FEP Medical Policy Manual

FEP 7.03.09 Heart Transplant

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Related Policies:

2.01.68 - Laboratory Tests Post Transplant and for Heart Failure
2.04.56 - Immune Cell Function Assay
7.03.08 - Heart/Lung Transplant
7.03.11 - Total Artificial Hearts and Implantable Ventricular Assist Devices

Heart Transplant

Description

Description

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

In 2021,41,354 transplants were performed in the United States procured from 13,863 deceased donors and 6,540 living donors.[2,] Heart transplants were the third most common procedure with 3,817 transplants performed from both deceased and living donors in 2021. As of June 2022, there were 3,443 patients on the waiting list for a heart transplant.[3,]

Most heart transplant recipients now are hospitalized as status 1 patients at the time of transplant. This shift has occurred due to the increasing demand for the scarce resource of donor organs resulting in an increased waiting time for recipients. Patients initially listed as status 2 candidates may deteriorate to a status 1 candidate before a donor organ becomes available. Alternatively, as medical and device therapy for advanced heart failure improves, some patients on the transplant list will recover enough function to be delisted. Lietz and Miller (2007) reported on survival for patients on the heart transplant waiting list, comparing the era between 1990 and 1994 with the era of 2000 to 2005.[4,] One-year survival for a UNOS status 1 candidate improved from 49.5% to 69.0%. Status 2 candidates fared even better, with 89.4% surviving 1 year compared with 81.8% in the earlier time period.

Johnson et al (2010) reported on waiting list trends in the U.S. between 1999 and 2008.[5,] The proportion of patients listed as status 1 increased, even as the waiting list and posttransplant mortality for this group have 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. Bakhtiyar et al (2020) evaluated survival among patients (N=95,323) wait-listed for heart transplantation between January 1, 1987 and December 29, 2017 using UNOS data.[6,] Results revealed 1-year survival on the wait list increased from 34.1% in 1987 to 1990 to 67.8% in 2011 to 2017 (difference in proportions, 0.34%; 95% confidence interval [CI], 0.32% to 0.36%; p<.001). One-year wait list survival also significantly increased for candidates with ventricular assist devices from 10.2% in 1996 to 2000 to 70% in 2011 to 2017 (difference in proportions, 0.60%; 95% CI, 0.58% to 0.62%; p<.001).

Alshawabkeh et al (2018) reported on the 1-year probability of the combined outcome of death or delisting due to clinical worsening for patients on the heart transplant waiting list, comparing the periods of April 1, 1986 to January 19, 1999 (early era) and January 20, 1999 to June 2, 2014 (current era).[7,] For adults without congenital heart disease (CHD), the probability of the combined outcome was lower in the current era compared with the early era, regardless of whether the patient was listed in status I (14.5% vs. 22.7%; p<.0001) or 2 (9.0% vs. 12.8%, p<.0001). When comparing the current and early eras in adults with CHD, a reduction in the probability of the combined outcome was demonstrated in those listed in status I (17.6% vs. 43.3%, respectively; p<.0001), whereas the outcome remained unchanged for those listed in status 2 (10.6% vs. 10.4%, respectively; p=.94).

In adults with CHD, factors associated with waitlist death or delisting due to clinical worsening within 1 year were also examined by Alshawabkeh et al (2016).[8,] A multivariate analysis identified that an estimated glomerular filtration rate less than 60 ml/min/1.73 m^2 (hazard ratio [HR], 1.4; 95% CI, 1.0 to 1.9; p=.043), albumin less than 3.2 g/dl (HR, 2.0; 95% CI, 1.3 to 2.9; p<.001), and hospitalization at the time of listing in the intensive care unit (HR, 2.3; 95% CI, 1.6 to 3.5; p<.001) or a non-intensive care hospital unit (HR, 1.9; 95% CI, 1.2 to 3.0; p=.006) were associated with waitlist death or delisting due to clinical worsening within 1 year.

Magnetta et al (2019) reported outcomes for children on the heart transplant waiting list, comparing the periods of December 16, 2011 to March 21, 2016 (era 1) and March 22, 2016 to June 30, 2018 (era 2).[9,] There was a significant decrease from era 1 to era 2 in the proportion of patients listed as status 1 (70% vs. 56%; p<.001), while the proportion of patients with CHD significantly increased across eras (49% to 54%; p=.018). The median time on the waitlist increased from 68 days to 78 days (p=.005). There were no significant differences across eras in the cumulative incidence of death on the waitlist among all candidates (subdistribution HR, 0.96; 95% CI, 0.80 to 1.14; p=.63) and among those listed status 1A (subdistribution HR, 1.16; 95% CI, 0.95 to 1.41; p=.14). Graft survival at 90 days was also similar across eras in the overall population and in those with CHD (p>.53 for both).

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 (Vo_2max), which is measured during maximal exercise, is a measure suggested as a critical objective criterion of the functional reserve of the heart. The American College of Cardiology and American Heart Association have adopted Vo_2max as a criterion for patient selection.[10,] Studies have suggested that transplantation can be safely deferred in those patients with a Vo_2max greater than 14 mL/kg/min. The importance of Vo_2max has also been emphasized by the American Heart Association when addressing heart transplant candidacy.[11,] In past years, a left ventricular ejection fraction of less than 20% or a New York Heart Association class III or IV status might have been used to determine transplant candidacy. However, as indicated by the American College of Cardiology 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 Vo_2max have been proposed as predictive models in adults.[12,13,14,15,] The Heart Failure Survival Scale and the Seattle Heart Failure Model (SHFM) are 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 on pharmacologic and device usage is incorporated into the model, permitting some estimation on the effects of current, more aggressive heart failure treatment strategies. Levy et al (2006) introduced the model using a multivariate analysis of data from the Prospective Randomized Amlodipine Survival Evaluation-1 heart failure trial (N=1125).[16,] Applied to the data of 5 other heart failure trials, SHFM correlated well with actual survival (r=0.98). SHFM has been validated in both ambulatory and hospitalized heart failure populations,[17,18,19,] but with a noted underestimation of mortality risk, particularly in Black adults and device recipients.[20,21,] None of these models has been universally adopted by transplant centers.

OBJECTIVE

The objective of this evidence review is to determine whether heart transplantation or retransplantation improves the net health outcome in patients with end-stage heart failure.

POLICY STATEMENT

Human heart transplantation may be considered **medically necessary** for select adults and children with end-stage heart failure when the following individual selection criteria are met.

Adult Individuals

1. Accepted Indications for Cardiac Transplantation
    1. Hemodynamic compromise due to heart failure demonstrated by any of the following 3 bulleted items,
        - Maximal oxygen consumption (Vo_2) <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.
2. Probable Indications for Cardiac Transplantation
    1. Maximal Vo_2 <14 mL/kg/min and major limitation of the individual'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 individual noncompliance with a regimen of weight monitoring, flexible use of diuretic drugs, and salt restriction.
3. The following conditions are inadequate indications for cardiac 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 Vo_2 >15 mL/kg/min.

Pediatric Individuals

1. Individuals with heart failure and persistent symptoms at rest who require 1 or more of the following:
    - Continuous infusion of intravenous inotropic agents; or
    - Mechanical ventilatory support; or
    - Mechanical circulatory support.
2. Individuals with heart disease and symptoms of heart failure who do not meet the above criteria but who have:
    - Severe limitation of exercise and activity (if measurable, such individuals would have a maximum Vo_2 <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 risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future; or

- Anatomic and physiologic conditions likely to worsen the natural history of congenital heart disease in infants with a functional single ventricle; or
- Anatomic and physiologic 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 individuals who meet the criteria for heart transplantation.

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

POLICY GUIDELINES

General Criteria

Potential contraindications for solid organ transplant subject to the judgment of the transplant center include the following:

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

Policy-specific potential contraindications include:

- Pulmonary hypertension that is fixed as evidenced by pulmonary vascular resistance >5 Wood units, or transpulmonary gradient ≥16 mm/Hg despite treatment[a]
- Severe pulmonary disease, despite optimal medical therapy, not expected to improve with heart transplantation[a]

[a] Some individuals may be candidates for combined heart and lung transplantation (see evidence review 7.03.08).

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

Cardiac-Specific Criteria

Specific criteria for prioritizing donor thoracic organs for transplant are provided by the Organ Procurement and Transplantation Network (OPTN) and implemented through a contract with UNOS. Donor thoracic organs are prioritized by UNOS on the basis of recipient medical urgency, distance from donor hospital, and pediatric status. Individuals who are most severely ill (status 1A) are given the highest priority. The following factors are considered in assessing the severity of illness: reliance on continuous mechanical ventilation, infusion of intravenous inotropes, and/or dependency on mechanical circulatory support (ie, total artificial heart, intra-aortic balloon pump, extracorporeal membrane oxygenator, ventricular assist device).

Additional criteria, which are considered in pediatric individuals , include diagnosis of an OPTN-approved congenital heart disease, presence of ductal dependent pulmonary or systemic circulation, and diagnosis of hypertrophic or restrictive cardiomyopathy while less than 1-year-old. Of 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 on the pediatric criteria.

Specific criteria for prioritizing donor thoracic organs for retransplant include severe coronary allograft vasculopathy, mild or moderate coronary allograft vasculopathy with a left ventricular ejection fraction less than 45%, coronary allograft vasculopathy with restrictive physiology, or symptomatic graft dysfunction without evidence of active rejection.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

While patients listed as status 1 are considered clear candidates for a heart transplant, Plans may want to consider a medical review of those patients listed as status 2 to determine whether patients meet the acceptable or probable indications for a heart transplant. Transplant centers may vary in their adherence to these criteria.

FDA REGULATORY STATUS

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

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

RATIONALE

Summary of Evidence

For individuals who have end-stage heart failure who receive a heart transplant, the evidence includes retrospective studies and registry data. Relevant outcomes are overall survival (OS), symptoms, and morbid events. Heart transplant remains a viable treatment for those with severe heart dysfunction despite appropriate medical management with medication, surgery, or medical devices. Given the exceedingly poor survival rates without transplantation for these patients, evidence of post-transplant survival is sufficient to demonstrate that heart transplantation provides a survival benefit. Heart transplantation is contraindicated for patients for whom the procedure is expected to be futile due to comorbid disease or for whom post-transplantation care is expected to worsen comorbid conditions significantly. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have had a prior heart transplant complicated by graft failure or severe dysfunction of the heart who receive a heart retransplant, the evidence includes systematic reviews, retrospective studies, and registry data. Relevant outcomes are OS, symptoms, and morbid events. Despite improvements in the prognosis for many patients with graft failure, cardiac allograft vasculopathy, and severe dysfunction of the transplanted heart, heart retransplant remains a viable treatment for those whose severe symptoms persist despite treatment with other medical or surgical remedies. Given the exceedingly poor survival rates without retransplantation for patients who have exhausted other treatments, evidence of post-transplant survival is sufficient to demonstrate that heart retransplantation provides a survival benefit in appropriately selected patients. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology Foundation and American Heart Association

Guidelines from the American College of Cardiology Foundation and the American Heart Association were updated in 2017.[67,] Evaluation for heart transplantation was recommended for patients in whom heart failure is assessed as refractory based on New York Heart Association functional class III

or IV (stage D) for heart failure after previous guideline-directed medical therapy, use of devices such as an implantable cardioverter-defibrillator or a cardiac resynchronization therapy device, or surgical management.

International Society for Heart and Lung Transplantation

In 2004, the International Society for Heart and Lung Transplantation (ISHLT) recommended that children with the following conditions be evaluated for heart transplantation (Table 1).[68,]

Table 1. Recommendations for Pediatric Heart Transplant

Recommendation	LOE
Diastolic dysfunction that is refractory to optimal medical/surgical management because they are at high risk of developing pulmonary hypertension and of sudden death	B
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	C

LOE B is based on a single randomized trial or multiple nonrandomized trials; LOE C is based primarily on expert consensus opinion.
LOE: level of evidence.

In 2016, the ISHLT published a 10-year update to its listing criteria for heart transplantation.[69,] The guidelines recommended the following updates or changes to the prior guideline:

- Recommended use of heart failure prognosis scores (eg, Seattle Heart Failure Model, Heart Failure Survival Score) along with a cardiopulmonary exercise test to determine prognosis and guide listing for transplantation for ambulatory patients.
- Periodic right heart catheterization for routine surveillance was not recommended in children.
- Carefully selected patients >70 years of age may be considered for cardiac transplantation.
- Pre-existing neoplasm, body mass index of ≥35 kg/m^2, diabetes with "end-organ damage (other than non-proliferative retinopathy) or poor glycemic control ... despite optimal effort," irreversible renal dysfunction, clinically severe symptomatic cerebrovascular disease, peripheral vascular disease, and frailty are considered relative contraindications to heart transplantation.
- Considering active smoking during the previous 6 months as a risk factor for poor outcomes after transplantation, active tobacco smoking is considered a relative contraindication for heart transplantation. Similarly, patients who remain active substance abusers (including alcohol) are not recommended to receive heart transplantation.

In 2016, this same ISHLT guideline update states the following regarding retransplantation indications:

"Retransplantation is indicated for those patients who develop significant CAV [(cardiac allograft vasculopathy)] with refractory cardiac allograph dysfunction, without evidence of ongoing acute rejection (Class IIa, Level of Evidence: C)."

The guideline cites the published consensus by Johnson et al (2007) on indications for retransplantation.[5,] It states that based on available data, appropriate indications for retransplantation include "the development of chronic severe CAV with symptoms of ischemia or heart failure, CAV without symptoms but with moderate to severe LV [(left ventricle)] dysfunction, or symptomatic graft dysfunction without evidence of active rejection." Retransplantation within the first 6 months after previous transplantation, especially with immunologic complications as a primary cause, was considered high-risk.

As a note on heart transplantation in children, the 2016 guideline update states, "although nearly half of all HTs [(heart transplants)] in children are done for CHD [(congenital heart disease)],... it should be noted that general considerations vary for more traditional indications, such as idiopathic dilated cardiomyopathy, for transplantation in the pediatric population....Thus, as these guidelines are translated to the younger patient, such prudence will need to be exercised."

In 2010, the guidelines from ISHLT on the care of heart transplant recipients include the following recommendations on cardiac retransplantation[70,]:

- "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."

American Heart Association

In 2007, the American Heart Association indicated that, based on level B (nonrandomized studies) or level C (consensus opinion of experts) evidence, heart transplantation is indicated for pediatric patients as therapy for the following indications:[71,]

- Stage D heart failure (interpreted as abnormal cardiac structure and/or function, continuous infusion of intravenous inotropes, or prostaglandin E_1 to maintain patency of a ductus arteriosus, mechanical ventilatory and/or mechanical circulatory support) associated with systemic ventricular dysfunction in patients with cardiomyopathies or 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) 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 Woods units/m^2 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/m^2 or the transpulmonary gradient to <15 mm Hg."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

Cardiac transplantation is covered under Medicare when performed in a facility approved by Medicare.[72,] The Centers for Medicare & Medicaid Services 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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2012	New policy	
March 2013	Replace policy	Policy updated with literature review. No change to policy statement.
March 2014	Replace policy	Policy updated with literature search. Policy statement on re-transplantation added and all other indications are considered investigational.
March 2015	Replace policy	Policy was updated with a literature review through September 2014, adding references 21, 25, and 28. Policy statements are unchanged.
March 2016	Replace policy	Policy updated with literature review through October 7, 2015; references 18, 21, 29, 36, 38, and 48 added. Policy statements unchanged.
December 2017	Replace policy	Policy updated with literature review through July 10, 2017; references 1-4, 20, 24, 31, 35-40, 43-45, 52-57, and 61 added. Policy statements unchanged.
December 2018	Replace policy	Policy updated with literature review through June 7, 2018; references 42, 51, and 56 added; reference 4 updated. Policy statements unchanged.
December 2019	Replace policy	Policy updated with literature review through June 10, 2019; no references added. Policy statements unchanged.
December 2020	Replace policy	Policy updated with literature review through June 12, 2020; references added. Policy statements unchanged.
December 2021	Replace policy	Policy updated with literature review through June 16, 2021; references added. Policy statements unchanged.
December 2022	Replace policy	Policy updated with literature review through June 10, 2022; reference added. Minor editorial refinements to policy statements; intent unchanged.