was mostly the common reason for transplantation in 4 case series, chemotherapy related cardiomyopathy was the most important reason for transplantation in the other series. Hospital mortality varied between 0% and 33%, with small sample size potentially explaining the observed variation, One large series reported similar short-term and long-term posttransplant survival of chemotherapy related (N=232) and other nonischemic cardiomyopathy (N=8890) patients. The 1-, 3-, and 5-year survival rates of were 86%, 79%, and 71% for patients with chemotherapy-related cardiomyopathy compared with 87%, 81%, and 74% for other transplant patients. Similar findings were observed for 1-year survival in smaller series. Two-, 5-, and 10-year survival rates among pretransplant malignancy patients were also comparable with other transplant patients. In addition to the nonmalignancy related factors such as cardiac, pulmonary, and renal dysfunction, two malignancy related factors were identified as independent predictors of 5-year survival. Malignancy-free interval (the interval between treatment of cancer and heart transplantation) of less than 1 year was associated with lower 5-year survival compared with a longer interval (<60% vs >75%). Patients with prior hematologic malignancies had an increased posttransplant mortality in three small series. 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.

Yoosabai (2015) conducted a retrospective review among 23,171 heart transplant recipient in the OPTN/UNOS database to identify whether pretransplant malignancy increases the risk of posttransplant malignancy.^[47] 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 [SHR], 1.51; $p < 0.01$), skin (SHR=1.55, $p < 0.01$), and solid organ malignancies (SHR=1.54, $p < 0.01$) on multivariate analysis.

ISHLT guidelines have recommended to stratify 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 work-up. The guideline also recommended that the specific amount of time to wait to transplant after neoplasm remission will depend on these factors and no arbitrary time period for observation should be used.

HIV

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. However, there is little data directly comparing outcomes for patients with heart transplants with and without HIV.

As of February 2013, the United Network for Organ Sharing (UNOS) policy on HIV-positive transplant candidates states: "A potential candidate for organ transplantation whose test for HIV is positive should not be excluded from candidacy for organ transplantation unless there is a documented contraindication to transplantation based on local policy." (Policy 4, Identification of Transmissible Diseases in Organ Recipients).^[48]

OLDER AGE

Cooper (2016) published a retrospective cohort study evaluating transplant outcomes in elderly patients, by using data from the United Network for Organ Sharing database. Data on three groups of patients 18-59, 60-69 and greater than or equal to 70 years of age were compared for five-year survival rates. The authors noted that patients greater than or equal to 70 had more ischemia and renal dysfunction than the 60-69 age group and received transplants from older donors who were more ill or had a history of drug abuse. Five-year survival rates were 26.9% for the 18-59 age group, 29.3% for the 60-69 age group, and 30.8% for the greater than or equal to 70 age group. The authors also noted limitations with this retrospective review including but not limited to potential risk of bias with patient transplant selection and quality of the data. The authors concluded the greater than or equal to 70 age group showed no significant difference in outcomes from the 60-69 age group and should not be excluded from receiving a transplant.

Kilic (2012) analyzed data from the UNOS on 5,330 patients age 60 and older (mean age 63.7 years) who underwent heart transplantation between 1995 and 2004.^[49] A total of 3,492 individuals (65.5%) survived to five years. In multivariate analysis, statistically significant predictors of five year survival included younger age (OR: 0.97, 95% CI: 0.95 to 1.00), younger donor age (OR: 0.99, 95% CI: 0.99-1.00), white race (OR: 1.23, 95% CI: 1.02 to 1.49), shorter ischemic time (OR: 0.93, 95% CI: 0.87-0.99), and lower serum creatinine (OR: 0.92, 95% CI: 0.87 to 0.98). In addition, hypertension, diabetes, and mechanical ventilation each significantly decreased the odds of surviving to five years. Patients with two or more of these factors had a 12% lower rate of five years survival than those with none of them.

Daneshvar (2011) examined data on 519 patients who underwent heart transplantation between 1988 and 2009 at a single institution, with a particular focus on survival differences by age group.^[50] There were 37 patients who were at least 70 years-old (group 1), 206 patients between 60 and 69 years (group 2), and 276 patients younger than 60 years (group 3). Median survival was 10.9 years in group one, 9.1 years in group two, and 12.2 years in group three (non-significant difference among groups). The five-year survival rate was 83.2% in group one, 73.8% in group two, and 74.7% in group three.

PULMONARY HYPERTENSION

Findings of several studies published in 2012 and 2013 suggested that patients with pulmonary hypertension who successfully undergo treatment can subsequently have good outcomes after heart transplant.^[51-54] For example, De Santo reported on 31 consecutive patients who had been diagnosed with unresponsive pulmonary hypertension at baseline right heart catheterization.^[51] After 12 weeks of treatment with oral sildenafil, right heart catheterization showed reversibility of pulmonary hypertension, allowing listing for heart transplant. Oral sildenafil treatment resumed following transplant. One patient died in the hospital. A right heart catheterization at three months post-transplant showed normalization of the pulmonary hemodynamic profile, thereby allowing weaning from sildenafil in the 30 patients who survived hospitalization. The reversal of pulmonary hypertension was confirmed at one year in the 29 surviving patients. Similarly, in a study by Perez-Villa and colleagues, 22 patients considered high-risk for heart transplant due to severe pulmonary hypertension were treated with bosentan. After four months of treatment, mean pulmonary vascular resistance (PVR) decreased from 5.6 to 3.4 Wood units. In a similar group of nine patients who refused participation in the study and served as controls, mean PVR during this time increased from 4.6 to 5.5 Wood units. After bosentan therapy, 14 patients underwent heart transplantation and the one-year survival rate was 93%.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF CARDIOLOGY, AND AMERICAN HEART ASSOCIATION

The accepted indications, probable indications, and contraindications for heart transplantation listed in the policy section of this policy reflect the 2005 update of the American College of Cardiology (ACC) and the American Heart Association (AHA) joint statement on diagnosis and management of chronic heart failure in the adult. They are unchanged in the 2009 update of the ACC/AHA statement.^[1]

Adult Patients

- I. Accepted Indications for Transplantation
 1. Hemodynamic compromise due to heart failure demonstrated by any of the following three bulleted items,
 - Maximal VO_2 (oxygen consumption) <10 mL/kg/min with achievement of anaerobic metabolism
 - Refractory cardiogenic shock
 - Documented dependence on intravenous inotropic support to maintain adequate organ perfusion,
 - or
 2. Severe ischemia consistently limiting routine activity not amenable to bypass surgery or angioplasty, or
 3. Recurrent symptomatic ventricular arrhythmias refractory to ALL accepted therapeutic modalities.
- II. Probable Indications for Cardiac Transplantation
 1. Maximal VO_2 <14 mL/kg/min and major limitation of the patient's activities, or
 2. Recurrent unstable ischemia not amenable to bypass surgery or angioplasty, or
 3. Instability of fluid balance/renal function not due to patient noncompliance with regimen of weight monitoring, flexible use of diuretic drugs, and salt restriction

III. The following conditions are inadequate indications for transplantation unless other factors as listed above are present.

1. Ejection fraction <20%
2. History of functional class III or IV symptoms of heart failure
3. Previous ventricular arrhythmias
4. Maximal $\dot{V}O_2 >15$ mL/kg/min

Pediatric Patients

1. Patients with heart failure with persistent symptoms at rest who require one or more of the following:
 - Continuous infusion of intravenous inotropic agents, or
 - Mechanical ventilatory support, or
 - Mechanical circulatory support.
2. Patients with pediatric heart disease with symptoms of heart failure who do not meet the above criteria but who have:
 - Severe limitation of exercise and activity (if measurable, such patients would have a peak maximum oxygen consumption <50% predicted for age and sex); or
 - Cardiomyopathies or previously repaired or palliated congenital heart disease and significant growth failure attributable to the heart disease; or
 - Near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator; or
 - Restrictive cardiomyopathy with reactive pulmonary hypertension; or
 - Reactive pulmonary hypertension and potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future; or
 - Anatomical and physiological conditions likely to worsen the natural history of congenital heart disease in infants with a functional single ventricle; or
 - Anatomical and physiological conditions that may lead to consideration for heart transplantation without systemic ventricular dysfunction.

INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

In 2016, The International Society for Heart and Lung Transplantation (ISHLT) updated their heart transplantation criteria in and made the following updates to their recommendations:^[55]

- 1.2 Use of heart failure prognosis scores. Heart failure prognosis scores should be performed along with cardiopulmonary exercise test to determine prognosis and guide listing for transplantation for ambulatory patients. An estimated one year survival as calculated by the Seattle Heart Failure Model (SHFM) of <80% or a Heart Failure Survival Score (HFSS) in the high/medium risk range should be considered as reasonable cut points for listing (Level of Evidence: C; primarily expert consensus opinion).
- 1.4.1 Age, obesity, and cancer as comorbidities and their implications for heart transplantation list.
 - Carefully selected patients >80 years of age may be considered for cardiac transplantation (Level of Evidence: C).
 - Pre-transplantation body mass index (BMI) >35kg/m² is associated with a worse outcome after cardiac transplantation. For such obese patients, it is reasonable

- to recommend weight loss to achieve a BMI of $\leq 35\text{kg/m}^2$ before listing for cardiac transplantation (Level of Evidence: C).
- 1.4.2 Diabetes, Renal dysfunction, and peripheral vascular disease.
 - Diabetes with end-stage damage or persistent poor glycemic control (glycosylated hemoglobin $>7.5\%$ or 58 mmol/mol) despite optimal effort is a relative contraindication for transplant (Level of Evidence: C).
 - Renal function should be assessed using estimated glomerular filtration rate (eGFR) or creatinine clearance under optimal medical therapy. It is reasonable to consider the presence of irreversible renal dysfunction (eGRF $<30\text{ ml/min1.73m}^2$) as a relative contraindication for heart transplantation alone (Level of Evidence: C).
 - Clinically severe symptomatic cerebrovascular disease may be considered a contraindication to transplantation when its presence limits rehabilitation and revascularization is not a viable option (Level of Evidence: C).
 - 1.5.3 Psychosocial evaluation. Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting may be regarded as having a relative contraindication to transplant. The benefit of heart transplantation in patients with severe cognitive-behavioral disabilities or dementia has not been established, has the potential for harm, and therefore, heart transplantation cannot be recommended for this sub-group of patients (Level of Evidence: C).
 - 1.8 Retransplantation. Retransplantation is indicated for those patients who develop significant CAV with refractory cardiac allograft dysfunction, without evidence of ongoing rejection (Level of Evidence: C).

THE AMERICAN HEART ASSOCIATION

The American Heart Association (AHA) Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group stated in 2007 that, based on level B (non-randomized studies) or level C (consensus opinion of experts), heart transplantation is indicated for pediatric patients as therapy for the following indications:^[56]

- Stage D heart failure (interpreted as abnormal cardiac structure and/or function, continuous infusion of intravenous inotropes, or prostaglandin E1 to maintain patency of a ductus arteriosus, mechanical ventilatory and/or mechanical circulatory support) associated with systemic ventricular dysfunction in patients with cardiomyopathies or previously repaired or palliated congenital heart disease,
- Stage C heart failure (interpreted as abnormal cardiac structure and/or function and past or present symptoms of heart failure) associated with pediatric heart disease and severe limitation of exercise and activity, in patients with cardiomyopathies or previously repaired or palliated congenital heart disease and heart failure associated with significant growth failure attributed to heart disease, pediatric heart disease with associated near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator, or in pediatric restrictive cardiomyopathy disease associated with reactive pulmonary hypertension,
- The guideline states that heart transplantation is feasible in the presence of other indications for heart transplantation, in patients with pediatric heart disease and an elevated pulmonary vascular resistance index $>6\text{ Woods units/m}^2$ and/or a transpulmonary pressure gradient $>15\text{ mm Hg}$ if administration of inotropic support or

pulmonary vasodilators can decrease pulmonary vascular resistance to <6 Woods units/m² or the transpulmonary gradient to <15 mm Hg.

SUMMARY

There is enough research to show that heart transplantation can improve survival for certain pediatric and adult patients. Guidelines based on research recommend heart transplant for people with certain indications. Therefore, heart transplant may be considered medically necessary in patients who meet the policy criteria.

There is enough research to show that heart retransplantation can improve survival for certain pediatric and adult patients who have had a prior transplant. Guidelines based on research recommend heart retransplantation for people with certain indications. Therefore, heart retransplantation may be considered medically necessary in patients who meet the policy criteria.

There is not enough research to show that heart transplantation or retransplantation improves health outcomes for all other indications. Therefore, heart transplantation or retransplantation is considered not medically necessary for indications when the policy criteria are not met.

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CODES

Codes	Number	Description
CPT	33940	Donor cardiectomy (including cold preservation)
	33944	Backbench standard preparation of donor cadaver heart allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, pulmonary artery, and left atrium for implantation
	33945	Heart transplant, with or without recipient cardiectomy
HCPCS	None	

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