Improved Outcomes of Pediatric Dilated Cardiomyopathy With Utilization of Heart Transplantation

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OBJECTIVES
We studied the outcomes of pediatric patients diagnosed with dilated cardiomyopathy (DCM) and their relation to epidemiologic and echocardiographic variables at the time of presentation.

BACKGROUND
The outcome of pediatric DCM patients ranges from recovery to a 50% to 60% chance of death within five years of diagnosis. The impact of heart transplantation and other emerging therapies on the outcomes of pediatric DCM patients is uncertain.

METHODS
We performed a retrospective study of the outcomes in 91 pediatric patients diagnosed with DCM from 1990 to 1999. Routine therapy included use of digoxin, diuretics, angiotensin-converting enzyme inhibitors, and heart transplantation.

RESULTS
At the time of last follow-up, 11 patients (12%) had died without transplantation; 20 (22%) underwent transplantation; 27 (30%) had persistent cardiomyopathy; and 33 (36%) had recovery of left ventricular systolic function. Overall actuarial one-year survival was 90%, and five-year survival was 83%. However, actuarial freedom from “heart death” (death or transplantation) was only 70% at one year and 58% at five years. Multivariate analysis found age <1 year (hazard ratio 7.1), age >12 years (hazard ratio 4.5), and female gender (hazard ratio 3.0) to be significantly associated with a greater risk of death or transplantation and a higher left ventricular shortening fraction at presentation (hazard ratio 0.92), with a slightly decreased risk of death or transplantation.

CONCLUSIONS
Pediatric DCM patients continue to have multiple outcomes, with recovery of left ventricular systolic function occurring most frequently. Utilization of heart transplantation has led to improved survival after the diagnosis of pediatric DCM.

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Although progress has been made in understanding the multiple infectious, metabolic, and myocardial protein mutation etiologies that result in a diagnosis of pediatric dilated cardiomyopathy (DCM) (1,2), the prognosis of DCM in infants, children, and adolescents has been guarded, with five-year survival reported to be no >64% (3–6). In the St. Louis area, survival after the diagnosis of DCM two decades ago was only 50% (7,8). These results led some institutions to recommend early consideration of heart transplantation for pediatric DCM (3–5,7).

The decision to proceed with heart transplantation for pediatric DCM is complicated by the possibility that these patients can demonstrate eventual improvement and resolution of left ventricular (LV) dilation and dysfunction (4,5,9). Besides heart transplantation, other new therapies such as metabolic component supplementation (10), angiotensin-converting enzyme (ACE) inhibition (11), and most recently beta-blockade (12) have been utilized as therapy that may also affect outcome and/or improvement in LV structure and function.

This study was done to delineate the recent course and multiple outcomes of pediatric DCM patients when heart transplantation was routinely used as a final therapeutic option and to determine if there were identifiers at the time of presentation that could determine which patients will recover cardiac function and which patients will require transplantation for survival.

METHODS

Patient population. Data for this review were collected with the approval of the Committees on Human Research at St. Louis Children’s Hospital and Cardinal Glennon Children’s Hospital, St. Louis, Missouri. Data were primarily collected using standardized collection forms of the North American Pediatric Cardiomyopathy Registry (13). Patients were eligible for the study if they were <21 years of
outcomes of interest. We also created a composite outcome termed “primary outcomes of interest.”

**Abbreviations and Acronyms**

- ACE = angiotensin-converting enzyme
- CI = confidence interval
- DCM = dilated cardiomyopathy
- ICU = intensive care unit
- IVGG = intravenous gamma globulin
- LV = left ventricular
- LVEDD = left ventricular end-diastolic dimension
- LVEF = left ventricular ejection fraction
- LVESD = left ventricular end-systolic dimension
- LVSF = left ventricular shortening fraction

Patients with structural congenital heart disease, valvular heart disease, arrhythmia-induced cardiomyopathy, and secondary cardiomyopathies, as a result of endocrine, renal, or oncologic (anthracycline toxicity) etiology, were excluded. Myocarditis was diagnosed if either endomyocardial biopsy or autopsy results fulfilled the Dallas criteria (14), or if the cardiomyopathy was associated with a prodromal viral illness and evidence of positive viral cultures or rising viral serologic titers on follow-up.

**Patient variables.** We retrospectively collected epidemiologic and clinical data recorded at the time of presentation. Etiologic work-up to search for myocarditis and/or genetic or metabolic cardiomyopathy included a thorough family history of myocardial disease; genetic, infectious, and metabolic testing; and occasionally endomyocardial biopsy. Medications begun within two weeks of presentation were recorded as diuretics, digoxin, ACE inhibitors, antiarrhythmic agents, intravenous gamma globulin (IVGG), or beta-blockers. Critical illness at the time of presentation requiring admission to the intensive care unit (ICU), with use of intravenous inotropic support or mechanical circulatory assistance, was recorded. M-mode echocardiographic data consisted of left ventricular shortening fraction (LVSF), left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), LV volume, and LV posterior wall and septal thicknesses. We analyzed LVSF as a raw value, but converted LV dimensions and wall thicknesses to the body surface area-appropriate z scores for analysis. Dilated cardiomyopathy was defined by the presence of LVSF or left ventricular ejection fraction (LVEF) $>2$ SD above the normal mean value for age and LVEDD or LV volume z score of $>2$.

Patients were followed yearly after presentation. Data on outcome, medications, and echocardiographic variables were recorded at each examination.

**Outcomes.** Death, heart transplantation, recovery of LV systolic function, and persistent cardiomyopathy were the primary outcomes of interest. We also created a composite outcome termed “heart death,” which combined patients who died or underwent heart transplantation. During follow-up, LV systolic function was determined to have recovered when LVSF fell within 2 SD of the mean value for body surface area. The indications for heart transplantation over the recruitment period were generally intractable cardiac failure leading to dependence on inotropic medications, growth failure, or both, and were consistent with American Heart Association guidelines (15).

**Statistical analysis**. Median values and ranges were calculated for all nonparametric data that did not follow a normal distribution, whereas mean values $\pm$ SD were calculated for parameters with normal distribution. Normality of the distribution was assessed by inspection of plots, including stem-and-leaf, box, and normal scores plots. The time-to-event data were not assumed to be normally distributed. We used the Kaplan-Meier product limit method, which does not assume an underlying form for the data. The SAS program (SAS Institute, Cary, North Carolina) calculated the corresponding estimates of the standard error, using Greenwood’s formula (16). A standard normal distribution is used to put the confidence interval (CI) on the time-to-event curve. Comparison of patient variables among patient outcomes was performed with the Fisher exact test for categorical variables and the Wilcoxon/Mann-Whitney $U$ test for continuous variables. Univariate analysis of patient variables related to outcome was performed using the Kaplan-Meier limit method, in conjunction with Cox proportional hazards analyses. Multivariate Cox proportional models were created based on the results of the univariate analyses. A value of $p < 0.05$ was utilized as the criterion for statistical significance. Analysis was carried out in SAS version 8.1. Standard SAS procedures, in particular, proc lifetest and proc phreg, were utilized. Models were validated using standard diagnostics, such as deviance on the basis of clinical significance, and model fit was assessed using plots and measures of information, such as Akaike’s information criterion.

**RESULTS**

**Patient population and presentation.** We identified 91 children who were diagnosed with DCM between the beginning of 1990 and the end of 1999 (Table 1). The age ranged from birth to 18 years; 23 (25%) were $<$1 year of age at presentation, 53 (48%) were between 1 and 12 years of age, and 25 (27%) were over 12 years of age. Almost four-fifths (79%) of the children presented with symptoms of congestive heart failure, and 35% underwent ICU admission at the time of presentation. The other children were identified during evaluation of a heart murmur, observation of cardiomegaly on a chest radiograph, or evaluation because of a family history of cardiomyopathy. One family had two children in the group; both experienced symptomatic heart failure during the study period. No other multiple family members with DCM were included in the subject group. A specific etiology for DCM was made in 39.5% (myocarditis 13%, dystrophin gene defect 12%, familial [history of at
least two family members] cardiomyopathy 9%, and metabolic disorders 5.5%. Metabolic disorders included mitochondrial myopathies (n = 3), Barth syndrome (n = 1), and long-chain fatty acid breakdown disorder (n = 1). Endomyocardial biopsies were performed within two weeks of diagnosis in 23 patients: 9 were diagnostic for myocarditis, 5 revealed endocardial fibroelastosis, and the other 9 showed nonspecific findings.

Treatment with ACE inhibitors was administered to 73% of patients within two weeks of diagnosis and to 86% of the subgroup of patients with congestive heart failure. Digoxin and diuretics were instituted with a similar frequency. After 1994, IVGG was given per the protocol of Drucker et al. (17) for a clinical suspicion of myocarditis, often before endomyocardial biopsy. Three patients were placed on mechanical circulatory support (two with extracorporeal membrane oxygenation and one with a ventricular assist device) at the time of presentation.

**Patient outcomes.** At the most recent follow-up, 11 (12%) of the 91 children died and did not receive a transplant. Of these 11 children, 4 had severe Duchenne’s muscular dystrophy and were not considered heart transplant candidates. Of the 20 (22%) who underwent heart transplantation, all but 4 were receiving inotropic support (United Network for Organ Sharing [UNOS] status 1) at the time of transplantation. Thus, 31 patients (34%) had “heart death.” Evidence of persistent cardiomyopathy was found in 27 children (30%) at their last follow-up, none of whom had undergone transplantation. Recovery of LV systolic function (improvement of LVSF within 2 SD from the mean value of the standardized population) at the time of last follow-up occurred in 33 children (37%). When patients with myocarditis were excluded from the analysis, there were similar proportions of patients with heart death (36%), persistent cardiomyopathy (30%), and recovery of LV systolic function (34%).

Within the first year after diagnosis, 90% of the transplantsations and 64% of the deaths occurred (Fig. 1). Although the majority (57%) of children who underwent recovery of LV systolic function did so in the first year, a substantial proportion returned to normal up to six years after presentation. Three of the seven children who died within a year of presentation were UNOS status 1 (inotrope-dependent) heart transplant candidates at the time of death. Two died in cardiogenic shock associated with multi-organ failure that precluded transplantation, and one was not considered for heart transplantation due to muscular dystrophy. One patient with idiopathic DCM died suddenly two years after presentation. The three late deaths, at five, six, and eight years after presentation, were in children with muscular dystrophy who were not considered heart transplant candidates. All three died with intractable heart failure associated with atrial flutter (n = 1) or fibrillation (n = 2).

Actuarial survival of the children from the time of diagnosis was 90% at one year (82 of 91) and 83% (76 of 91) at five years (Fig. 2). Death after transplantation has not occurred in this cohort, and no child with recovery of LV systolic function has died. Freedom from “heart death” decreased from 70% at one year to 58% at five years after presentation (Fig. 3).

**Relation of outcomes to characteristics at presentation.** Different age groups at the time of presentation had different frequencies of outcomes during follow-up (Table 2). Fifty-seven percent of children presenting with DCM at <1 year of age and 47% presenting at >12 years of age at the time of diagnosis had a heart death, whereas 49% of those children who were diagnosed with DCM between 1 and 12 years of age had recovery of LV systolic function. However, there were considerable proportions of each age group among the various outcome groups (Table 2). Recovery of LV systolic function occurred in 48% of children whose diagnosis occurred in conjunction with admission to an ICU. However, recovery also occurred in 23% of patients whose diagnosis did not occur in conjunction with an ICU admission.

Median baseline z scores for LVEDD and LVESD were significantly higher in patients with heart death and significantly lower in patients whose LV systolic function recovered to normal. The opposite was true for median baseline LVSF values, which were significantly lower in patients with heart death and significantly higher in patients with recovery of LV systolic function. The large overlap of individual echocardiographic variables among the outcome

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics at Presentation (n = 91)</th>
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<tbody>
<tr>
<td>Median age (range) at presentation (yrs)</td>
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<tr>
<td>Male gender</td>
</tr>
<tr>
<td>Caucasian</td>
</tr>
<tr>
<td>African American</td>
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<tr>
<td>Presentation characteristics</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>ICU admission at presentation</td>
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<tr>
<td>Arrhythmia</td>
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<tr>
<td>Asymptomatic</td>
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<tr>
<td>Etiology of dilated cardiomyopathy</td>
</tr>
<tr>
<td>Myocarditis</td>
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<tr>
<td>Dystrophin gene defects</td>
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<tr>
<td>Familial</td>
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<tr>
<td>Metabolic</td>
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<tr>
<td>Idiopathic</td>
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<tr>
<td>Medications initiated within 2 weeks of presentation</td>
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<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>All patients</td>
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<tr>
<td>With heart failure</td>
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<td>Diuretics</td>
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<td>With heart failure</td>
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<td>ACE inhibitors</td>
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<td>With heart failure</td>
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<td>IVGG*</td>
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<td>All patients</td>
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<td>With heart failure</td>
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*Intravenous gamma globulin (IVGG) used after 1994. ACE = angiotensin-converting enzyme; ICU = intensive care unit.
groups negated correlating an individual patient’s outcome with LV size and systolic function at the time of presentation, despite the significant differences in echocardiographic variables for the outcome groups as a whole. Race, family history of cardiomyopathy, presence of congestive heart failure, etiology of cardiomyopathy, presence of arrhythmia, or use or non-use of any particular medication did not differ significantly among the outcome groups.

Risk factors for outcome. Univariate analysis identified female gender ($p = 0.02$), age $<1$ year ($p = 0.002$), age $>12$ years ($p = 0.006$), lower LVSF $z$ scores ($p = 0.006$), and higher LVESD $z$ scores ($p = 0.03$) as variables at presentation significantly associated with death or transplantation. Admission to an ICU at the time of diagnosis ($p = 0.017$) was, interestingly, significantly associated with recovery of systolic function.

Figure 1. Time to outcome after presentation among 91 children with dilated cardiomyopathy. The percentage of patients with a given outcome (transplantation, recovery, or death) is shown as a function of year of follow-up. Patients are censored from ongoing follow-up once they have undergone transplantation, died, or had recovery of left ventricular systolic function. Thus, the figure represents new outcomes that occurred in the cardiomyopathy patients available for follow-up at the given time interval.

Figure 2. Overall survival for 91 children with dilated cardiomyopathy (95% confidence bands are shown). Last follow-up times are indicated by “+” for patients alive at the end of the study.
Multivariate analysis identified no variables that predicted a return to normal systolic function. Hazards ratios for increased risk of death or transplantation were 7.1 (95% CI 2.6 to 19.2) for age <1 year, 4.5 (95% CI 1.6 to 12.7) for age >12 years, and 3.0 (95% CI 1.4 to 6.2) for female gender. Higher LVSF at presentation was associated with a slight decreased risk of death or transplantation (odds ratio 0.92, 95% CI 0.87 to 0.98).

**DISCUSSION**

Recent epidemiologic studies in Australia and the U.S. have found pediatric DCM to occur with an incidence of 1.13 to 1.24 per 100,000 children (1,2). Pediatric DCM has multiple causes, including infection, mutations of myocardial cytoskeletal and structural proteins, and disorders of myocardial metabolism. Although most cases of pediatric DCM are idiopathic, diagnostic algorithms (18) have increased the proportion of pediatric DCM cases with a known cause. This trend is reflected in our study, in which a cause of DCM was identified in nearly 40% of children.

Pediatric DCM may have any of several outcomes. Reported five-year survival rates range between 50% and 60% (3–8). These grim statistics have led investigators to recommend early consideration of heart transplantation for these children (3–5,7). Cardiac transplantation was routinely used as a final therapeutic strategy for our patients, and these children had a five-year survival rate of more than 80%. Additional therapies were also utilized in this group before transplantation, which may have contributed to improved outcome. The use of ACE inhibitors has been reported to be associated with improvement of LV dysfunction in children (11,19). Larger adult studies, however, have not noted improvement, but inhibition of progression of LV dilation and dysfunction with ACE inhibitor administration (20). Preliminary evidence indicates that beta-blocker therapy can improve LV dysfunction in pediatric DCM (21). Retrospective studies have suggested that administration of IVGG leads to improvement of LV dysfunction in pediatric LV systolic dysfunction thought to be due to myocarditis (17), but those results were not replicated in a randomized, placebo-controlled study in adults with acute-onset DCM (22). Refinements in critical care and inotropic support undoubtedly improved the survival rate of patients who were critically ill in an ICU and also helped end-stage patients to survive until transplantation. Two of the three patients placed on mechanical support ultimately survived: one with residual cardiomyopathy and one whose LV systolic function recovered. However, the proportions of patients who either died or received a transplant (those who had a heart death) were similar to previous, older outcome studies.

**Table 2.** Significant Dilated Cardiomyopathy Patient Characteristics at Presentation That Were Associated With a Specific Outcome

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Median LVEDD z Score (Range)</th>
<th>Median LVESD z Score (Range)</th>
<th>Median LVSF Raw Score (Range)</th>
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<tbody>
<tr>
<td><strong>p Value</strong></td>
<td></td>
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</tr>
<tr>
<td>Recovery</td>
<td>0.0048* (Fisher exact test)</td>
<td>0.0219* (Wilcoxon-Mann-Whitney U test)</td>
<td>0.0008† (Fisher exact test)</td>
</tr>
<tr>
<td>Myopathy</td>
<td>0.0005† (Fisher exact test)</td>
<td>0.0005† (Fisher exact test)</td>
<td>0.0033† (Fisher exact test)</td>
</tr>
<tr>
<td>Heart death</td>
<td>0.0008† (Fisher exact test)</td>
<td>0.0005† (Fisher exact test)</td>
<td>0.0033† (Fisher exact test)</td>
</tr>
</tbody>
</table>

*ICU = intensive care unit; LVEDD and LVESD = left ventricular end-diastolic and -systolic diameter, respectively; LVSF = left ventricular shortening fraction.
Thus, it would appear the primary factor that improved survival in this group of pediatric DCM patients was heart transplantation.

The limited donor pool for heart transplantation and the potential for recovery of LV dysfunction make identification of profiles that lead to either death or transplantation versus recovery of function of critical importance for patients with pediatric DCM. Poorer initial LV systolic function at presentation was only mildly associated with a greater risk of death or transplantation and correlates with similar findings in the National Australian Childhood Cardiomyopathy Study (6). Although median LV systolic function at presentation was significantly different among the outcome groups, the large overlap of values precludes using this and other echocardiographic variables as predictors for clinical decision-making. Furthermore, severe illness on presentation leading to ICU admission was associated with patients who recovered their LVEF on follow-up. These findings are consistent with patients who present with “fulminant myocarditis,” who tend to have good outcomes despite critical illness at the time of presentation (23).

Age <1 year or >12 years was associated with an increased risk of death or transplantation in this cohort. These findings are similar to the age-specific determinants of outcome in pediatric DCM in a recent Finnish population-based study (5). Older studies relating age of presentation to outcome with pediatric DCM have given conflicting results (3,4,7,8,24,25). The substantial proportions of infants and adolescents who recover their LVEF or do not die or undergo transplantation make age-specific predictors of outcome difficult to apply to direction of therapies like heart transplantation. The group of patients age 1 to 12 years at presentation not only had a smaller proportion die or undergo transplantation, but also had a greater proportion who recovered their LVEF, as compared with the infant and adolescent groups. This group of children conceivably may have had a greater proportion of DCM due to myocarditis, compared with the known tendency toward many lethal metabolic cardiomyopathies to present in infancy (26) and the tendency toward cardiomyopathies due to dystrophin mutations to present in adolescence.

In our study, female gender was found to be a poor predictor of outcome. The reason for this result is uncertain. Female gender has been associated with late cardiomyopathies in anthracycline-treated survivors of childhood cancer (27). However, young adult women with idiopathic DCM have been reported to have a poor outcome (28). One study of adult DCM patients found high soluble interleukin-2 receptor serum levels, a measure to T-lymphocyte activation, to be associated with poorer ejection fractions and cardiac output and to occur more frequently in female patients (29). Further study is needed to confirm this finding and to investigate potential immunologic or hormonal factors that may contribute to this phenomenon.

Our results confirm those of earlier studies, which have found that most major clinical events occur within one year of presentation (3,5,25). The high proportion of deaths or transplantation that occurred within one year after presentation suggests many patients with pediatric DCM, even those without a multi-system metabolic disease, are not diagnosed until they have end-stage disease that is not effectively palliated with the medical therapies used to treat them.

**Study limitations.** This study, although as large as or larger than previous outcome studies of pediatric DCM, suffers from a relatively small sample size that limits identification of risk factors for outcome. Follow-up of the patient population is short and cannot address the long-term outcomes of patients who receive a transplant, have persistent cardiomyopathy, or show recovery of LVEF. The age distribution of this cohort of patients does not reflect the finding of large epidemiologic studies that most pediatric DCM cases are diagnosed in infancy (1,2). This difference in age distribution may reflect a decreased ascertainment of infantile DCM in our referral region in the 1990s, or simply may be due to chance. The cohort had a higher percentage of DCM cases diagnosed with a specific etiology, compared with population-based studies, with a greater proportion of cardiomyopathies due to dystrophin mutations (1,2). The presence of a large, national muscular dystrophy center at Washington University may explain the presence of these phenomena in this patient population.

This study’s retrospective design further limits the number of variables to be studied. In addition, although diagnostic evaluations and initial therapeutic strategies were similar among the group, a standardized evaluation and therapeutic protocol were not followed within the group. Multiple physicians initiated, manipulated, and terminated therapy in different ways. This limitation prevented studying the effects of when and how cardiac medications were manipulated or terminated in relation to the outcomes.

**Conclusions.** Despite these limitations, this study nevertheless illustrates the improvement of survival in infants, children, and adolescents diagnosed with pediatric DCM offered by routine use of heart transplantation. Pediatric heart transplantation, however, is a time-limited therapy, with a currently estimated half-life of 13 years for a pediatric cardiac allograft (30). Furthermore, pediatric donor organs, especially for infant recipients, are scarce, and substantial numbers of potential pediatric recipients die before receiving an organ (31).

The potential for routine use of beta-blockade (32), resynchronization therapy (33), or statin therapy (34) to potentiate ventricular remodeling, improve survival, and prevent or delay transplantation remains to be fully evaluated in the pediatric population. Refinements in the diagnosis of myocarditis may improve prognostication of outcomes and potentially determine application of immunosuppressive/modulating therapy (35). The limitations of heart transplantation as therapy for pediatric DCM make it imperative that application of these new therapies for the
treatment of adult heart failure be extended to the treatment of pediatric DCM.

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REFERENCES


