Heart Transplant

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.

Background

In the United States, approximately 5.8 million people have heart failure and 300,000 die each year from this condition. (1) 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 due to 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 2005 to 2010, the primary causes of heart failure in patients undergoing transplant operations were non-ischemic cardiomyopathy (53%) and ischemic cardiomyopathy (38%). Approximately 3% of the heart transplants during this time period were in adults with congenital heart disease. (2)

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. In 2012, 2,378 heart transplants were performed in the U.S. There were 3,648 patients on the waiting list as of November 11, 2013. (2) 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. The chronic shortage of donor hearts has led to the prioritization of patients awaiting transplantation to ensure greater access for individuals most likely to derive benefit. (Prioritization criteria are issued by the United Network for Organ Sharing [UNOS] and are described in the Policy Guidelines).

From 2005 to 2010, approximately 3% of heart transplants were repeat transplantations. (2) Heart retransplantation raises ethical issues due to the lack of sufficient donor hearts for initial transplants. UNOS does not have separate organ allocation criteria for repeat heart transplant recipients.

Related Policies

2.01.68 Laboratory Tests for Heart Transplant Rejection
Human heart transplantation may be considered medically necessary for selected adults and children with end-stage heart failure when patient selection criteria are met.

**Adult Patients**

I. Accepted Indications for Transplantation

1. Hemodynamic compromise due to heart failure demonstrated by any of the following 3 bulleted items:
   - Maximal V02 (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;

2. Severe ischemia consistently limiting routine activity not amenable to bypass surgery or angioplasty;

3. Recurrent symptomatic ventricular arrhythmias refractory to ALL accepted therapeutic modalities.

Or,

II. Probable Indications for Cardiac Transplantation:

1. Maximal VO2 <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 insufficient 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 VO2 >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.

Heart retransplantation after a failed primary heart transplant may be considered **medically necessary** in adult or pediatric patients who meet criteria for heart transplantation.

Heart transplantation is considered **investigational** in all other situations.

**Policy Guidelines**

Potential contraindications, subject to the judgment of the transplant center:

1. Known current malignancy, including metastatic cancer.
2. Recent malignancy with high risk of recurrence.
3. Untreated systemic infection making immunosuppression unsafe, including chronic infection.
4. Other irreversible end-stage disease not attributed to heart or lung disease.
6. Systemic disease that could be exacerbated by immunosuppression.
7. Psychosocial conditions or chemical dependency affecting ability to adhere to therapy.
Policy specific potential contraindications

1. Pulmonary hypertension that is fixed as evidenced by pulmonary vascular resistance (PVR) greater than 5 Woods units, or trans-pulmonary gradient (TPG) greater than or equal to 16 mm/Hg despite treatment*

2. Severe pulmonary disease despite optimal medical therapy, not expected to improve with heart transplantation*

*Some patients may be candidates for combined heart-lung transplantation (see policy No.7.03.08).

Patients must meet the United Network for Organ Sharing (UNOS) guidelines for 1A, 1B, or 2 Status and not currently be Status 7.

Transplantation may now be considered appropriate in HIV (human immunodeficiency virus)-infected patients, who meet specific criteria, related to viral suppression, immune reconstitution.

Cardiac Specific

The United Network for Organ Sharing (UNOS) prioritizes donor thoracic organs according to the severity of illness, with those patients who are most severely ill (status 1A) given highest priority in allocation of the available organ as follows (3):

Adult Patients (18 years of age or older)

Status 1A

A patient is admitted to the listing transplant center hospital and has at least one of the following devices or therapies in place:

a. Mechanical circulatory support for acute hemodynamic decompensation that includes at least one of the following:
   1. Left and/or right ventricular assist device implanted;
   2. Total artificial heart;
   3. Intra-aortic balloon pump; or
   4. Extracorporeal membrane oxygenator (ECMO)

b. Mechanical circulatory support.

c. Continuous mechanical ventilation.

d. Continuous infusion of inotropes and continuous monitoring of left ventricular filling pressures.

e. If criteria a, b, c, and d are not met, such status can be obtained by application to the applicable Regional Review Board.

Status 1B

A patient has at least one of the following devices or therapies in place:
A patient who does not meet Status 1A or 1B is listed as Status 2 by application to the applicable Regional Review Board.

**Pediatric Patients**

A candidate listed as *Status 1A* meets at least one of the following criteria:

- Requires assistance with a ventilator;
- Requires assistance with a mechanical assist device (e.g., ECMO);
- Requires assistance with a balloon pump;
- A candidate younger than 6 months-old with congenital or acquired heart disease exhibiting reactive pulmonary hypertension at greater than 50% of systemic level. Such a candidate may be treated with prostaglandin E (PGE) to maintain patency of the ductus arteriosus;
- Requires infusion of high dose or multiple inotropes; or

A candidate who does not meet the criteria specified in a, b, c, d, or e may be listed as *Status 1A* if the candidate has a life expectancy without a heart transplant of less than 14 days, such as due to refractory arrhythmia.

A candidate listed as *Status 1B* meets at least one of the following criteria:

- Requires infusion of low dose single inotropes;
- Younger than 6 months-old and does not meet the criteria for Status 1A; or
- Growth failure, i.e., greater than 5th percentile for weight and/or height, or loss of 1.5 standard deviations of expected growth (height or weight) based on the National Center for Health Statistics for pediatric growth curves.

A candidate who does not meet the criteria for *Status 1A or 1B* is listed as Status 2.

Note: Pediatric heart transplant candidates who remain on the waiting list at the time of their 18th birthday without receiving a transplant continue to qualify for medical urgency status based upon the pediatric criteria.

**Status 7** patients are considered temporarily unsuitable to receive a thoracic organ transplant.

**Rationale**

**Literature Review**

Due to the nature of the population, there are no randomized controlled trials (RCTs) comparing heart transplantation with alternatives, including ventricular assist devices. Reviews are based on case series
and registry data. RCTs have been published on related topics e.g., comparing surgical technique, infection prophylaxis regimens, or immunosuppressive therapy but are not germane to this policy. The following is a summary of evidence based on registry and case series data.

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 candidate 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. In 2007, Lietz and Miller reported on patient survival on the heart transplant waiting list, comparing the era between 1990 and 1994 to the era of 2000 to 2005. (4) 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.

In 2010, Johnson and colleagues reported on waiting list trends in the U.S. between 1999 and 2008. (5) 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.

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. (6) 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. (7) 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. (8-11) 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 (12) introduced the model using multivariate analysis of data.
from the PRAISE1 heart failure trial (n=1,125). Applied to the data of 5 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 (13-15) but with a noted underestimation of mortality risk, particularly in blacks and device recipients. (16, 17) None of these models has been universally adopted by transplant centers.

Initial Heart Transplant

Survival

According to the OPTN using available U.S. data as of September 27, 2013, the 1-year survival rate after heart transplant was 88.0% for males and 86.2% for females. (18) Three-year survival rates were 79.3% for males and 77.2% for females and 5-year survival rates were 73.2% for females and 69.0% for males.

Several studies have analyzed factors associated with survival in heart transplant patients. For example, a 2012 study by Kalic and colleagues analyzed prospectively collected data from the United Network for Organ Sharing (UNOS) registry. (19) 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 9 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).

A 2013 study examined characteristics of patients who survived longer than 20 years after heart transplantation at a single center in Spain. (20) Thirty-nine heart transplant recipients who survived over 20 years post-transplant were compared to 98 patients who died between 1 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).

Pediatric Considerations

According to OPTN data, in 2013, 193 heart transplants were performed in children younger than 18 years. (3) Five-year survival rates by age group were less than 1 year: 71.7% (95% CI, 66.3% to 77.1%); 1 to 5 years: 74.6% (95% CI, 68.6% to 80.6%); 6 to 10 years: 77.3% (95% CI, 70.2% to 84.5%); and 11 to 17 years: 72.1% (95% CI, 67.1% to 77.1%).

A retrospective analysis of OPTN data focusing on the adolescent population was published by Savia et al in 2014. (21) From 1987 to 2011, heart transplants were performed in 99 adolescents (age, 13-18 years) 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.

In 2010, the International Society for Heart and Lung Transplantation (ISHLT), 532 heart transplants in children younger than 18 years of age were reported worldwide in 2010. (22) 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 1- to 10-year-olds, and 11.9 years for 11- to 17-year-olds.

Noting that children listed for heart transplantation have the highest waiting list mortality of all solid organ transplant patients, Almond et al 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. (23) Of 3098 children (<18 years of age) listed between 1999 and 2006, a total of 1874 (60%) were listed as Status 1A. Of those, 30% were placed on ventilation and 18% were receiving extracorporeal membrane oxygenation. Overall, 533 (17%) died, 1943 (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 nonwhite 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.

A retrospective review of pediatric cardiac transplantation patients was published by Auerbach et al in 2011. (24) 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, 0-23.6 years). Overall graft survival was 82% at 1 year and 68% at 5 years; the most common causes of graft loss were acute rejection and graft vasculopathy. Overall, patient survival was 82% at 1 year and 72% at 5 years. In multivariate analysis, the authors found that congenital heart disease (HR=1.6; 95% CI, 1.02 to 2.64) and requiring mechanical ventilation at the time of transplantation (HR=1.6; 95% CI, 1.13 to 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 1 center.
Heart Retransplantation

Survival

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). (25) 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 2008, Tjang et al published a systematic review of the literature on clinical experience with adult heart retransplantation that identified 22 studies. (26) 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%-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.

A recent representative study was published in 2013 by Saito et al. (27) This was a retrospective review of data on 593 heart transplants performed at their institution, 22 of which (4%) were retransplants. The mean interval between initial and repeat transplant was 5.1 years. The indications for a repeat transplant were acute rejection in 7 patients (32%), graft vascular disease in 10 patients (45%), and primary graft failure in 5 patients (23%). Thirty-day mortality after cardiac retransplantation was 32% (7/22 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 1 year or less between the primary and repeat transplantation significantly increased the risk of mortality. Three of 9 patients (33.3%) with less than 1 year between the primary and retransplantation survived to 30 days. In comparison, 12 of 13 patents (92%) with at least 1 year between primary and retransplantation were alive at 30 days after surgery.

Pediatric Considerations

As with initial heart transplants, children waiting heart retransplantation have high waitlist mortality. A 2014 study by Bock et al evaluated data on 632 pediatric patients who were listed for a heart retransplant at least 1 year (median, 7.3 years) after the primary transplant. (28) Patients’ median age was 4 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% (159/632). However, waitlist mortality decreased significantly after 2006 (31% before 2006 and 17% after 2006, p<0.01).

Previously, in 2005, Mahle et al reviewed data on heart retransplants in the pediatric population, using UNOS data. (29) A total of 219 retransplantations occurring between 1987 and 2004 were identified. The median age at initial transplant was 3 years old, and the median age at retransplantation was 9 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%]), nonspecific graft failure (n=34 [18%]) and acute rejection (n=19 [9%]). Retransplantation was
associated with worse overall survival than initial transplantation. One- 5-, and 10-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 infection (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 to Heart Transplant**

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. (30) In fact, carcinogenesis, primarily skin cancers, is 2 to 4 times more common in heart transplant patients, likely due to the higher doses of immunosuppression necessary for the prevention of allograft rejection. (31) The incidence of *de novo* cancer in heart transplant patients approaches 26% at 8 years post-transplant. 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. (32, 33) 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 heart failure patients may not have another option. A small study (n=33) of survivors of lymphoproliferative cancers who subsequently received cardiac transplant had 1-, 5-, and 10-year survival rates of 77%, 64%, and 50%, respectively. (34) By comparison, overall 1-, 5-, and 10-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 has been controversial, due to the long-term prognosis for HIV positivity and the impact of immunosuppression on HIV disease. Although HIV-positive transplant recipients may be a research interest of some transplant centers, the minimal data regarding long-term outcome in these patients consist primarily of case reports and abstract presentations of liver and kidney recipients. Nevertheless, some transplant surgeons would argue that HIV positivity is no longer an absolute contraindication to transplant due to the advent of highly active antiretroviral therapy (HAART), which has markedly changed the natural history of the disease.

As of February 2013, the OPTN 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). (35)

In 2006, the British HIV Association and the British Transplantation Society Standards Committee published guidelines for kidney transplantation in patients with HIV disease. (36) These criteria may be extrapolated to other organs:

- CD4 count greater than 200 cells/mL for at least 6 months
- Undetectable HIV viremia (less than 50 HIV-1 RNA copies/mL) for at least 6 months
- Demonstrable adherence and a stable HAART regimen for at least 6 months
- Absence of AIDS-defining illness following successful immune reconstitution after HAART.

**Older age**

A 2011 study by Daneshvar and colleagues 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. (37) 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 1, 9.1 years in group 2, and 12.2 years in group 3 (non-significant difference among groups). The 5-year survival rate was 83.2% in group 1, 73.8% in group 2, and 74.7% in group 3.

In 2012, Kilic and colleagues 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. (38) A total of 3,492 individuals (65.5%) survived to 5 years. In multivariate analysis, statistically significant predictors of 5-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 5 years. Patients with 2 or more of these factors had a 12% lower rate of 5-years survival than those with none of them.
Pulmonary Hypertension

Findings of several studies published in 2012 and 2013 suggest that patients with pulmonary hypertension who successfully undergo treatment can subsequently have good outcomes after heart transplant. (39-42) For example, De Santo and colleagues reported on 31 consecutive patients who had been diagnosed with unresponsive pulmonary hypertension at baseline right heart catheterization. (39) 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 3 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 1 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. (40) After 4 months of treatment, mean pulmonary vascular resistance (PVR) decreased from 5.6 to 3.4 Wood units. In a similar group of 9 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 1-year survival rate was 93%.

Practice Guidelines and Position Statements

The accepted indications, probable indications, and contraindications for heart transplantation listed in the policy and guideline sections of this policy reflect the 2005 update of the ACC/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. (6)

The International Society for Heart and Lung Transplantation (ISHLT) in the 2006 Listing Criteria for Heart Transplantation (43) include guidelines regarding:

- Diastolic dysfunction that is refractory to optimal medical/surgical management because they are at high risk of developing pulmonary hypertension and of sudden death (based on level of evidence B [a single randomized trial or multiple nonrandomized trials]).
- Advanced systemic right ventricular failure (Heart Failure Stage C described as patients with underlying structural or functional heart disease and past or current symptoms of heart failure) that is refractory to medical therapy (level of evidence C [primarily expert consensus opinion]).

ISHLT’s 2006 Guidelines for the Care of Cardiac Transplant Candidates included the following statements on potential contraindications to heart transplantation (44):

- “Patients should be considered for cardiac transplantation if they are ≤70 years of age.”
- “Carefully selected patients >70 years of age may be considered for cardiac transplantation.”
- For patients with preexisting neoplasms, “cardiac transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy and negative metastatic workup.”
- For obese patients, “it is reasonable to recommend weight loss to achieve a BMI of <30 kg/m2 or percent BMI of <140% of target before listing for cardiac transplantation.”
• “Diabetes with end-organ damage other than nonproliferative retinopathy or poor glycemic control (glycosylated hemoglobin [HbA1C] >7.5) despite optimal effort is a relative contraindication for transplant.”
• “It is reasonable to consider the presence of irreversible renal dysfunction (eGFR <40 mL/min) as a relative contraindication for heart transplantation alone.”
• “Peripheral vascular disease may be considered as a relative contraindication for transplantation when its presence limits rehabilitation and re-vascularization is not a viable option.”
• “It is reasonable to consider active tobacco smoking as a relative contraindication to transplantation. Active tobacco smoking during the previous 6 months is a risk factor for poor outcomes after transplantation.”
• “A structured rehabilitative program may be considered for patients with a recent (24 months) history of alcohol abuse if transplantation is being considered.... Patients who remain active substance abusers (including alcohol) should not receive heart transplantation.”
• “Mental retardation or dementia may be regarded as a relative contraindication to transplantation.” (Level of Evidence: C).
• “Patients who have demonstrated an inability to comply with drug therapy on multiple occasions should not receive transplantation.”

The 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 (45):

• 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:
  o systemic ventricular dysfunction in patients with cardiomyopathies or
  o previous 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) in pediatric heart disease associated with:
  o severe limitation of exercise and activity (peak maximum oxygen consumption <50% predicted); or
  o systemic ventricular dysfunction in pediatric patients with cardiomyopathies or previously repaired or palliated congenital heart disease when heart failure is associated with significant growth failure attributed to heart disease
  o near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator
  o pediatric restrictive cardiomyopathy disease associated with reactive pulmonary hypertension; or
pediatric heart disease and an elevated pulmonary vascular resistance index >6 Woods units/m2 and/or a transpulmonary pressure gradient >15 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.

The 2010 guidelines from the ISHLT include the following recommendations on cardiac Retransplantation (46):

- “Retransplantation is indicated in children with at least moderate systolic heart allograft dysfunction and/or severe diastolic dysfunction and at least moderate CAV (cardiac allograft vasculopathy).”
- “It is reasonable to consider listing for retransplantation those adult HT [heart transplant] recipients who develop severe CAV not amenable to medical or surgical therapy and symptoms of heart failure or ischemia.”
- “It is reasonable to consider listing for retransplantation those HT recipients with heart allograft dysfunction and symptomatic heart failure occurring in the absence of acute rejection.”
- “It is reasonable to consider retransplantation in children with normal heart allograft function and severe CAV.”

U.S. Preventive Services Task Force Recommendations
Not applicable.

Summary

Heart transplant is considered medically necessary as the literature, consisting of case series and registry data, continues to demonstrate that heart transplantation provides a survival benefit in appropriately selected patients, compared to the exceedingly poor expected survival without transplantation. Heart transplantation is contraindicated in patients in whom the procedure is expected to be futile due to comorbid disease or in whom post-transplantation care is expected to significantly worsen comorbid conditions.

Heart retransplantation after a failed primary heart transplant is medically necessary, as evidence suggests it provides a survival benefit in patients who still meet criteria for heart transplantation and do not have contraindications.

Medicare National Coverage

Cardiac transplantation is covered under Medicare (Publication 100-3, Manual 260.9) when performed in a facility that is approved by Medicare as meeting institutional coverage criteria, approximately 108 programs across the nation. (47)

The Centers for Medicare and Medicaid Services (CMS) has stated that under certain limited cases, exceptions to the criteria may be warranted if there is justification and if the facility ensures safety and efficacy objectives.
References


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<th>Section:</th>
<th>Surgery</th>
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<td>April 15, 2015</td>
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<tr>
<td>Subsection:</td>
<td>Transplant</td>
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<td>March 9, 2012</td>
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Policy History

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<tr>
<td>March 2012</td>
<td>New Policy</td>
<td>Policy updated with literature review. No change to policy statement</td>
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<tr>
<td>March 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature search. Policy statement on re-transplantation added and all other indications are considered investigational</td>
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<td>March 2014</td>
<td>Update Policy</td>
<td>Policy was updated with a literature review through September 2014, adding references 21, 25, and 28. Policy statements are unchanged.</td>
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Keywords

Cardiac (Heart) Transplant
Heart Transplant
Heart Transplantation
Transplant, Cardiac (Heart)

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 20, 2015 and is effective April 15, 2015.

Signature on file

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