Cardiomyopathy and heart transplantation in children
W. Robert Morrow, MD

Cardiomyopathy is one of the most common causes of death in children with heart disease. Increasingly, dilated cardiomyopathy is recognized to be familial, and specific gene products related to the myocyte cytoskeleton and contractile proteins have been identified. Other associations with metabolic disease, dysmorphic syndromes, and neuromuscular disease are important to establish, particularly in pediatric patients, to guide therapy and patient selection for transplantation. Survival in children with dilated cardiomyopathy depends on accurate diagnosis and aggressive therapy. Patients may respond to conventional treatment for heart failure or may deteriorate, requiring mechanical support. Extracorporeal membrane oxygenation has been used effectively for mechanical support in children until improvement occurs or as a bridge to transplantation. For those who are listed, the mortality rate while waiting for a donor organ averages approximately 20%. Survival after transplantation is good, with an intermediate survival rate of approximately 70%. Late survival remains to be determined in the current cyclosporin era but may in fact be improving. However, increased organ donation or strategies to increase the size of the organ donor pool, such as xenotransplantation, are needed to significantly reduce the rate of mortality while waiting.

Cardiomyopathy and cardiac transplantation in children
Cardiomyopathy is one of the leading causes of death in infants and children with heart disease [1,2•]. Yet prospects for survival in this group of patients have never been better, owing to progress in medical therapy of heart failure, largely reported in adults, and improving results of cardiac transplantation [3••]. Increasing appreciation for genetic and metabolic etiologies has led to earlier detection of cardiomyopathy in patients with familial disease, specific therapy in some with metabolic cardiomyopathy, and more selective use of cardiac transplantation in others [2••,4]. However, despite the rapidly increasing availability of genetic and metabolic diagnosis, specific metabolic therapy is available, regrettably, in only rare instances, and hopes for specific gene therapy for most cardiomyopathies are as yet unrealized. Survival is good after cardiac transplantation, but on average 20% of patients die waiting for a donor heart [5–7,8•]. There is also concern regarding long-term survival in pediatric heart transplant recipients, an area where expectations for greater longevity are clearly justified. In this article we review recent developments in the diagnosis and treatment of myocardial disease in children, specifically dilated cardiomyopathy, and discuss results of cardiac transplantation in pediatric patients.

Classification of cardiomyopathy
For the purposes of this review, we define cardiomyopathy as diseases of heart muscle excluding ischemic and hypertensive cardiomyopathy [2•]. The World Health Organization classification of cardiomyopathy is still widely employed in the evaluation of children. However, this classification of cardiomyopathy is only loosely related to the major pathophysiologic alterations found in patients with cardiomyopathy. These are reduced systolic function, diastolic dysfunction, adrenergic dysfunction, and, in the case of hypertrophic cardiomyopathy, obstruction. The understanding of pathophysiology is of at least equal clinical importance to the description of pathology, although the latter is useful in understanding natural history and prognosis. Most patients have mixed pathophysiology. Patients with dilated cardiomyopathy typically have systolic and diastolic dysfunction as well as alterations in adrenergic tone. Also, a variety of etiologies account for similar if not identical clinical pathophysiologic varieties of cardiomyopathy, and different pathophysiologies may be present in different patients with the same etiology.
From a clinical perspective, the pathophysiologic classification of cardiomyopathy is currently most useful in guiding treatment. However, cardiomyopathy in children may also be classified according to certain other clinical associations, including the presence of biochemical abnormalities at diagnosis, encephalopathy (including developmental delay), associated dysmorphic features, coexisting neuromuscular disease, or cardiomyopathy without other associations [4]. This classification is useful in formulating an approach to diagnosis in which associated metabolic disease, neuromuscular disease, malformation syndromes, and familial associations may exist. Recognizing underlying neuromuscular, metabolic, and genetic disease is key to guiding decisions regarding the use of selective therapy or cardiac transplantation [1,2•,4].

**Etiology of cardiomyopathy**

Dilated cardiomyopathy has also been termed idiopathic, a designation that may no longer be relevant. Cardiomyopathy may have a variety of causes, including genetic, infectious, metabolic, and toxic, among others. Exhaustive lists of possible etiologies have been published elsewhere [1,4]. Table 1 summarizes the more common etiologies encountered in clinical practice and some of the most important uncommon diagnoses.

<table>
<thead>
<tr>
<th>Table 1. Dilated cardiomyopathy: etiology</th>
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<tbody>
<tr>
<td><strong>Viral</strong></td>
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<tr>
<td>Coxsackievirus A and B</td>
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<tr>
<td>Echovirus</td>
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<tr>
<td>Adenovirus</td>
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<tr>
<td>Mumps</td>
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<tr>
<td><strong>Metabolic</strong></td>
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<tr>
<td>Thyrotoxicosis</td>
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<td>Hypothyroidism</td>
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<td>Carnitine deficiency syndrome</td>
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<td>Leigh disease</td>
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<td>Barth syndrome</td>
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<td>*MELAS syndrome</td>
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<td>*MERRF syndrome</td>
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<tr>
<td>Kearns-Sayre syndrome</td>
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<td>Stengers syndrome</td>
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<tr>
<td><strong>Toxic</strong></td>
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<tr>
<td>Anthracycline toxicity</td>
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<tr>
<td>Hemachromatosis</td>
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<tr>
<td>Alcohol</td>
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<tr>
<td><strong>Neuro/Muscular</strong></td>
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<tr>
<td>Friedreich ataxia</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
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<tr>
<td>Becker muscular dystrophy</td>
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<tr>
<td><strong>Familial/Genetic</strong></td>
</tr>
<tr>
<td>X-linked</td>
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<tr>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Autosomal dominant dilated cardiomyopathy with conduction defects</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Isolated ventricular noncompaction</td>
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<td>Tachyarrhythmia induced</td>
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*Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
*Myoclonic epilepsy, ragged red fibers

Dilated cardiomyopathy has often been thought of as a sequela of viral myocarditis. It is indeed clear that viral myocarditis may lead to sustained cardiac dysfunction [9,10]. The presence of viral genome and inflammatory infiltrate on biopsy in patients with chronic ventricular dilatation and dysfunction also supports this view [9,10,11••]. In the clinical setting of an acutely deteriorating patient, the distinction between viral myocarditis and dilated cardiomyopathy may be difficult.

**Familial dilated cardiomyopathy**

Increasingly, dilated cardiomyopathy is being recognized to be familial because of a history of affected parents or siblings [2]. From 20% to 65% of dilated cardiomyopathy cases may be familial [2,11••]. Mestrioni et al. [11••] found a number of presentations among those patients with familial dilated cardiomyopathy and distinguished five subtypes. These included patients with autosomal dominant inheritance and isolated dilated cardiomyopathy, X-linked inheritance with defects of the dystrophin gene, autosomal dominant inheritance with subclinical skeletal muscle disease, dilated cardiomyopathy with conduction defects, and other rare forms. X-linked dilated cardiomyopathy, also involving a dystrophin gene defect isolated to myocardium, has been well described [12]. This progressive cardiomyopathy typically occurs in adolescent males and follows an X-linked transmission pattern. In the series by Mestrioni et al. [11••], autosomal dominant transmission of dilated cardiomyopathy is the most common pattern, followed by autosomal recessive and X-linked inheritance. Currently, at least 10 genes have been mapped to loci in families with autosomal dominant dilated cardiomyopathy [2•,11••], although not all have identified gene products (Table 2). In addition to the dystrophinopathies, defects of other cytoskeletal proteins and of contractile proteins have been demonstrated to cause dilated cardiomyopathy [11••,12–15].

Several genetic syndromes of importance are seen in children and illustrate the genetic complexity of dilated cardiomyopathy. Barth syndrome, 3-methylglutaconic aciduria, is characterized by dilated cardiomyopathy, skeletal myopathy, neutropenia, and mitochondrial abnormalities and is rapidly progressive. with death in infancy and X-linked inheritance[4]. Duchenne muscular dystrophy and Becker muscular dystrophy, both of which affect children with skeletal muscle weakness, are associated with cardiomyopathy and defects of the dystrophin gene. Although X-linked inheritance has been clearly demonstrated, carriers of Duchenne muscular dystrophy have also been demonstrated to have evidence of cardiomyopathy by echocardiography, and there are reports of carriers presenting with severe symptoms [16–18]. In addition,
other familial dilated cardiomyopathies have been described with defects of the G4.5 gene of chromosome Xq28, including left ventricular noncompaction and cardiomyopathy [19]. Ichida et al. [20] recently reviewed the clinical features of isolated noncompaction of the ventricular myocardium in the Japanese population. This entity is characterized by ventricular dysfunction, systemic embolization, ventricular arrhythmia, and prominent left ventricular trabeculations. Although X-linked transmission has been proposed, the equal representation of females among affected family members in this series suggests other potential inheritance patterns.

Other causes of dilated cardiomyopathy

Cardiomyopathy may also be caused by toxic exposure and may be preceded by viral infection. The most common toxic cardiomyopathy commonly encountered in children is the cardiomyopathy caused by anthracycline toxicity following treatment for childhood cancer. Viral etiologies have been established as the major source of the cardiomyopathy in patients with HIV infection [21]. Cardiomyopathy may be associated with neuromuscular disease and metabolic disease [4,22]. Patients with neuromuscular disease or metabolic disease usually have some form of recognizable encephalopathy or muscle weakness at presentation. These entities have been thoroughly reviewed, and an in depth discussion of these is beyond the scope of this report [4,22]. It is particularly important to identify metabolic disease that may be treatable, such as some forms of carnitine deficiency and 3-hydroxyacyl coenzyme A dehydrogenase deficiency, or diseases that may recur in patients who undergo cardiac transplantation (storage disease).

Schwartz et al. [4] reviewed the diagnostic evaluation of cardiomyopathy in infants and children. History and physical examination will direct the nature of the evaluation to be undertaken. Clearly, family history and evaluation of first-degree relatives for cardiomyopathy is important in patients with isolated cardiomyopathy. First-degree relatives should undergo electrocardiographic and echocardiographic studies, since many affected individuals are asymptomatic. In all patients, routine electrolytes, creatinine, blood urea nitrogen, magnesium, calcium, and glucose measurements should be obtained. An electrocardiogram may give specific indications of hypertrophic cardiomyopathy, storage disease, and certain familial forms of cardiomyopathy, and may exclude an anomalous left coronary artery. When the clinical presentation with dilated cardiomyopathy in an infant in the first 3 months of life is compatible with anomalous left coronary artery, echocardiography and angiography should be performed to make or exclude the diagnosis. When metabolic acidosis is present or the patient is hypoglycemic or hyperammonemic, a more thorough metabolic evaluation is indicated [4]. This is also true in patients with encephalopathy. Urine for amino acids and organic acids, serum lactate and pyruvate, quantitative ketones, blood for acyl carnitine, T₄, and thyroid-stimulating hormone, and creatine kinase should be obtained. For patients with dysmorphic features, developmental delay, or failure to thrive, a karyotype is also indicated. Endomyocardial biopsy, although not without risk, has been shown to be safe and efficacious in infants and children [24] and should be performed if other diagnostic studies fail to reveal a definitive diagnosis. As noted earlier, biopsy may be useful in excluding acute myocarditis, but cellular infiltrates may be seen in patients with cardiomyopathy. Although routine histology usually demonstrates myocyte hypertrophy and variable degrees of fibrosis,

### Table 2. Dilated cardiomyopathy: genetics

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Loci</th>
<th>Gene/Product</th>
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<tbody>
<tr>
<td>X-linked DCM</td>
<td>Xp21</td>
<td>Dystrophin</td>
</tr>
<tr>
<td>Duchene MD</td>
<td>Xp21</td>
<td>Dystrophin</td>
</tr>
<tr>
<td>Becker MD</td>
<td>Xp21</td>
<td>Dystrophin</td>
</tr>
<tr>
<td>Barth syndrome</td>
<td>Xq28</td>
<td>Tafazzin (G4.5)</td>
</tr>
<tr>
<td>Isolated ventricular</td>
<td>Xq28</td>
<td>G4.5</td>
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<tr>
<td>noncompaction</td>
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<td></td>
</tr>
<tr>
<td>Cardiomyopathy with MD</td>
<td>17q12-21</td>
<td>Alpha sarcoglycan</td>
</tr>
<tr>
<td>Familial DCM (autosomal)</td>
<td>1q21</td>
<td>Lamin A/C</td>
</tr>
<tr>
<td>Familial DCM with</td>
<td>1q32</td>
<td>-</td>
</tr>
<tr>
<td>conduction defects</td>
<td>2q31</td>
<td>-</td>
</tr>
<tr>
<td>Systemic carnitine</td>
<td>22q</td>
<td>Carnitine palmitoyl transferase</td>
</tr>
<tr>
<td>deficiency</td>
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DCM, dilated cardiomyopathy; MD, muscular dystrophy.

**Diagnostic evaluation**

Infants and children with cardiomyopathy present with symptoms and signs of congestive heart failure or with arrhythmia, syncope, or sudden death. Myocarditis may be present in 2 to 15% of children who present with congestive failure but may be more common in infants [1]. The diagnosis of myocarditis may be established with endomyocardial biopsy by standard histologic criteria or by demonstration of viral genome in cardiac tissue [2,9,10,11••,23]. In fact, many patients with familial dilated cardiomyopathy may have associated cellular infiltrate [11••]. A careful history often reveals symptoms of chronicity, which favor a diagnosis of cardiomyopathy over myocarditis (poor feeding, exertional fatigue). Often a diagnosis of cardiomyopathy is made by exclusion of myocarditis on biopsy and lack of improvement of cardiac function over months following a presentation with acute failure.
myocardial biopsy is necessary for the diagnosis of cardiac phosphorylase kinase deficiency. Skeletal muscle biopsy, nerve conduction velocity studies, and electromyography are useful in patients with suspected neuromuscular disease.

**Treatment of myocardial disease**

**Stabilization**

Infants and children with dilated cardiomyopathy often present with congestive heart failure and are frequently profoundly ill, requiring aggressive medical management to achieve stabilization. In addition to supplemental oxygen and diuretic therapy, these children require inotropic support with dobutamine and dopamine, and many require mechanical ventilation. The addition of myocardial phosphodiesterase inhibitors, such as milrinone, may be very useful in providing additional inotropic support and afterload reduction. Correction of acidosis with sodium bicarbonate is important, provided the patient has adequate ventilation. Arrhythmia management is key and may require the use of intravenous therapy for those with intractable ventricular arrhythmia.

Recent studies have demonstrated the usefulness of examining tissue for viral genome and may establish the etiology of myocarditis [9,10,11••]. However, polymerase chain reaction studies are seldom useful in the management of acutely ill children. Frequently, patients who present with a clinical presentation compatible with myocarditis are often treated empirically with either γ-globulin or corticosteroids. Some evidence exists suggesting that γ-globulin may be useful in reducing morbidity and mortality of myocarditis in children [25•]. More aggressive treatment of myocarditis with other immunosuppressants and cytolytics has also been proposed [26]. Patients with cardiac failure who fail to respond to therapy and continue to deteriorate, whether due to myocarditis or cardiomyopathy, should be considered for mechanical support and are potential candidates for cardiac transplantation.

**Mechanical support in children**

A number of investigators have demonstrated the efficacy of providing mechanical support of the circulation, principally by extracorporeal membrane oxygenation (ECMO) in children with refractory heart failure [27–32]. Patients with myocarditis or cardiomyopathy who progress to cardiogenic shock despite maximal inotropic support should be placed on mechanical support, provided contraindications do not exist. In children, the primary modality for mechanical support continues to be ECMO. Left ventricular assist devices are applicable only in some adolescent patients, although devices for smaller children are currently being evaluated [30–32]. When patients with left ventricular failure are placed on ECMO, left ventricular ejection may cease, leading to left atrial hypertension and pulmonary venous congestion. Adequate decompression of the left atrium is essential in reducing left ventricular wall stress and preventing pulmonary complications of pulmonary venous congestion. Seib et al. [33] has described the technique for blade and balloon atrial septostomy in patients requiring ECMO and demonstrated the superiority of this technique to surgical decompression. Patients with myocarditis may improve and be weaned from support. It is clear that a majority of patients with acute cardiac failure can either be weaned from support or are successfully transplanted, although the rate of mortality while waiting is certainly significant [27,28]. It is most important to progress to mechanical support prior to cardiac arrest or onset of generalized organ failure. The prognosis for full recovery with or without transplant is much poorer if cardiac arrest has occurred prior to instituting mechanical support.

**Chronic heart failure management**

Studies in adults with heart failure have shown substantial benefit for aggressive treatment of heart failure. In addition to the beneficial effects of digoxin and diuretics, therapy directed at the pathophysiology of the activation of the sympathetic axis have proven benefit. Children with heart failure should receive digoxin, diuretics including spironolactone, and angiotensin-converting enzyme inhibitors. Studies of heart failure treatment directed at reducing the effects of adrenergic activation have been limited in children. The benefit of metoprolol in the treatment of heart failure [34] and initial studies with carvedilol have shown encouraging results [35]. However, owing to the small number of pediatric patients with heart failure at any individual center, these studies have had low statistical power. Also, the pathophysiology of heart failure in children may be different. Children characteristically present with fewer symptoms for any given degree of left ventricular dysfunction and have worse ventricular function at presentation. Therefore, the end points for improvement in children may in fact be different from those in studies in adults. Prospective multicenter trials are currently underway to evaluate the effect of beta-blockade in pediatric cardiomyopathy patients. The use of beta-blockade should be undertaken cautiously until further evidence of efficacy is forthcoming.

Patients with severe systolic dysfunction and severe left ventricular dilatation should be treated with anticoagulants, preferably coumadin, to prevent the development of intracardiac thrombus and systemic embolization. Arrhythmia should be treated aggressively, as sudden death is a common cause of death for patients with dilated cardiomyopathy. Predictors of sudden death in dilated cardiomyopathy are few. Clearly preexisting
arrhythmia is a risk factor for sudden death in children [36]. QT dispersion may be associated with greater arrhythmia and therefore be a risk factor for sudden death [37]. Patients with more severe cardiomyopathy, such as greater degrees of ventricular dilatation and worse systolic dysfunction, as well as patients with pulmonary hypertension, may be more likely to die suddenly. Since many anti-arrhythmic agents have negative inotropic effects, treatment may lead to a deterioration in cardiac function. Amiodarone may be the best agent for treating arrhythmia, particularly in patients listed for cardiac transplantation. Although experience is limited, the use of implantable defibrillators has been effective in pediatric patients large enough for these devices [38]. Patients who continue to deteriorate should be considered for mechanical support [27–32].

Cardiac transplantation

Indications for listing

The registry of the International Society for Heart and Lung Transplantation (ISHLT) records 4178 cardiac transplant procedures in children, ranging from 147 in 1987 to 324 in 1998 [3], although the frequency of transplantation has declined slightly since a peak of 395 in 1993. The indications for cardiac transplantation in children were recently reviewed by Fricker et al. [39••]. Patients with refractory symptomatic heart failure are candidates for listing for transplantation provided contraindications do not exist. Serious central nervous system, renal, hepatic, and pulmonary dysfunction are contraindications in children as in adults. Patients with Becker muscular dystrophy may be successfully transplanted depending on the severity of their skeletal myopathy.

Pulmonary hypertension may be a contraindication to transplant in some patients with dilated cardiomyopathy. The upper limit of pulmonary resistance associated with successful cardiac transplantation has not been established [39••,40,41,42,43]. Transplantation in patients with pulmonary arteriolar hypertension in excess of 5 Wood units or a transpulmonary gradient greater than 15 mm Hg is potentially contraindicated. However, if pulmonary resistance is reactive and decreases with the administration of oxygen, nitric oxide, or prostaglandin, transplantation is not necessarily contraindicated. All patients with elevated pulmonary resistance must undergo hemodynamic testing to establish both resting and best pulmonary arteriolar resistance and transpulmonary gradient prior to transplantation or exclusion from listing. Best values should always include response to oxygen and nitric oxide, but the latter may be omitted if resistance falls into an acceptable range with other interventions (inotropic agents, intravenous afterload reduction, prostaglandin)[43]. When the response is marginal, repeat values after a 1- to 2-week course of intravenous inotropic support, afterload reduction, and pulmonary vasodilatation may demonstrate improvement. Patients known to have marginal values should be tested at least every 6 months while waiting for transplantation, since reactive pulmonary hypertension may worsen and become fixed. Patients with fixed elevation of pulmonary resistance on the basis of cardiac failure may be candidates for heart-lung transplantation. Fricker et al. [39••] discuss other potential contraindications to transplantation.

Outcome of listing for transplantation

Very few studies have addressed pretransplant mortality in infants and children after listing for cardiac transplantation. However, death after listing is not the only potential outcome of listing for transplantation. Any of four potential outcomes may occur after listing, including death while waiting, transplantation, removal from the list, or continuing on the list waiting for transplantation. Competing outcome analysis has been used to describe outcome after listing for transplant in pediatric patients in the Pediatric Heart Transplant Study (PHTS)[5–7,8•]. McGiffin et al. [5] reported outcome of listing in 264 pediatric patients listed for transplantation over a 1-year period. Patients ranged in age from 3 days to 17.9 years, with a mean age of 4.7 years. In this initial report from the PHTS, 60% of patients underwent transplantation by 6 months after listing, 23% died while waiting, 14% remained on the list awaiting transplantation, and 4% improved and were removed from the list. In a separate analysis of infants (less than 6 months of age) who were listed for transplantation [6], nearly one third of infants died awaiting transplantation, although 60% did undergo transplantation by 6 months. Only 6% remained on the list awaiting transplantation. The use of blood type O donors (universal donor) in non-blood type O recipients resulted in more deaths while waiting among blood type O patients. In older children, death was more likely to occur in Status 1 patients and patients requiring mechanical ventilation [7]. UNOS policy now prioritizes allocation of type O donor hearts to type O recipients. In addition, under new urgency status categories (Status 1a, Status 1b, and Status 2) prostaglandin-dependent infants with greater than 50% systemic pulmonary artery pressure (prostaglandin-dependent, single-ventricle physiology) are prioritized to Status 1a, the most urgent status. Whether these changes ultimately lead to more equitable organ distribution remains to be determined.

Survival after transplantation

A number of institutions have reported excellent early and intermediate survival in both infants and children [44–54] following cardiac transplantation. When all age groups and diagnoses are analyzed together, an actuarial survival of at least 75 to 85% at 1 year and 65 to 75% at 5
years is seen. Survival data reported by the Registry of the ISHLT are more or less in keeping with other multicenter studies and single-institution experiences [3]. Shaddy et al. [55] and Canter et al. [56] have reported survival in infants and older children in the PHTS experience. Survival in the recent PHTS experience indicates some improvements over time [8]. One-year survival among infants less than 1 year of age at transplant was 82% in the most recent analysis, compared with 70% in the initial PHTS experience [8,55,56]. Five-year survival in pediatric patients in the PHTS study was also virtually identical to survival among adults and was approximately 70% (Fig. 1). There was no difference in survival between patients with congenital heart disease and those with cardiomyopathy. A number of individual programs have recently reported survival in excess of 90% (Morrow WR, Frazier EA, unpublished data, 1999) [57,58]. Four-year survival has improved at Arkansas Children’s Hospital from the first to the second half of our transplant experience (Morrow WR, Frazier EA, unpublished data, 1999). An initial survival of 61% at 4 years is now 94% in the current era. The most current analysis of data from the ISHLT registry also demonstrates a generally improving survival rate over the period of data collection. Factors accounting for this apparently improving survival rate have not yet been determined.

**Late survival**

Attention has recently turned to late survival in children after cardiac transplantation. In particular, there is concern about increasing attrition with age because of late complications such as late rejection due to noncompliance and occurrence of graft atherosclerosis. Few data are available regarding long-term survival in pediatric heart transplant recipients. Late survival at Stanford was disappointingly low, with a reported 10-year survival rate of 60% [8]. Importantly, many patients underwent transplantation prior to the cyclosporin era. The ISHLT registry report gives an 8-year actuarial survival rate of approximately 55% for all ages [3]. Long-term survival among patients transplanted early in the pediatric heart transplant experience of some institutions appears to be less favorable than current survival [59]. Ultimately, improvements in early survival will translate into better late survival. Since most late deaths occur due to rejection or rejection-related complications such as graft vasculopathy [60,61], the development of new immunosuppressive agents promises to lead to improving long-term survival as well. Death from myocardial infarction remains decidedly uncommon within 5 years of transplantation in children, although a disturbing increase in sudden deaths has been observed [61]. Data from the recent Loma Linda experience indicate that late survival in neonates may in fact be superior to that in older infants [62]. With improved rejection surveillance and treatment in these high-risk patients and with new, more effective immunosuppressive regimens on the horizon, mortality from rejection can potentially be reduced. Likewise, since graft atherosclerosis is at least in part a rejection phenomenon, improved treatment of rejection could lead to a reduced incidence and severity of graft coronary disease.

**Conclusions**

In the past, the diagnosis of dilated cardiomyopathy in children was associated with a generally poor prognosis. However, with improved diagnosis, hopefully before
symptoms become severe, and with improved medical therapy, it is likely that many children will survive without transplantation. The promise of specific therapy for most patients with dilated cardiomyopathy is as yet unrealized. However, when medical therapy fails, heart transplantation is effective and can provide good intermediate-term survival. Lack of availability of donors results in significant mortality while waiting among pediatric patients awaiting heart transplantation, although most eventually undergo successful transplantation. In fact, this mortality rate is virtually equal to the 5-year mortality rate after transplantation. Survival after transplantation in infants and children is equal to or better than survival in adults. Despite late survival estimates of 50% at 10 years, early and intermediate survival rate may be improving, based on recent studies at individual institutions (Morrow WR, Frazier EA, unpublished data, 1999) [57,58] and multicenter studies [3,8]. The recent development of new immunosuppressive agents may also significantly affect long-term survival by reducing the incidence and severity of acute and chronic rejection. However, increased organ donation or strategies to increase the size of the organ donor pool, such as xenotransplantation [63••], are needed to significantly reduce overall mortality.

Acknowledgment
The author is indebted to the members of the Pediatric Heart Transplant Study Group for their dedication and support.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as: • Of special interest
•• Of outstanding interest


This review deals with etiology, diagnosis, and treatment issues in a comprehensive fashion. The author is expert in both the genetics of cardiomyopathy and treatment by cardiac transplantation.


The annual report of the ISHLT Registry provides an excellent overview of survival of transplantation in children. In addition to cardiac transplantation, the Registry Report provides information on heart-lung and lung transplantation.


This summary is truly excellent and deals with the genetics of cardiomyopathy in a comprehensive way. The authors also give useful insight into associated disease states and the management of pediatric patients presenting with cardiomyopathy.


This report from the Pediatric Heart Transplant Study is the first to emphasize the need for competing outcomes analysis to correctly analyze outcome after listing for transplantation. It sets the standard for statistical analysis in the setting of multiple, potentially mutually exclusive, outcomes.


In this article, data are presented from an impressive series of patients with dilated cardiomyopathy. The authors define subtypes of familial cardiomyopathy and in doing so propose a useful framework for classification. The paper includes an informative discussion on the genetics of dilated cardiomyopathy.


Although not a controlled study, this report provides useful and encouraging data in pediatric patients with myocarditis.


Fricker FJ, Addonizio L, Bernstein D, et al.: Heart transplantation in children: indications. Report of the Ad Hoc Subcommittee of the Pediatric Committee of the American Society of Transplantation (AST). Pediatric Transplantation 1999, 3(4):333–342. This is an important review of the current indications for cardiac transplantation in children authored by leaders in the field. The group also considers a number of controversial issues with regard to transplantation and provides insight on managing patients with potential contraindications.


