Indications for Heart Transplantation in Pediatric Heart Disease: A Scientific Statement From the American Heart Association 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

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Circulation 2007;115;658-676; originally published online Jan 29, 2007;
DOI: 10.1161/CIRCULATIONAHA.106.180449
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

AHA Scientific Statement

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Charles E. Canter, MD, Chair; Robert E. Shaddy, MD; Daniel Bernstein, MD; Daphne T. Hsu, MD; Maryanne R.K. Chrisant, MD; James K. Kirklin, MD; Kirk R. Kanter, MD, FAHA; Robert S.D. Higgins, MD; Elizabeth D. Blume, MD; David N. Rosenthal, MD; Mark M. Boucek, MD; Karen C. Uzark, RN, PhD, FAHA; Alan H. Friedman, MD; James K. Young, MD

Background—Since the initial utilization of heart transplantation as therapy for end-stage pediatric heart disease, improvements have occurred in outcomes with heart transplantation and surgical therapies for congenital heart disease along with the application of medical therapies to pediatric heart failure that have improved outcomes in adults. These events justify a reevaluation of the indications for heart transplantation in congenital heart disease and other causes of pediatric heart failure.

Methods and Results—A working group was commissioned to review accumulated experience with pediatric heart transplantation and its use in patients with unrepaired and/or previously repaired or palliated congenital heart disease (children and adults), in patients with pediatric cardiomyopathies, and in pediatric patients with prior heart transplantation. Evidence-based guidelines for the indications for heart transplantation or retransplantation for these conditions were developed.

Conclusions—This evaluation has led to the development and refinement of indications for heart transplantation for patients with congenital heart disease and pediatric cardiomyopathies in addition to indications for pediatric heart retransplantation. **(*Circulation*. 2007;115:658-676.)**

Key Words: AHA Scientific Statements ■ pediatrics ■ transplantation

Heart transplantation has been used for the treatment of end-stage pediatric heart disease for nearly 4 decades,[1] with the first infant heart transplantation performed in the late 1960s. The development of cyclosporine-based immunosuppression regimens 20 years ago stimulated an increased application of heart transplantation in pediatric patients with intractable heart failure.[2,3] Transplantation at that time was also initially applied as primary therapy in infants with hypoplastic left heart syndrome[4,5] owing to the extraordinarily high mortality associated with early experience with conventional surgical palliation.[6–8] In 1985, the Registry of the International Society for Heart and Lung Transplantation (ISHLT)[9] recorded the occurrence of 41 pediatric heart transplantations. In 1995, the registry recorded 370 pediatric heart transplantations. At that time, consensus indications[10,11] for heart transplantation for pediatric heart disease included the following:

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on November 17, 2006. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0393. To purchase additional reprints: Up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 410-528-4121, fax 410-528-4264, or e-mail kelle.ramsay@wolterskluwer.com.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.106.180449**

- Need for ongoing intravenous inotropic or mechanical circulatory support
- Complex congenital heart disease not amenable to conventional surgical repair or palliation or for which the surgical procedure carried a higher risk of mortality than transplantation
- Progressive deterioration of ventricular function or functional status despite optimal medical care with digitalis, diuretics, and angiotensin-converting enzyme (ACE) inhibitors
- Malignant arrhythmia or survival of cardiac arrest unresponsive to medical treatment, catheter ablation, or an automatic implantable defibrillator
- Progressive pulmonary hypertension that could preclude cardiac transplantation at a later date
- Growth failure secondary to severe congestive heart failure unresponsive to conventional medical treatment
- Unacceptably poor quality of life

Over the past decade, the registry has recorded a steady range of 347 to 386 pediatric (ages newborn to 18 years) heart transplantations performed annually around the world. This volume is approximately 10% of the total heart transplantations recorded in the database over this time period.[12] Within this time frame, overall, significant improvements have occurred in survival after heart transplantation[9] and for staged, palliative surgery for hypoplastic left heart syndrome.[6–8] New medical therapies, such as the use of β-blockers proven to improve survival with heart failure in adults, are being applied to pediatric heart failure.[13,14] Furthermore, heart transplantation has been increasingly utilized in adults with congenital heart disease and previous surgery as they develop progressive, end-stage disease.[15–17] Retransplantations have formed an increasing percentage of pediatric heart transplantations.[9]

These developments directly affect treatment and outcomes in pediatric heart disease and provide an impetus for reevaluation of guidelines for use of heart transplantation. In this document, pediatric heart disease is defined as (1) cardiomyopathies presenting from the neonatal period to 18 years of age; (2) repaired and unrepaired congenital heart disease from infancy to adulthood; and (3) previously transplanted pediatric patients from infancy to 18 years of age. All recommendations in this document follow the format of previous American Heart Association guidelines:

- Class I: Conditions for which there is evidence and/or general agreement that heart transplantation is useful and effective.
- Class II: Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of heart transplantation.
  - Class IIA: Weight of evidence/opinion is in favor of usefulness/efficacy.
  - Class IIB: Usefulness/efficacy is less well established by evidence/opinion.
- Class III: Conditions for which there is evidence and/or general agreement that heart transplantation is not useful.

The levels of evidence on which these recommendations are given are limited to level B (nonrandomized studies) and level C (consensus opinion of experts) because of the lack of randomized clinical trials for therapy for pediatric heart disease.

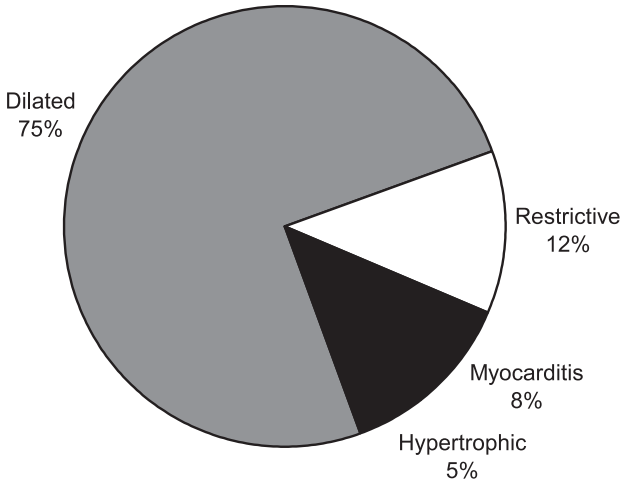

Figure 1. Distribution of cardiomyopathy subtypes within PHTSG recipients[20] transplanted with a diagnosis of cardiomyopathy. Reprinted from Canter et al,[20] with permission of the publisher. Copyright © 2007, Blackwell Publishing.

Disease Processes That Lead to Consideration of Heart Transplantation

Pediatric Cardiomyopathies

Dilated Cardiomyopathy

Dilated cardiomyopathy is the most common form of cardiomyopathy in children, with a population incidence of 0.58 per 100 000 children,[18] and makes up >50% of the cardiomyopathies observed in the pediatric age group.[18,19] Within the Pediatric Heart Transplant Study Group (PHTSG; Figure 1), 76% of the transplantations for cardiomyopathy are for dilated cardiomyopathy.[20]

Many reports of the natural history, clinical course, and outcome of pediatric dilated cardiomyopathy are from single centers, and they have included a wide variety of causes and inconsistent inclusion criteria across studies. These studies report a highly variable 5-year survival rate of 40% to 80%.[21–25] Gradual improvement and, in some cases, complete resolution of the cardiomyopathy has occurred in every reported series. A recent study[26] of the outcomes after diagnosis of dilated cardiomyopathy in 91 children showed that survival at 1 and 5 years after diagnosis was 90% and 83%, respectively. In that cohort, however, freedom from death or transplantation was 70% and 58%, respectively.[26]

Predictors of outcome in children with dilated cardiomyopathy have been evaluated in many studies,[27–31] with variable findings. Severity of dysfunction has been found to be predictive of outcome in some studies[29] but not in others.[32] Similarly, the presence of arrhythmia[24] has and has not been associated with a greater risk of death. Similar to results in adults, the shape of the ventricle is important prognostically, with a more spherical shape associated with a poorer outcome.[29] Patients with improvement in function in the first 6 months after presentation have better survival than those who

do not demonstrate improvement.[32] High end-diastolic pressure[33] and endocardial fibroelastosis[29] have also been reported to adversely affect survival. Ventricular size and mass at presentation have not been found predictive of outcome.[33] Younger age at presentation has been reported to be associated with a better outcome[28] and with a worse outcome[34] or to bear no relation to outcome.[33] Symptoms appear to provide poor prognostic capability because even asymptomatic patients with incidental discovery of dilated cardiomyopathy can have a poor prognosis.[34]

Studies[35–37] of pediatric myocarditis suggest a 50% to 80% chance for resolution of their dilated cardiomyopathies within 2 years after presentation. Interestingly, an acute presentation with severe symptomatology, so-called fulminant myocarditis,[37] has a high likelihood of resolution. Children placed on extracorporeal membrane oxygenator (ECMO) support for myocarditis have been reported to have a high rate of survival.[38] The registry of the Extracorporeal Life Support Organization has reported that myocarditis has the highest survival of any diagnostic group, with 58% of subjects able to be weaned from support.[39] Similarly, ventricular assist devices have been used to allow pediatric patients with myocarditis and severe heart failure to recover, with ultimate removal of the device without transplantation.[40,41] These findings suggest that a diagnosis of myocarditis may be a positive prognostic factor in pediatric dilated cardiomyopathy and that a need for inotropic and/or mechanical circulatory support in pediatric patients with myocarditis does not necessarily indicate a poor prognosis.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is the second most common type of cardiomyopathy observed in children, comprising 25.5% of patients in the Australian registry[18] and 42% of patients in the American registry.[19] Hypertrophic cardiomyopathy, however, is a relatively infrequent diagnosis leading to pediatric heart transplantation. Figure 1 demonstrates that only 5% of the cardiomyopathy patients transplanted within the PHTSG carried a diagnosis of hypertrophic cardiomyopathy.[20]

Both the American and Australian pediatric cardiomyopathy registries[42,43] demonstrate that pediatric hypertrophic cardiomyopathy encompasses a heterogeneous group of diseases with diverse genetic origins and clinical phenotypes. Inborn errors of metabolism constitute nearly 7.5% of the cases in the American registry. Approximately one fourth of the cases in the American and Australian registries are composed of malformation syndromes such as Noonan's syndrome and Beckwith-Wiedemann syndrome.

Both registries demonstrate consistent findings that age at presentation of <1 year, lower presenting echocardiography shortening fraction, and higher presenting echocardiographic left ventricular posterior wall thickness were risk factors for death or transplantation in their patients with hypertrophic cardiomyopathy. In the Australian registry,[43] the presence of concentric left ventricular hypertrophy as opposed to asymmetrical septal hypertrophy increased the risk of death or transplantation. Within the American registry,[42] hypertrophic cardiomyopathies associated with characteristics of dilated or restrictive cardiomyopathy carried a greater risk of death or transplantation.

Restrictive Cardiomyopathy

Restrictive cardiomyopathy, as defined by the World Health Organization, is a disorder of diastolic function characterized by restrictive filling with normal ventricular size and wall thickness.[44] Although the exact incidence of restrictive cardiomyopathy is unknown, it is the least common type of cardiomyopathy and represents only 2.5% to 3% of cardiomyopathies that present in childhood.[18,19] A number of recent case series[45–47] of pediatric restrictive cardiomyopathy have documented that it is less amenable to medical or surgical treatment and thus is more likely to lead to consideration for heart transplantation than other types of cardiomyopathies. This tendency is reflected within the PHTSG (Figure 1), in which restrictive cardiomyopathy represents 12% of the cardiomyopathy patients who have undergone transplantation.[20] Restrictive cardiomyopathy can be manifested as a solitary abnormality, although restrictive filling patterns of the left ventricle can be seen in patients with dilated[48] or hypertrophic[49] cardiomyopathies. Mortality rates in pediatric restrictive cardiomyopathy as high as 63% within 3 years of diagnosis and 75% within 6 years of diagnosis have been reported.[50,51]

Pediatric restrictive cardiomyopathy is associated with a high incidence of pulmonary hypertension, in addition to thromboembolic events and sudden death.[45–47,52] Because of these complicating factors, some have recommended immediate listing for heart transplantation at the time of presentation of pediatric restrictive cardiomyopathy.[52] Other studies,[45–47] including those based on results from the Australian pediatric cardiomyopathy registry,[53] are less supportive of urgent cardiac transplantation at the time of presentation. However, careful observation of these patients is warranted to avoid the development of irreversible pulmonary hypertension that might preclude an orthotopic heart transplantation.[46]

Congenital Heart Disease

Heart Transplantation as Primary Therapy for Congenital Heart Disease

The poor results with palliative therapy for single-ventricle lesions associated with multiple levels of obstruction to systemic cardiac output (hypoplastic left heart syndrome) 20 years ago[6–8] stimulated the use of heart transplantation as primary therapy for congenital heart lesions that were believed to be unamenable to surgical repair or palliation. The success of heart transplantation as a therapy for hypoplastic left heart syndrome led pediatric transplantation centers to apply heart transplantation as primary therapy in other conditions for which there was a poor natural history with standard surgical therapy. These conditions have included pulmonary atresia with intact septum and right ventricle–dependent coronary circulation[54,55] and complex heterotaxy syndromes[56,57] in which a functional single ventricle can be

TABLE 1. No. of Donors and Heart Waiting List Additions <1 Year of Age, 1995 to 2005*

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Donors	70	53	59	57	53	63	62	65	63	67	53
Waiting list additions	186	156	190	180	137	142	180	191	133	171	118

Data from the Organ Procurement and Transplant Network Database as of January 15, 2006.[62]

*The data in this table were supported in part by Health Resources and Services Administration contract No. 231-00-0115.

associated with anomalous pulmonary venous return and severe atrioventricular or semilunar valve disease.

A decade ago, comparison of survival in infants born with hypoplastic left heart syndrome continued to favor primary transplantation over staged, palliative surgery.[58,59] However, application of decision analysis modeling[60] suggested that the treatment strategy for hypoplastic left heart syndrome (primary transplantation versus staged, palliative surgery) was influenced by the mortality of the initial palliative surgical procedure and donor organ availability. The success of transplantation as primary therapy for hypoplastic left heart syndrome was also limited by the relatively high risk of death in infant heart transplantation candidates awaiting transplantation.[61]

Within the past 10 years, survival with staged, palliative surgery for hypoplastic left heart syndrome has continued to improve.[6–8] However, as is illustrated in Table 1, the number of heart donors <1 year of age has remained the same.[62] These phenomena have led to a decreased use of heart transplantation as primary therapy for hypoplastic left heart syndrome[63] and an increased proportion of infant heart transplantations performed for cardiomyopathies.[9]

Heart Transplantation as Therapy in Previously Repaired or Palliated Congenital Heart Disease

The success of reparative or palliative surgery in the treatment of congenital heart disease has led to an expectation that these patients will survive to adulthood and has spawned a new discipline in cardiology: treatment of the adult with congenital heart disease.[64] However, this therapy is virtually never curative, and ongoing morbidity and mortality occur in the form of myocardial dysfunction, valvular heart disease, residual pulmonary hypertension, and arrhythmias.[64,65] As is illustrated in Figure 2 from the PHTSG and Cardiac Transplant Research Database,[66] heart transplantation has been performed after congenital heart disease surgery in patients from infancy through adolescence and into middle age. These patients comprise ≈40% of the recipients in the PHTSG database but only 1.6% of the Cardiac Transplant Research Database, proportions similar to those found in the ISHLT database.[9,12]

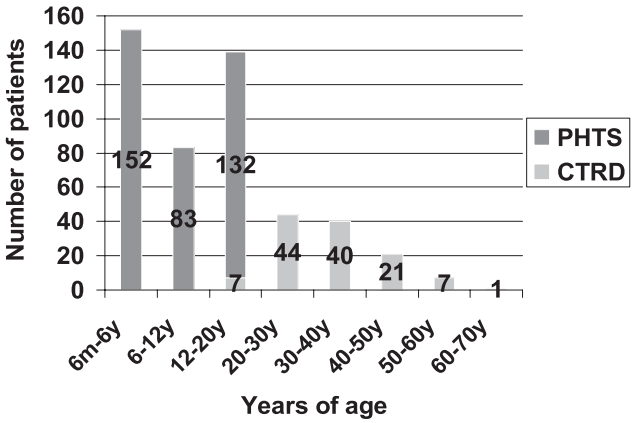

Figure 2. Number of patients transplanted because of congenital heart disease within the PHTSG database and the Cardiac Transplant Research Database (CTRD).[66] Data represent the 367 (40%) of 923 heart transplant recipients with congenital heart disease in the PHTSG from 1993 to 2002 and the 121 (1.6%) of 7345 heart transplant recipients with congenital heart disease in the Cardiac Transplant Research Database from 1990 to 2002. Reprinted from Lamour et al,[66] with permission of the publisher. Copyright © 2005, the American College of Cardiology Foundation.

Table 2 displays the distribution of various congenital heart lesion diagnoses that lead to heart transplantation within the PHTSG/Cardiac Transplant Research Database.[66] Single-ventricle lesions,[67–70] D-transposition of the great vessels (especially after the Mustard or Senning procedure),[71,72] and corrected or L-transposition of the great vessels,[73] lesions known to be associated with risk of ongoing deterioration into adulthood, are not surprisingly common diagnoses that lead to heart transplantation.

Congenital heart disease is a risk factor for increased mortality in both pediatric and adult heart transplantation,[9,12] primarily owing to increased risks in the perioperative period. The presence of previous surgical adhesions, aortopulmonary collateral vessels, increased pulmonary vascular resistance, and the impact of anomalies of pulmonary and systemic venous return and the malalignment of great vessels in these patients can lead to increased graft ischemia times, perioperative bleeding, and postoperative early graft failure. However, in those patients who survive past the perioperative period, the survival for children and adults transplanted for

TABLE 2. Anatomic Diagnoses in Heart Transplant Recipients >6 Months of Age Within the PHTSG and CTRD Databases With Previously Repaired or Palliated Congenital Heart Disease

Diagnosis	n (N=488)	%
Single ventricle	176	36%
D-transposition of the great arteries	58	12%
Right ventricular outflow tract lesions	49	10%
Ventricular/atrial septal defect	38	8%
Left ventricular outflow tract lesions	38	8%
L-transposition of the great arteries	39	8%
Complete AV canal	37	8%
Other	53	11%

AV indicates atrioventricular.

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congenital heart disease is as good as or better than survival in other diagnostic groups.[15–17,66,74]

Evaluation of patients after surgical repair or palliation of congenital heart disease can be difficult. Overall, most will have some degree of exercise intolerance that can affect physical functioning.[75–81] The chronic nature of their exercise limitations may lead to discrepancies with absolute exercise tolerance and perceived quality of life.[82–84] However, a recent study has found the severity of exercise intolerance in adults with congenital heart disease correlated with an increased risk for hospitalization and death[85] similar to that for adults with heart failure due to other causes.

Patients born with a single functional ventricle palliated by cavopulmonary connections or the Fontan procedure are especially susceptible to ongoing deterioration in their cardiac status with age.[67–70] Aside from symptoms of overt heart failure, these patients may develop protein-losing enteropathy, a condition characterized by low serum albumin and immunoglobulins, increased peripheral edema and ascites, elevation of fecal α-1 antitrypsin, and a poor prognosis for survival.[86,87] Protein-losing enteropathy may occur in these patients even in the presence of relatively low central venous pressures and preserved cardiac output.[87] When heart transplantation has been performed in patients with protein-losing enteropathy after the Fontan procedure, the protein-losing enteropathy has resolved in nearly all patients.[88,89]

Retransplantation in Pediatric Heart Transplant Recipients

As a result of improved early and late management, the cohort of pediatric heart transplant recipients surviving for 5 years, 10 years, or longer is growing. Early success after transplantation is tempered by an ongoing annual risk of death or graft loss of 2% to 3%, with 70% of events attributable to cardiac failure due to graft vasculopathy, rejection, or a combination of both.[9] The survival half-life after pediatric transplantation is 12.5 years, which indicates that the likelihood of graft survival >25 years after heart transplantation is low. The limited lifespan of the allograft is a particularly important concern in the field of pediatric heart transplantation because "late" graft failure occurs while recipients are in the teenaged and young-adult years.

An early multicenter review of retransplantation in 17 patients from 4 pediatric centers reported 1- and 3-year survival rates of 71% and 47%, respectively.[90] Graft vasculopathy with or without chronic rejection was the indication for retransplantation in 65% of this group. The linearized rates of rejection or infection were not different between the primary and retransplant populations. More recently, Dearani et al[91] reported results of listing for retransplantation in 32 children: 10 died waiting, and 22 underwent retransplantation. Graft vasculopathy was the indication for transplantation in 16 of 22 patients, and graft failure or intractable rejection was present in 6 patients. Three-year survival in the retransplantation group was similar to primary transplantation (82% versus 77%, respectively). Two of the 4 deaths occurred in patients transplanted for primary graft failure. Kanter et al[92] reported similar survival and posttransplantation morbidities compared with primary transplantation in 17 patients who underwent 20 retransplantation procedures.

TABLE 3. Indications for Retransplantation in Pediatric Heart Transplant Recipients Within the UNOS/ISHLT Registry

	n (N=219)	%
Primary failure	10	5
Hyperacute rejection	7	3
Acute rejection	19	9
Graft vasculopathy	111	51
Chronic rejection	16	7
Nonspecific graft failure	34	16
Other	22	10

Adapted from Mahle et al,[95] with permission of the publisher. Copyright © 2005, the American Association for Thoracic Surgery.

The importance of graft vasculopathy in limiting the lifespan of pediatric allografts is underscored by recent studies that have documented a 3% to 7% annual incidence of angiographically diagnosed graft vasculopathy in pediatric heart transplant recipients.[9,93] Data from the PHTSG[94] reported an overall incidence of angiographically apparent graft vasculopathy at 1, 3, and 5 years after pediatric heart transplantation of 2%, 9%, and 17%, respectively. Moderate to severe disease (≥50% stenosis in ≥1 primary or ≥2 branch coronary vessels) occurred in 6% of patients at 5 years. Once graft vasculopathy was angiographically apparent, prognosis was poor: 24% of patients with any degree of graft vasculopathy and 50% of patients with moderate to severe graft vasculopathy died or suffered graft loss within 2 years of diagnosis.[94]

More recently, Mahle et al[95] reported an analysis of United Network for Organ Sharing (UNOS) records for 219 retransplantation procedures performed among 4227 pediatric heart transplantations. In that series, the indication for retransplantation was graft vasculopathy in 51%. A list of the indications for retransplantation is shown in Table 3. One-, 5-, and 10-year survival rates were 79%, 53%, and 44%, respectively, and were significantly lower than the survival rates reported for primary transplantation. Retransplantation was an independent risk factor for mortality after transplantation, with an odds ratio of 1.67. Risk factors for lower survival after retransplantation included an intertransplantation interval <180 days and the need for mechanical ventilation. After exclusion of patients with early graft failure, 1-year survival was similar after retransplantation compared with primary transplantation (86% versus 83%, respectively); however, by 5 years, survival was significantly worse in retransplantation than in primary transplant recipients. These results have been replicated in studies of pediatric retransplantation within the ISHLT[96] and the PHTSG[97] databases, in which retransplantation for primary graft failure or rejection and/or within the first 6 to 12 months after transplantation was associated with poor survival. These results are similar to the results of studies of retransplantation in adult recipients,[98–100] in which risk factors for death after retransplantation have included shorter intertransplantation interval, chronic renal dysfunction, and the indication of primary graft failure or intractable acute rejection.

TABLE 4. Heart Failure Staging in Pediatric Heart Disease

Stage	Interpretation	Clinical Examples
A	At risk for developing heart failure	Congenital heart defects
		Family history of cardiomyopathy
		Anthracycline exposure
B	Abnormal cardiac structure and/or function	Univentricular hearts
	No symptoms of heart failure	Asymptomatic cardiomyopathy
		Repaired congenital heart disease
C	Abnormal cardiac structure and/or function	Repaired and unrepaired congenital heart defects
	Past or present symptoms of heart failure	Cardiomyopathies
D	Abnormal cardiac structure and/or function	Same as stage C
	Continuous infusion of intravenous inotropes or prostaglandin E_1 to maintain patency of a ductus arteriosus	
	Mechanical ventilatory and/or mechanical circulatory support	

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Heart Failure in Pediatric Heart Disease

Pediatric heart disease encompasses a wide diversity of ages and heterogeneous causes that can lead to intractable symptoms that limit survival and markedly diminish quality of life. This diversity of age and origin with different natural histories limits the compatibility of pediatric heart disease and adult heart disease. Guidelines that are developed for the management of heart failure in adult heart disease thus appropriately state their inapplicability to pediatric heart disease.[101] Characterization of heart failure in pediatric heart disease is further limited by its relative rarity. A small population of patients with disease limits the analysis of risk factors and predictors of mortality, as well as the ability to develop randomized clinical trials to test the efficacy of potential therapies.

There have been a number of proposed classifications and grading systems for heart failure in pediatric heart disease, including the Ross classification[102] and, more recently, the New York University Pediatric Heart Failure Index.[103] These schemes tend to grade severity of symptoms at a given point in time as opposed to being a measure of outcome for mortality or long-term disability.

As an adjunct to recent guidelines for the management of heart failure in adult heart disease,[104] the evolution and progression of heart failure was divided into 4 stages, from an "at risk" stage to an "end" stage. Recently published guidelines[105] for management of heart failure in children have adapted these stages to pediatric heart disease (Table 4). Stage A (at-risk stage) includes patients born with congenital heart defects, a family history of cardiomyopathy, or exposure to a cardiotoxic agent such as anthracyclines. Stage B (preclinical stage) includes patients with abnormalities of ventricular size, shape, and/or function with no past or present symptoms of heart failure. Examples of such patients would include those with cardiomyopathies with asymptomatic left ventricular dysfunction or those with repaired congenital heart defects with residual ventricular dilatation and/or reduced ejection. Stage C (present or past history of heart failure) represents a progression of stage B patients to overt symptoms of heart failure. Stage D (end stage) includes patients with persistent symptoms at rest who require continuous infusion of intravenous inotropic agents, mechanical ventilatory support, and/or mechanical circulatory support.

Heart Transplantation as Therapy for Stage D Heart Failure in Pediatric Heart Disease

Outcomes after pediatric heart transplantation have improved considerably, with 1-year survival rates approaching 90% and estimated conditional (recipients surviving 1 year after transplantation) graft half-lives of 17.5 years for children who have received transplants at between 1 and 10 years of age and 13.7 years for adolescents.[9] More than 90% of pediatric recipients report no activity limitations at 1, 3, and 5 years after transplantation.[9] Normal psychological and cognitive functioning has been observed in approximately 70% to 80% of pediatric transplant recipients in follow-up evaluations.[106–109] Thus, pediatric heart transplantation currently offers an opportunity for survival with excellent functional status and an apparent chance for good quality of life for patients at risk for imminent mortality from pediatric heart disease.

The risk of mortality once stage D heart failure evolves within pediatric heart disease has not been studied formally; however, such outcomes may be approximated from studies of outcomes of pediatric patients listed for heart transplantation. According to current UNOS pediatric listing stratification,[110] pediatric patients with stage D heart failure are listed as status 1A or 1B candidates. Reports from individual institutions[111,112] indicate patients listed as UNOS status 1 candidates experience a waiting list mortality rate that exceeds 20%. A recent analysis of outcomes after listing for pediatric heart transplantation has been performed within the PHTSG.[113] Figure 3 illustrates a competing risk analysis of outcomes after listing for transplantation as a status 1, 1A, or 1B within the PHTSG database. From 1993 to 1998, there was a 20% risk of mortality within 2 months without transplantation for pediatric patients listed as status 1 transplantation candidates. The overall risk of death while waiting

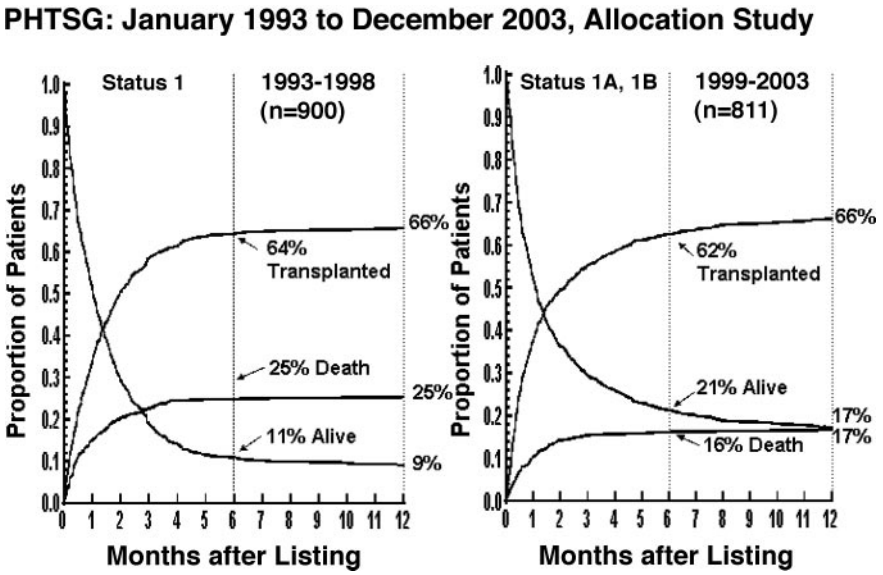

Figure 3. Competing outcome results for pediatric patients listed as UNOS status 1 from 1993 to 1998 and UNOS status 1A or 1B from 1999 to 2003.[113] The curves illustrate the proportions of patients transplanted, patients who died while awaiting transplantation, and patients alive waiting for transplantation at the indicated times after listing. Reprinted from Addonizio et al,[113] with permission of the publisher. Copyright © 2005, the International Society for Heart and Lung Transplantation.

for transplantation has substantially lessened within the recent era. Data from patients listed as status 1A or 1B from 1999 to 2003 demonstrate an ≈15% risk of death without transplantation within 2 months of listing compared with an ≈20% risk of dying within the same time frame for patients listed as status 1 from 1993 to 1998. These data suggest that stage D pediatric heart failure patients have a high risk for imminent death that can be effectively palliated with heart transplantation. Given that pediatric patients with stage D heart failure and myocarditis have the potential for recovery, even if they require mechanical circulatory support,[39–41] a need for initial inotropic or mechanical support in pediatric patients with myocarditis may not be an indication for commitment to cardiac transplantation as destination therapy.

Heart Transplantation as Therapy for Stage C Heart Failure in Pediatric Heart Disease

Patients with pediatric heart disease who experience symptoms of heart failure but are not dependent on inotropes or mechanical circulatory and/or ventilatory support would be listed as UNOS status 2 heart transplantation candidates.[110] Figure 4 displays the competing risk analysis of outcomes after listing as a UNOS status 2 heart transplantation candidate within the PHTSG.[113] It is notable that status 2 heart transplantation candidates represent only ≈25% of pediatric patients listed for transplantation within the PHTSG database. From 1993 to 1998, PHTSG patients listed as status 2 had a 7% risk of death without transplantation 6 months after listing and an 8% risk by 12 months after listing. In the recent (1999 to 2003) era, risk of death without transplantation has decreased to 3% and 4% at 6 and 12 months after listing, respectively. This apparent low risk of death while waiting for transplantation as a status 2 candidate must be tempered by a high risk for deterioration (change in listing status to status 1, 1A, or 1B) observed in these patients. Figure 5[114] demonstrates that by 3 months after listing, PHTSG patients listed as UNOS status 2 heart transplantation candidates had an ≈20% chance of death while waiting for transplantation or

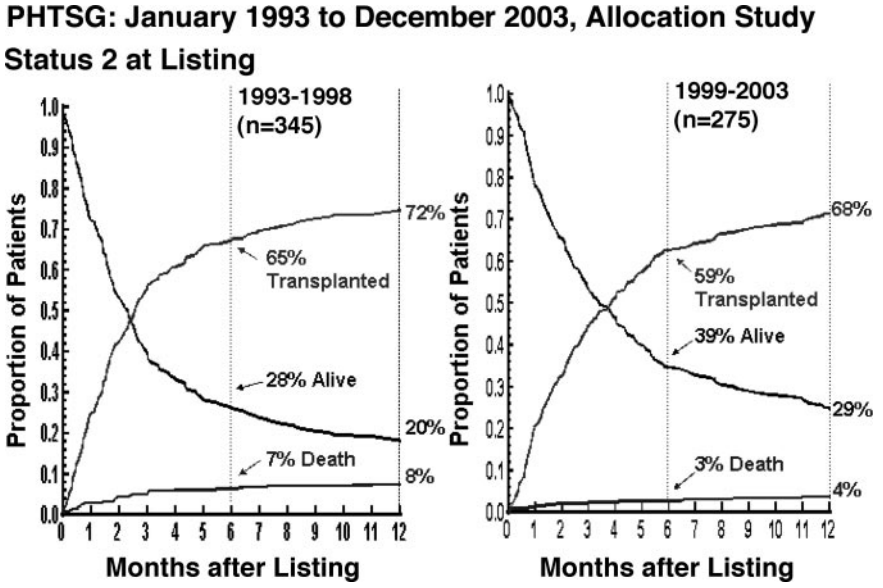

Figure 4. Competing outcome results for pediatric patients listed as UNOS status 2 from 1993 to 1998 and from 1999 to 2003.[113] The curves illustrate the proportions of patients transplanted, patients who died while awaiting transplantation, and patients alive waiting for transplant at the indicated times after listing. Patients were censored from ongoing analysis when urgency status was changed to UNOS status 1, 1A, or 1B. Reprinted from Addonizio et al,[113] with permission of the publisher. Copyright © 2005, the International Society for Heart and Lung Transplantation.

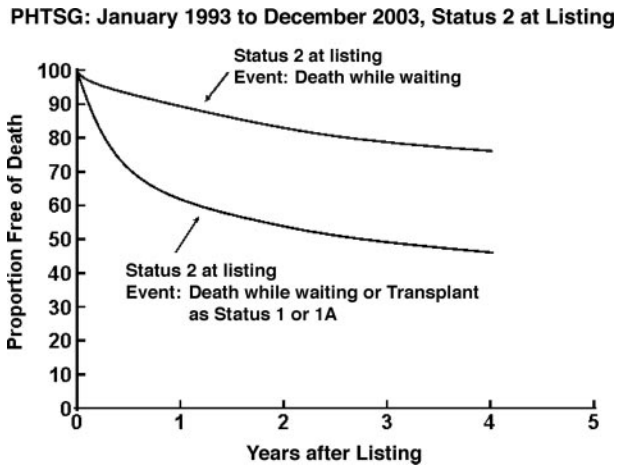

Figure 5. Outcome curve for patients listed as UNOS status 2 in the PHTSG.[114] The upper curve shows freedom from death while awaiting transplantation at UNOS status 2 urgency status. The bottom curve demonstrates freedom from death while awaiting transplantation combined with freedom from deterioration in urgency status to UNOS status 1 or 1A. Adapted from Kirklin et al,[114] with permission of the publisher. Copyright © 2006, the International Society for Heart and Lung Transplantation.

deterioration to status 1, 1A, or 1B at the time of transplantation, which increased to nearly 40% by 12 months after listing. Thus, a large number (>35%) of stage C pediatric heart failure patients deteriorated to stage D heart failure after being listed for transplantation within the PHTSG database.

An oxygen consumption treadmill exercise test has been the cornerstone for the determination of eligibility for heart transplantation in ambulatory heart failure patients with adult heart disease. Peak oxygen consumption ($\dot{V}O_2$max) in adult heart disease of <12 mL · kg^{-1} · min^{-1} has been associated with a very poor 1-year survival rate; those with a $\dot{V}O_2$max of 12 to 14 mL · kg^{-1} · min^{-1} have had severe clinical limitations; but patients with a $\dot{V}O_2$max >14 mL · kg^{-1} · min^{-1} have a survival rate likely to equal or exceed survival expected with transplantation.[115,116] The effects of body surface area, sex, and especially younger age can potentially lead to underestimation or overestimation of severity of disease with use of absolute $\dot{V}O_2$max. Studies utilizing percent predicted $\dot{V}O_2$max for age and sex[117–119] have found that outcomes in adult heart failure patients with a <50% predicted $\dot{V}O_2$max correlated with outcomes in studies that used an absolute $\dot{V}O_2$max maximum cutpoint of 14 mL · kg^{-1} · min^{-1}. Other exercise-related markers such as peak exercise cardiac output[120] and enhanced ventilatory response to exercise[121] also have a prognostic value; however, adult guidelines[11,122] for heart transplantation candidacy in ambulatory heart failure patients have generally used a peak $\dot{V}O_2$max of >15 mL · kg^{-1} · min^{-1} or <55% of predicted $\dot{V}O_2$max as thresholds for proceeding with evaluation for heart transplantation. Augmentation of peak $\dot{V}O_2$max information with other routinely obtained measures of known prognostic importance in adult heart failure have been formulated into heart failure survival scores to further refine assessments of heart failure severity in ambulatory adult patients.[123]

Recent[118,124] studies correlating $\dot{V}O_2$max with survival in adult patients with heart failure suggest that improvement in survival, primarily due to the widespread use of β-blockers, should lead to reconsideration of a $\dot{V}O_2$max between 10 and 14 mL · kg^{-1} · min^{-1} as an indication for consideration of heart transplantation. However, correlation of survival curves that used a cutpoint of <50% predicted $\dot{V}O_2$max versus <14 mL · kg^{-1} · min^{-1} continues to show close correlation for patients taking β-blockers.[118]

The use of exercise testing is challenging in pediatric heart disease. Variations exist in protocols and instrumentation, quite apart from the wide variation in results due to variation in patient's age, muscle mass, and size.[125,126] Cycle ergometry is often used, which generally produces a lower $\dot{V}O_2$max than values obtained with a treadmill. Exercise testing is also limited to patients >7 to 8 years of age. Studies evaluating exercise performance after repair of various congenital heart lesions have noted decreased exercise performance compared with normal patients, often as a result of chronotropic incompetence.[75–78]

Normative data on $\dot{V}O_2$max in pediatric patients reveal that minimum values in tested normal subjects were ≈60% of mean values in patients with a body surface area of ≥1 m^2.[125] Fredriksen et al[79] have reported that pediatric patients with repaired tetralogy of Fallot and left ventricular outflow tract lesions generally have mean $\dot{V}O_2$max values ≥70% of mean values for healthy control subjects. Patients with Mustard repairs (atrial switch) of transposition of the great vessels had lower values, with average $\dot{V}O_2$max values of 70% of normal at 7 to 8 years of age but only 55% to 60% of normal in adolescents. A recent study[127] of patients with biventricular and univentricular repairs of pulmonary atresia with intact septum also found an age-related decrease in maximal oxygen consumption regardless of type of repair. $\dot{V}O_2$max measurements in adult patients with various types of congenital heart disease[78] have demonstrated an overall profound impairment of exercise capacity, with mean $\dot{V}O_2$max for various lesions varying from 16 to 20 mL · kg^{-1} · min^{-1}. The authors of that study, however, cautioned that adults with congenital heart disease who perceived themselves as healthy were likely underrepresented in their patient population.

Patients with single-ventricle physiology are known to have poor exercise performance, with measured $\dot{V}O_2$max values only 55% to 65% of normal.[80,81,128] Exercise studies[129] from the multi-institutional Pediatric Clinical Research Network on 389 Fontan patients in the first 2 decades after repair found that only 18% of the group achieved a normal (>80% predicted) $\dot{V}O_2$max. Mean $\dot{V}O_2$max with standard deviation was 27.3±6.3 mL · kg^{-1} · min^{-1} (67% of that predicted for age and sex). However, some preadolescents with single-ventricle lesions who have undergone aggressive volume-unloading surgical strategies have been found to have $\dot{V}O_2$max values in the range of other repaired congenital heart defects with biventricular repairs.[130]

Studies utilizing exercise test data as prognostic factors for outcome in children with pediatric heart disease have not been performed; however, a recent study in adults[85] has confirmed previous studies that demonstrated poor exercise tolerance in adults with congenital heart disease but also

found a correlation between severity of exercise impairment and increased risk of hospitalization due to heart failure and death. Further studies investigating the relationship of exercise performance to survival are needed before exercise data in pediatric heart disease can be used in the same fashion as in adult heart disease for evaluation for heart transplantation; however, a $\dot{V}O_2$max <50% of that predicted for age and sex appears to be a relative marker for substantial exercise intolerance in patients with pediatric heart disease.

Blood levels of cardiac natriuretic peptides such as brain natriuretic peptide (BNP) have also been shown to correlate with functional status, morbidity, and mortality in adult patients with heart failure due to adult heart disease, even with administration of β-blocker therapy.[131–134] However, even in symptomatic patients, a wide range of BNP levels exist, with a substantial minority of patients exhibiting BNP values <100 pg/mL.[135] The combination of BNP values and $\dot{V}O_2$max testing may optimize prediction of outcome. A recent study in adults[136] has found that a <50% predicted $\dot{V}O_2$max and a BNP <109 pg/mL were associated with a 1-year survival rate of >90% for the patients affected, compared with only ≈60% for patients with BNP levels >109 pg/mL and a <50% predicted $\dot{V}O_2$max.

Initial studies of BNP levels in pediatric heart failure have demonstrated a positive correlation with severity of illness and functional status.[137–140] These studies were not designed to assess BNP levels as a way to assess outcome. BNP levels are briefly elevated at birth and then decline rapidly during the first week of life to levels generally lower than observed in adults.[141] Interestingly, patients with univentricular hearts palliated with the Fontan procedure have substantial exercise limitations but BNP levels <100 pg/mL.[138,139] Some evidence[142] exists that patients with univentricular hearts may have abnormal natriuretic peptide secretion and function. With further experience, measurement of BNP levels may ultimately prove valuable in assessing outcomes in stage C heart failure in pediatric heart disease.

Malnutrition with secondary growth retardation is a well-known complication of pediatric heart failure.[143–145] Delayed growth with retarded bone age is commonly observed in pediatric heart transplantation candidates.[146,147] Pediatric transplant recipients have generally exhibited normal growth rates after transplantation, but their absolute heights and weights tend to be in the lower range of normal.[148,149] However, some children will continue to demonstrate a decrement in skeletal maturation after transplantation.[146] Although these studies have demonstrated normal rates of increase in height and weight after transplantation, they do not demonstrate evidence of acceleration of these rates after transplantation.[146,147] Thus, although pediatric patients may have normal growth rates after heart transplantation, transplantation does not appear to stimulate "catch-up" growth in children with growth retardation due to pediatric heart disease.

Malignant, life-threatening arrhythmias and pediatric survival of near sudden death that cannot be effectively treated with medications or implantable defibrillators have been long-standing indications for cardiac transplantation regardless of severity of heart failure.[10,11] Use of implantable internal defibrillators in infants and small children has been associated with complication rates as high as 30%[150,151] owing to size limitations and difficulties in implantation. These difficulties with internal defibrillators in small patients can lead to consideration for transplantation at an earlier stage than would occur in adolescents or adults. However, these devices continue to become smaller, and innovative implantation techniques are evolving that will expand the use of internal defibrillators for life-threatening pediatric arrhythmias.[152,153]

The contribution of malignant arrhythmia and sudden death to mortality and morbidity in stage C and D pediatric heart failure remains unclear. Analysis[154] using the PHTSG database of the prevalence of sudden death in pediatric patients awaiting transplantation suggests substantially lower rates of sudden death than have been observed in adult heart transplantation candidates and no influence of listing status on its occurrence.

Evaluation of Comorbidities in Patients With Pediatric Heart Disease

Formal, structured evaluations of patients with pediatric heart disease referred for heart transplantation are an important part of the transplantation process. The purpose of these evaluations is 4-fold.[155] A comprehensive assessment of the cardiovascular anatomy and hemodynamics is performed. This generally includes assessment of pulmonary vascular resistance; however, the frequent anomalies of systemic and pulmonary venous return, pulmonary arterial fistulas and malformations, and accessory sources of collateral pulmonary blood flow observed in congenital heart disease must also be clearly delineated because of their impact on the surgical procedure. Assessment for the presence of chronic noncardiac disease and magnitude of dysfunction in other organ systems occurs. The magnitude of sensitization to human leukocyte antigens and human leukocyte antigen–specific antibodies is assessed. Substantial sensitization does not preclude transplantation but will influence donor selection and immunosuppression protocols.[156] Finally, psychosocial evaluation of the patient and the patient's family is performed to screen for the presence of existing psychological, cognitive, behavioral, and adjustment disorders.

Concomitant Disease in Other Organ Systems

Irreversible pulmonary, renal, hepatic, or systemic disease, coexisting neoplasm, insulin-dependent diabetes mellitus with end-organ damage, and active peptic ulcer disease or diverticulosis have been considered traditional contraindications to heart transplantation.[10,11,157] A need for renal dialysis at the time of transplantation has been identified as a risk factor for survival to 5 years in pediatric recipients[6] and to 1 year in adults.[12] Given the nephrotoxicity of immunosuppressant medication and the risk of progressive renal dysfunction after transplantation,[158] patients with irreversible moderate to severe renal dysfunction and end-stage heart disease are increasingly treated with combined heart-kidney transplantation.[159,160] Similar strategies[161] of combined heart-liver transplantation have been used in the presence of irreversible hepatic dysfunction.

Cardiomyopathy frequently is observed in muscular dystrophy patients. The Becker's variant of dystrophin-associated muscular dystrophy may be associated with a disproportionately severe cardiomyopathy in the presence of relatively preserved skeletal muscle strength. Cardiac trans-

plantation has been used in this situation,[162–164] in which there were no substantial limitations in respiratory muscle strength and the underlying skeletal myopathy had a slow progressive course. Anthracycline toxicity can lead to dilated cardiomyopathy with end-stage heart failure in survivors of pediatric neoplasms. Heart transplantation has been performed successfully in such survivors without effect on outcome, provided their risk of recurrent neoplasm is low.[165,166]

Diabetes mellitus is generally not present in pediatric patients evaluated for heart transplantation to the degree that it occurs in adult candidates. Studies in adults[157] have provided conflicting evidence of the effects of diabetes mellitus on heart transplantation outcomes; however, diabetes mellitus–associated comorbid conditions of obesity, hyperlipidemia, and vascular disease may influence infection and transplant coronary arteriopathy in heart transplant recipients. Obesity has been considered a relative contraindication to heart transplantation in adults, but evidence for a direct effect on mortality after transplantation is lacking.[157] An increased risk of infections, especially postoperative wound infections, has been observed.[167,168] Excessive weight gain after heart transplantation may occur.[169] Within the PHTSG database, very few patients listed for heart transplantation had weight-to-height ratios >2 standard deviations from normal, which suggests that obese pediatric patients are rarely listed for heart transplantation.[170] However, obesity may increase the risk of hypertension, hyperlipidemia, and insulin resistance in pediatric patients[171] in a manner similar to that in adults, with potential adverse effects on blood pressure, lipid profiles, and coronary arteriopathy in pediatric transplant recipients.

Presence of Infection

Seropositivity for hepatitis B virus surface antigen before transplantation is frequently associated with clinical liver disease after transplantation. An ISHLT/UNOS registry study[172] demonstrated that the majority of deaths in hepatitis B–seropositive heart transplant recipients were related to hepatitis B, even though these patients had a similar survival to seronegative patients after transplantation. Studies of heart transplant recipients from regions where hepatitis B infection is endemic have found that reactivation of hepatitis B infection after transplantation is common but could be controlled with lamivudine.[173] Heart transplant recipients with preoperative hepatitis C infection have also been found to be at risk for the development of potentially fatal liver disease within the first 5 years after transplantation.[174,175]

Human immunodeficiency virus (HIV) infection has been a contraindication to heart transplantation owing to very poor outcomes for heart transplantation in HIV-positive patients in the past.[176] Recent medical advances in the multidrug treatment protocols have improved outcomes in HIV disease, with increased death due to end-stage organ failure as opposed to AIDS-associated opportunistic infections. These advances have led to a reappraisal of the use of liver and kidney transplantation in HIV-infected patients.[177,178] A recent case report[179] has documented medium-term survival after heart transplantation in an HIV-positive adult, but further experience with heart transplantation in this setting has yet to come.

Pulmonary Vascular Resistance

Pediatric heart disease is associated with a myriad of mechanisms that may increase pulmonary artery pressures and pulmonary vascular resistance, such as left atrial hypertension due to systemic ventricular dysfunction, anatomic obstruction to pulmonary venous return, pulmonary veno-occlusive disease, pulmonary arteriolar constriction, anatomic obstruction of the large pulmonary arteries, increased pulmonary blood flow from congenital heart disease with left-to-right shunting, and accessory sources of pulmonary blood flow from aorto-pulmonary collaterals. One or all of these mechanisms may occur in any given patient with pediatric heart disease. Discontinuity or severe obstruction within large pulmonary arteries can lead to differing pulmonary pressure and vascular resistance in one portion of a patient's pulmonary bed compared with another.

The potential complexity of the interaction of these factors in pediatric heart disease can make measurement of pulmonary vascular resistance in some patients with pediatric heart disease problematic or even impossible; however, assessment of pulmonary vascular resistance in a patient with pediatric heart disease considered for heart transplantation is critical because of the well-established risk of postoperative heart failure and mortality in patients undergoing heart transplantation with high pulmonary vascular resistance.[180–184] This experience has led to recommendations in adults that heart transplantation should not be performed if the pulmonary vascular resistance index exceeds 6 Woods units/m^2 [10,11] or if the transpulmonary gradient is >15 mm Hg.[184]

Infants with hypoplastic left heart syndrome palliated with prostaglandin infusion to maintain ductal patency will have systemic pulmonary artery pressures but can be transplanted successfully owing to low or reversible pulmonary vascular resistance; however, the progression of pulmonary vascular disease due to irreversible elevation of pulmonary resistance is a well-known phenomenon in the pathophysiology of congenital heart disease. Thus, the potential to develop irreversible pulmonary vascular disease that would preclude heart transplantation in the future has been an indication for pediatric heart transplantation in the past[10,11] and a consideration leading to elevation of urgency status.[110]

With the application of heart transplantation to pediatric heart disease, patients have frequently been encountered whose baseline pulmonary vascular resistance index exceeds 6 Woods units/m^2 or who have transpulmonary gradients >15 mm Hg. Partial or complete reversibility of elevations of pulmonary vascular resistance and transpulmonary gradient can be observed in patients acutely tested with pulmonary vasodilators such as nitroprusside, prostaglandins, and nitric oxide.[180,185–188] Prolonged administration of inotropic agents has also been associated with pulmonary resistance reduction.[185] In these studies, heart transplantation was performed successfully in patients with baseline elevated pulmonary vascular resistance that demonstrated reversibility to a pulmonary vascular resistance index <6 Woods units/m^2 or transpulmonary gradient <15 mm Hg. In patients with congenital heart disease, the presence of 1 lung with a normal pulmonary vascular resistance has been sufficient to allow for successful orthotopic heart transplantation.[15] Reports[189,190]

also exist that pediatric patients who demonstrate reversibility in their pulmonary vascular resistance can successfully undergo orthotopic heart transplantation even if the pulmonary vascular resistance index exceeds 6 Woods units/m^2 or the transpulmonary gradient exceeds 15 mm Hg.

Patients demonstrating fixed, irreversible elevated pulmonary vascular resistance have not been accepted for orthotopic heart transplantation and have been evaluated for heterotopic heart transplantation[186,191] or heart-lung transplantation. However, the definition of true fixed, elevated pulmonary resistance is becoming increasingly uncertain. New pulmonary vasodilators such as sildenafil and bosentan have been shown to lower pulmonary vascular resistance in pediatric patients with primary and secondary pulmonary hypertension.[192,193] Bosentan has been successfully used to lower pulmonary resistance in adult heart transplant recipients who were previously considered ineligible for heart transplantation.[194] Furthermore, utilization of ventricular assist devices for mechanical circulatory support has been associated with normalization of high pulmonary vascular resistance in adult patients.[195,196] As experience in mechanical ventricular assist devices increases in pediatric heart failure,[197,198] their use and the use of pulmonary vasodilators will likely redefine what truly constitutes fixed, irreversible elevation of pulmonary vascular resistance that would preclude orthotopic heart transplantation in pediatric heart disease.

Psychosocial Evaluation

Several psychosocial variables have been considered absolute or relative contraindications to transplantation in adults, such as use of illicit drugs, alcohol abuse, mental retardation (IQ <50), and documented medical noncompliance.[157,199] Substance abuse, noncompliance, and psychological problems have been associated with increased morbidity and mortality after heart transplantation in adults.[200–203] Limited studies in pediatric heart transplant recipients[204,205] have shown correlations between difficulties with family adjustment issues and functioning with noncompliance and late rejection.

Developmental delay with abnormalities in behavioral and cognitive development are known to occur in a significant minority of pediatric heart transplant recipients from infancy through adolescence.[106–108,206,207] Developmental delay is commonly encountered in pediatric patients listed for heart transplantation, especially those patients with congenital heart disease.[208] Previous consensus reports[209] on the indications for heart transplantation in children have emphasized the need for case-by-case assessment of patients with developmental disability rather than arbitrary denials. This issue is especially important in the assessment of patients with chromosomal abnormalities associated with developmental and cognitive impairment and pediatric heart disease. Down's syndrome (trisomy 21) is a relatively common anomaly associated with cognitive impairment that has a high prevalence of congenital heart disease. Patients with Down's syndrome have a wide continuum of functional ability. Case reports have documented successful renal transplantation and bone marrow transplantations in patients with Down's syndrome.[210–212] However, Down's syndrome patients are rarely referred for heart transplantation.[213] Experience in bone marrow transplantation in patients with Down's syndrome raises concerns about increased infection from intrinsic immunologic abnormalities, chemotherapeutic toxicity, and potential increased risk of posttransplantation malignancy.[212,213] This limited experience with Down's syndrome underscores the need for comprehensive evaluation of patients with chromosomal anomalies with pediatric heart disease to determine the potential impact of all of the clinical manifestations of the anomaly before and after transplantation.

Recommendations

Cardiomyopathies and Congenital Heart Disease in Pediatric Patients

Class I

- Heart transplantation is indicated as therapy for stage D heart failure associated with systemic ventricular dysfunction in pediatric patients with cardiomyopathies or previous repaired or palliated congenital heart disease (Level of Evidence B).
- Heart transplantation is indicated as therapy for stage C heart failure in pediatric heart disease associated with severe limitation of exercise and activity. If measurable, such patients would have a peak maximum oxygen consumption <50% predicted for age and sex (Level of Evidence C).
- Heart transplantation is indicated as therapy for stage C heart failure associated with 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 attributable to the heart disease (Level of Evidence B).
- Heart transplantation is indicated as therapy for stage C heart failure in pediatric heart disease with associated near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator (Level of Evidence C).
- Heart transplantation is indicated as therapy for stage C heart failure in pediatric restrictive cardiomyopathy disease associated with reactive pulmonary hypertension (Level of Evidence C).
- In the presence of other indications for heart transplantation, heart transplantation is feasible 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 (Level of Evidence B).

Class IIA

- Heart transplantation is indicated as therapy for stage C heart failure in pediatric heart disease associated with reactive pulmonary hypertension and a potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future (Level of Evidence C).
- Certain anatomic and physiological conditions likely worsen the natural history of congenital heart disease in infant patients with a functional single ventricle, which can lead to use of heart transplantation as primary therapy.

These conditions include (1) severe stenosis (stenoses) or atresia in proximal coronary arteries; (2) moderate to severe stenosis and/or insufficiency of the atrioventricular and/or systemic semilunar valve(s); and (3) severe ventricular dysfunction (Level of Evidence C).
- Several anatomic and physiological conditions likely worsen the natural history of previously repaired or palliated congenital heart disease in pediatric patients with stage C heart failure that may lead to consideration for heart transplantation without severe systemic ventricular dysfunction, including (1) pulmonary hypertension and a potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future; (2) severe aortic or systemic A-V valve insufficiency that is not considered amenable to surgical correction; (3) severe arterial oxygen desaturation (cyanosis) that is not considered amenable to surgical correction; and (4) persistent protein-losing enteropathy despite optimal medical-surgical therapy (Level of Evidence C).

Class IIB

- The efficacy of heart transplantation as therapy for pediatric heart disease is not established for patients with previous infection with hepatitis B or hepatitis C or with HIV infection (Level of Evidence B).
- The efficacy of heart transplantation for pediatric heart disease is not established for patients with a history of recent use of illicit drugs or tobacco or a recent history of alcohol abuse (Level of Evidence B).
- The efficacy of heart transplantation for pediatric heart disease is not established for patients with a history of psychological, behavioral, or cognitive disorders; poor family support structures; or documented noncompliance with previous therapies that could interfere with successful performance of care regimens after transplantation (Level of Evidence B).

Class III

- Heart transplantation for pediatric heart disease is not efficacious when heart disease is associated with severe, irreversible disease in other organ systems or when it is part of a severe, irreversible, multisystemic disease process. Multiorgan transplantation may be considered (Level of Evidence C).
- Orthotopic heart transplantation for pediatric heart disease is not efficacious when heart disease is associated with severe, irreversible, fixed elevation of pulmonary vascular resistance (Level of Evidence C).
- Heart transplantation is not feasible in the presence of severe hypoplasia of the central branch pulmonary arteries or pulmonary veins (Level of Evidence C).
- The limited supply of pediatric donors, especially infant donors, makes heart transplantation not a feasible standard therapy for any specific congenital heart lesion (Level of Evidence B).

Cardiac Retransplantation in Pediatric Patients

Class I

- Retransplantation is indicated in children with abnormal ventricular function and at least moderate graft vasculopathy (Level of Evidence B).

Class IIA

- Retransplantation is indicated in children with normal ventricular function and at least moderate graft vasculopathy (Level of Evidence B).

Class III

- Retransplantation should not be performed during an episode of ongoing acute allograft rejection, even in the presence of graft vasculopathy (Level of Evidence B).
- Retransplantation is not efficacious when performed during the first 6 months after primary transplantation (Level of Evidence B).

Adults With Previously Repaired Congenital Heart Disease

Class I

- Severe systemic ventricular dysfunction after repair of congenital heart disease in adults when accompanied by persistent or recurrent stage D heart failure symptoms despite optimal medical therapy (Level of Evidence B).
- Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities (Level of Evidence B).
- In the presence of other indications for heart transplantation, heart transplantation is feasible in adult patients with congenital 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 and/or pulmonary vasodilators can decrease pulmonary vascular resistance to <6 Woods units/m^2 or the transpulmonary gradient to <15 mm Hg (Level of Evidence B).

Class IIA

- Heart transplantation is indicated as therapy for stage C heart failure in adults with previously repaired or palliated congenital heart disease associated with severe limitation of exercise and activity. Such patients would have peak maximum oxygen consumption of <15 mL $\cdot$ kg^{-1} $\cdot$ min^{-1} or $<50\%$ predicted for age and sex (Level of Evidence C).
- Several anatomic and physiological conditions likely worsen the natural history of previously repaired or palliated congenital heart disease in adults (especially compared with ischemic or dilated cardiomyopathy) and enhance the advisability of cardiac transplantation, including (1) pulmonary hypertension and a potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future; (2) severe aortic or systemic A-V valve insufficiency that is not considered amenable to surgical correction; (3) severe arterial oxygen desaturation (cyanosis) that is not considered amenable to surgical correction; and (4) persistent protein-losing enteropathy despite optimal medical-surgical therapy (Level of Evidence C).

Class III

- Heart transplantation is generally not indicated in adults with previously repaired or palliated congenital heart dis-

ease with a peak maximal oxygen consumption of >15 mL · kg^{-1} · min^{-1} or >50% predicted for age and sex without other indications (Level of Evidence C).

- Orthotopic heart transplantation for pediatric heart disease is not efficacious when heart disease is associated with severe, irreversible, fixed elevation of pulmonary vascular resistance (Level of Evidence C).
- Heart transplantation is not feasible in the presence of severe hypoplasia of the central branch pulmonary arteries or pulmonary veins (Level of Evidence C).
- Heart transplantation should not be performed in adults with previously repaired or palliated congenital heart disease in whom comorbidities exist that would otherwise preclude heart transplantation in adults (Level of Evidence C).

Disclosures

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Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Ownership Interest	Consultant/Advisory Board	Other
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit.

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Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit.

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Correction

In the article, "Indications for Heart Transplantation in Pediatric Heart Disease: A Scientific Statement From the American Heart Association 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," by Canter et al, which was published online before print January 29, 2007, and appeared in the February 6, 2007, issue of *Circulation* (*Circulation*. 2007;115:658–676), an author's name was misspelled. "Allen H. Friedman" should have read "Alan H. Friedman." The name has been corrected in the current online version of the article (http://circ.ahajournals.org/cgi/content/full/115/5/658). We regret the error.

DOI: 10.1161/CIRCULATIONAHA.106.182633

(***Circulation.*** **2007;115:e385.)**

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