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Ventricular Remodeling and Survival are More Favorable for Myocarditis Than For Idiopathic Dilated Cardiomyopathy in Childhood: An Outcomes Study from the Pediatric Cardiomyopathy Registry

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Susan R. Foerster MD, Washington University at St. Louis, Saint Louis, MO; Charles E. Canter MD, Washington University at St. Louis, Saint Louis, MO; Amy Cinar PhD, New England Research Institutes, Inc. Watertown, MA; Lynn A. Sleeper ScD, New England Research Institutes, Inc., Watertown, MA; Steven A. Webber MD, University of Pittsburgh, Pittsburgh, PA; Elfriede Pahl MD, Northwestern University, Chicago, IL; Paul F. Kantor MD, Hospital for Sick Children, Toronto, ON, Canada; Jorge A. Alvarez PhD, University of Miami, Miami, FL; Steven D. Colan MD, Children's Hospital Boston, Boston, MA; John L. Jefferies MD, Baylor College of Medicine, Houston, TX; Jacqueline M. Lamour MD, Albert Einstein College of Medicine, New York, NY; Renee Margossian MD, Children's Hospital Boston, Boston, MA; Jane E. Messere RN, Children's Hospital Boston, Boston, MA; Paolo G. Rusconi MD, University of Miami, Miami, FL; Robert E. Shaddy MD, University of Pennsylvania, Philadelphia, PA; Jeffrey A. Towbin MD, University of Cincinnati, Cincinnati, OH; James D. Wilkinson MD, MPH, University of Miami, Miami, FL; Steven E. Lipshultz MD, University of Miami, Miami, FL for the Pediatric Cardiomyopathy Registry (PCMR)

Correspondence to:
Susan R. Foerster, MD
Washington University in St. Louis
1 Children's Place, NWT 8
St. Louis, MO 63110
Email: Foerster_s@kids.wustl.edu
Ph: 314-454-6095
Fax: 314-454-2561

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Abstract

***Background*—**Myocarditis is one cause of a new-onset dilated cardiomyopathy phenotype in children, with small studies reporting high rates of recovery of left ventricular (LV) function.

***Methods and Results*—**The presenting characteristics and outcomes of children with myocarditis diagnosed clinically and with biopsy confirmation (BCM, n=119) or with probable myocarditis diagnosed clinically or by biopsy alone (PM, n=253) were compared to children with idiopathic dilated cardiomyopathy (IDCM, n=1123). Characteristics at presentation were assessed as possible predictors of outcomes. The distributions of time to death, transplantation, and echocardiographic normalization in the BCM and PM groups did not differ (P≥0.5), but both groups differed significantly from the IDCM group (all P≤0.003). In children with myocarditis, lower LVFS z-score at presentation predicted greater mortality (hazard ratio [HR]=0.85, 95% CI 0.73-0.98, P=0.03) and greater LV posterior wall thickness predicted transplantation (HR=1.17, 95% CI 1.02-1.35, P=0.03). In those with decreased LVFS at presentation, independent predictors of echocardiographic normalization were presentation with an LVEDD z-score >2 (HR=0.36, 95% CI 0.22-0.58, P<0.001) and greater septal wall thickness (HR=1.16, 95% CI 1.01-1.34, P=0.04).

***Conclusions*—**Children with biopsy-confirmed or probable myocarditis had similar proportions of death, transplant, and echocardiographic normalization 3 years after presentation and better outcomes than those of children with IDCM. In children with myocarditis who had impaired LV ejection at presentation, rates of echocardiographic normalization were greater in those without LV dilation and in those with greater septal wall thickness at presentation.

***Clinical Trial Registration*—**http://clinicaltrials.gov. Unique Identifier: NCT00005391.

Key Words: cardiomyopathy, mortality, myocarditis, pediatrics, remodeling

Introduction

While myocarditis and idiopathic dilated cardiomyopathy (IDCM) are considered distinct diseases (1), myocarditis frequently presents with a phenotype of new-onset dilated cardiomyopathy (2,3). It is the next most common diagnosis associated with a new-onset dilated cardiomyopathy phenotype after IDCM in multicenter pediatric registries (4-6).

When established histopathologic criteria (7) (the "Dallas criteria") have been used to diagnose myocarditis by endomyocardial biopsy in small single center studies in children, myocardial recovery occurs in > 50% of cases (8-12). The Dallas criteria, however, are felt to have relatively low sensitivity (13); and strong clinical and laboratory evidence of myocarditis can be identified in patients with negative biopsies (14,15).

The Pediatric Cardiomyopathy Registry (PCMR) is a multi-institutional, long-term study of children with cardiomyopathy (ClinicalTrials.gov identifier NCT00005391). While a previous PCMR analysis found children diagnosed with myocarditis to have lower risks for death and transplantation than children with IDCM (4), the degree of normalization of left ventricular function and size remains undetermined. The PCMR myocarditis cohort includes children with myocarditis who had endomyocardial biopsies which supported a pathologic diagnosis of myocarditis, and many where the diagnosis was made clinically with or without an associated negative endomyocardial biopsy. The objectives of the present analysis were: 1) to determine the magnitude of difference in left ventricular recovery between children with myocarditis and IDCM; 2) to determine the difference in

mortality, transplantation and echocardiographic normalization of PCMR patients with a clinical diagnosis of myocarditis confirmed by endomyocardial biopsy compared to the other children diagnosed with myocarditis; and 3) to assess the factors at presentation that may aid in predicting these outcomes. We hypothesized that myocarditis diagnosed clinically with biopsy confirmation would have better outcomes than myocarditis diagnosed without *both* criteria, and better outcomes than those with IDCM.

Methods

The PCMR has enrolled more than 3,500 infants, children, and adolescents with cardiomyopathy. Subjects were enrolled retrospectively if they were diagnosed with cardiomyopathy between 1990 and 1995, and prospectively thereafter. The PCMR has a standardized data collection protocol and manual of operations. At some institutions, local data collectors trained by the Data Coordinating Center (New England Research Institutes) and the Administrative Coordinating Center (University of Miami) collect baseline and annual data based on automated notification from the Data Coordinating Center. At other institutions, the University of Miami Data Collection Travel Team visits regularly to collect required data. Data collectors abstract clinical, echocardiographic (most recent study in the annual reporting period), and treatment data from the medical records of children until death or heart transplantation occurs. The data collection forms differed for retrospectively and prospectively enrolled patients, with limited data on family history, hospitalization, and medications for the prospective cohort. All centers obtain Institutional Review Board approval or waiver for data transmission to the PCMR Data Coordinating Center and analyses of the database.

Patients are eligible for PCMR enrollment if they are less than 18 years old and if they have one of the following: echocardiographic evidence of cardiomyopathy; pathologic diagnosis of cardiomyopathy at autopsy or endomyocardial biopsy; or other clinical evidence of cardiomyopathy provided by the cardiologist (16). A dilated cardiomyopathy phenotype in the PCMR is defined as a left ventricular fractional shortening (LVFS) less than 2 standard deviations (SD) for age and a left ventricular end-diastolic dimension (LVEDD) or volume greater than 2 SD for body surface area, evidence from autopsy or myocardial tissue analysis, or the presence of other compelling evidence from the investigator (4). The 14 clinical exclusion criteria include associated congenital heart disease, endocrine disorders known to cause myocardial damage, chemotherapy or pharmacologic-associated cardiotoxicity, chronic arrhythmia, pulmonary parenchymal or vascular disease, or immunologic disease.

The causal diagnosis of cardiomyopathies within the PCMR is subdivided into 6 broad areas: *neuromuscular disorder*, when muscular dystrophies or other neuromuscular disease coexists; *familial,* made in the presence of specifically identified genetic cardiomyopathies, existence of cardiomyopathy in multiple family members, or upon family screening; *malformation syndrome*, when identified congenital malformation syndromes coexist; and *metabolic*, when a specific disorder of metabolism or a mitochondrial disorder coexists. A diagnosis of *myocarditis* is made with a presentation of new-onset cardiac symptoms and/or echocardiographic abnormalities developing after a history of recent respiratory, gastrointestinal, or other suspected viral infection. A

diagnosis of "*idiopathic*" is made when no specific causal diagnosis is identified in the medical record.

Three groups of children were analyzed for this study. A biopsy-confirmed myocarditis (BCM) group consisted of 119 subjects who carried a causal diagnosis of myocarditis and also had endomyocardial biopsy evidence of *both* inflammatory infiltration and cellular necrosis, as per the Dallas criteria (7). The probable myocarditis group (PM) consisted of 253 subjects who were either: 1) given a causal diagnosis of myocarditis but did not undergo endomyocardial biopsy or had biopsies described as "borderline" or nondiagnostic; or 2) given a causal diagnosis of IDCM but had endomyocardial biopsies demonstrating both inflammatory infiltration and myocellular necrosis (n=19), as has been done in other studies evaluating IDCM patients with endomyocardial biopsy (15,17,18). An idiopathic dilated cardiomyopathy group consisted of 1123 subjects who were given a causal diagnosis of IDCM and had negative biopsies, if performed. All descriptions for biopsies performed in patients in each group were reviewed by a senior investigator (CEC) before any child was included in the three groups.

Statistical Methods

Patient characteristics were compared among the BCM, PM, and IDCM diagnostic groups using a Fisher exact test for categorical variables and a Kruskal-Wallis test or analysis of variance for continuous variables, according to whether the distribution of the variable approximates a normal distribution. Alpha was set at 0.05, and all tests were two-sided.

Study outcomes were death, heart transplantation, and "echocardiographic normalization". Echocardiographic normalization was defined as attaining both an age-adjusted LVFS z-score of -2 or more and a body-surface-area-adjusted LVEDD z-score of 2 or less (19) noted from the most recent echocardiogram results available in each annual reporting period of PCMR patients.

A competing-risks analysis was performed for each diagnostic group, and the cumulative incidence rates of study outcomes were calculated (20). P-values were obtained from competing-risks Cox proportional hazards regression (21). Augmented Cox proportional hazards modeling for competing risks (22) was used to simultaneously identify risk factors for mortality and transplantation in children with myocarditis and included tests of interaction to investigate potential differential risk factors for the BCM and PM groups. Factors with a univariate P-value less than 0.2 were considered in the multivariable analyses, with staged assessment of collinearities.

In the combined BCM and PM cohort, a second set of analyses focused on echocardiographic normalization was performed in children presenting with decreased LVFS (z-scores < -2). A primary comparison of interest was between those with and without a dilated left ventricle (LVEDD z-scores > 2 vs. ≤ 2) at presentation. These subgroups were chosen on the basis of the work by Felker et al. (23), who suggested that an echocardiographic pattern of reduced left ventricular ejection with a lack of left ventricular dilation at presentation was a marker for fulminant myocarditis, which has a

particularly favorable outcome in children and adults with myocarditis (24,25). Cox proportional hazards modeling was used to identify predictors of echocardiographic normalization, with time to normalization censored at death or transplant. Excluded from modeling of recovery were 14 children with both normal LVFS and LVEDD z-scores at diagnosis, and 4 children with normal LVFS in the presence of dilation, due to limited numbers.

The SAS statistical software package, version 9.1 (SAS Institute, Cary, North Carolina), was used for all analyses. Competing risks analyses were performed using an SAS macro provided by Tai (20) and an R macro by Fine and Gray (21).

Results

Clinical Profiles at Presentation

The median follow-up time for survivors not undergoing heart transplantation was 3.1 years ([Q1,Q3], 0.9 to 6.2 years) in the BCM group and 2.7 years ([Q1,Q3], 1.0 to 6.0 years) in the PM group. Median follow-up time for survivors with IDCM not undergoing heart transplantation was 1.9 years ([Q1,Q3], 0.4 to 4.3 years). Complete data for some variables were not available for all children, especially with regard to hospitalization and specific therapies due to differing data collection for the prospective and retrospective cohorts (Table). Although all groups were similar with regard to sex and race/ethnicity, the children with IDCM tended to be diagnosed at a younger age than the myocarditis groups: the percentage of children presenting before 1 year of age was 47% in the IDCM

group and 33% and 25% in the PM and BCM groups, respectively (P<0.001). The age distributions of the BCM and PM groups were not significantly different.

Although at least three-quarters of the children in each group were hospitalized, had congestive heart failure, and were treated with congestive heart failure therapy within 30 days of presentation, a significantly greater proportion of the BCM group had these characteristics than did either of the other groups. Among children with hospitalization data, 82% of the BCM group was admitted to an intensive care unit, compared to about 50% of the PM or IDCM groups (P<0.001).

None of the patients were recorded to have been diagnosed with giant cell or eosinophilic myocarditis. Data on viral serologic testing and the presence of virus in the myocardium by polymerase chain reaction (PCR) techniques were very limited in the database. It was documented that viral serology or PCR was performed in 94 patients. Of these, 31 (33%) had a positive finding, which included 10 cytomegalovirus, 6 Coxsackie virus, 5 enterovirus, 3 adenovirus, 2 Epstein-Barr virus, 2 herpes simplex virus, and 1 each of hepatitis B virus, respiratory syncytial virus, and parvovirus.

More than two-thirds of each group demonstrated left ventricular dilation (LVEDD z-score >2) and more than 90% had evidence of decreased left ventricular systolic function (LVFS z-score < -2) at presentation (Table). However, the IDCM group had a higher mean (±standard deviation) LVEDD z-score [4.8±2.6] than that of the BCM [3.8±2.4] and PM [3.4±2.7] groups (P<0.001) and a lower median LVFS z-score (median -9.7) than

that of the two myocarditis groups (-9.1 and -8.6), respectively (P=0.001). In addition, the myocarditis groups had significantly higher LV posterior and septal wall thickness z-scores than did the IDCM group, but all group medians were within one standard deviation of normal (z-score = -1 to +1).

Outcomes

The analyzed outcomes of echocardiographic normalization, heart transplantation, or death occurred in more than 70% of children in each group within 3 years of presentation, with the remainder having persistent echocardiographic abnormalities in LV size or systolic function (Figures 1A-1C). All groups continued to experience events, primarily echocardiographic normalization, more than 3 years after presentation. Both the BCM and the PM group had 4 subjects die greater than 3 months after presentation. All of these late deaths were attributed to heart failure and persistent LV dysfunction except for one patient who died from a respiratory syncytial virus infection superimposed on chronic heart failure. No patient died after echocardiographic normalization. The one patient (in the BCM group) reported to have transplantation after echocardiographic normalization was noted to have "global LV dysfunction" on the echocardiogram report, suggesting an error in the specific LVFS and LVEDD measurements on that study.

In the BCM, PM, and IDCM groups there were 10, 17, and 168 deaths, respectively. In the BCM, PM, and IDCM groups there were 21, 38, and 323 transplants, respectively. The distributions of time to death, transplantation, and echocardiographic normalization in the BCM and PM groups did not differ by group ($P \geq 0.5$), but both groups differed significantly from the IDCM group (all $P \leq 0.003$) (Figure 1). For example, at 3 years after presentation, 6% and 7%

of the BCM and PM groups, respectively, had died without heart transplantation; 19% and 17% had received heart transplantation; and 54% and 52% had achieved echocardiographic normalization. In the IDCM group, 17% had died without transplantation, 33% had undergone heart transplantation, and only 21% had achieved echocardiographic normalization at 3 years.

Characteristics at Presentation Associated with Death, Transplantation or Echocardiographic Normalization

Because outcomes did not differ between the BCM and PM groups, they were combined in competing risk factor analyses for death and transplantation. Tests of interaction found no evidence that risk factors differed between BCM and PM children. The following factors at presentation had P-values less than 0.2 in univariate Cox proportional hazards models for death (controlling for myocarditis group) and were assessed in multivariable modeling: congestive heart failure (hazard ratio [HR] 2.56; 95% confidence interval [CI] 0.76 to 8.61; P=0.13) and LVFS z-score (HR 0.85; 95% CI 0.73 to 0.98; P=0.03). The multivariable model indicated that only LVFS z-score at presentation was independently a significant risk factor for death (n=305).

The following univariate risk factors at presentation had P-values less than 0.2 in Cox proportional hazards models for transplantation (again controlling for myocarditis group) and were assessed in multivariable modeling: congestive heart failure (HR 2.02; 95% CI 0.85 to 4.82; P=0.12), older age at diagnosis of cardiomyopathy (HR 1.03 per year; 95% CI 1.00 to 1.06; p=0.10), higher end-diastolic posterior wall thickness z-score (HR 1.17;

95% CI 1.02 to 1.35; p=0.025), and lower end-diastolic posterior wall to septal thickness ratio (HR 0.91 per 0.1 unit decrease; 95% CI 0.84 to 0.98; P=0.018). The multivariable model indicated that only posterior wall thickness z-score at presentation independently predicted transplantation (n=228).

In children with myocarditis presenting with reduced systolic function, Cox modeling for echocardiographic normalization found an LVEDD z-score greater than 2 at presentation highly predictive for lower rates of normalization (HR 0.39; 95% CI 0.27 to 0.59; P<0.001). Controlling for this factor, other risk factors in bivariable models were: age category at diagnosis (HR 2.01 for 1 to < 6 years vs. < 1 year; 95% CI 1.25 to 3.23; P=0.03); a family history of sudden death (HR 10.73; 95% CI 1.97 to 58.39; P=0.006); increasing LV septal wall thickness (HR 1.16; 95% CI 1.01 to 1.34; P=0.04); and use of intravenous gamma globulin (IVIG) (HR 2.99; 95% CI 1.69 to 5.29; P< 0.001).

Multivariable analysis resulted in a two-variable model in those presenting with decreased systolic function (N=170): LVEDD z-score greater than 2 at presentation was associated with a lower chance for echocardiographic normalization (HR 0.36; 95% CI 0.22 to 0.58; P<0.001), whereas a greater septal wall thickness at presentation was associated with an increased likelihood of echocardiographic normalization (HR 1.16; 95% CI 1.01 to 1.34; P=0.04). The use of IVIG was not an independent predictor of echocardiographic normalization because of its association with LVEDD z-score at presentation: 27% of those with z-scores of 2 or below and only 12% of those with z-scores above 2 received IVIG.

Children with myocarditis and a LVFS z-score of less than 2 without LV dilation at presentation had a faster and higher rate of echocardiographic normalization by 3 years, compared to those with dilation (72% vs. 46% respectively; P<0.001 (Figures 2A, 2B). They also had a substantially lower rate of transplantation (4% vs. 23%; P=0.016), but the proportion of deaths without transplantation did not differ significantly (10% vs. 5%; P=0.45).

Discussion

The PCMR and the National Australian Childhood Cardiomyopathy Study (4,5) have established that children with a new-onset dilated cardiomyopathy phenotype have a better prognosis if they are diagnosed with myocarditis than with IDCM. However, these studies did not evaluate differences in the resolution of echocardiographic abnormalities between subgroups. Recent single-center case series of pediatric myocarditis diagnosed histopathologically by the Dallas criteria and treated with IVIG, steroids, and/or other immunosuppressants have reported a majority of children with myocarditis will demonstrate resolution of their dilated cardiomyopathy phenotype within a few months after presentation (9-12). Furthermore, Gagliardi et al (9) found biopsy-dependent differences in response to therapy. In their study, LV function normalized in 77% of patients with biopsies showing "active" myocarditis by the Dallas criteria when treated with prednisone and cyclosporine compared to only 46% of patients diagnosed with "borderline" myocarditis who received the same treatment.

We also found that the dilated cardiomyopathy phenotype resolved in the majority of children with myocarditis within the PCMR; in addition, we noted that histopathologic findings using the Dallas criteria were not related to outcomes. We observed that the dilated cardiomyopathy phenotype can resolve years after its initial presentation, even in patients with IDCM.

A marked disparity in outcomes exists in children with a new-onset dilated cardiomyopathy phenotype associated with myocarditis compared to those with idiopathic cardiomyopathy, which means that differentiating these diseases is an important part of the initial diagnostic and treatment plan. Clinical differentiation on the basis of a preceding viral prodrome as is used in adults (26,27) may be more difficult in children, given their increased frequency of viral infections or viral syndromes in general (6). In Arola's (28) study of idiopathic pediatric dilated cardiomyopathy in Finland, 47% of the patients reported a recent respiratory or gastrointestinal illness. This experience would make histopathologic analysis of endomyocardial biopsies an attractive option for diagnosing pediatric myocarditis.

However, numerous recent reviews of adult myocarditis (2,3,14) have concluded that the diagnosis of myocarditis should not be based on histologic findings alone, due to the lack of association of biopsy findings in large cohorts of patients with suspected myocarditis, inconsistencies with clinical and histological features of myocarditis, and the inherent insensitivity of histologic diagnosis, including with use of the Dallas criteria. Thus, although our study is limited by the lack of a central laboratory to evaluate

endomyocardial biopsies and echocardiographic findings, and a common and specific prospective, non-invasive evaluative protocol for the clinical diagnosis of myocarditis, our results indicate that children listed in the PCMR who were suspected of having myocarditis clinically, with or without biopsy confirmation, had substantially better outcomes than did children with a the diagnosis of IDCM.

Although outcomes were poorer in the IDCM group, a substantial proportion of these children (21%) exhibited LV echocardiographic normalization by 3 years after diagnosis. Recovery of LV function in pediatric IDCM has been observed in single center reviews in proportions similar to what we observed (29-31). Some of these patients may truly have had myocarditis; in our own cohort, a few children given a causal diagnosis of IDCM had biopsies diagnostic of myocarditis.

Many cases of IDCM are hypothesized to evolve from an initial viral infection of the heart (32) and multiple studies have identified viral genomes within the myocardium of IDCM patients (33-35). One study found a correlation with disappearance of myocardial viral genomes and LV recovery in adults with IDCM (36). "Recovery" may also reflect the effects of pharmacotherapy. A recent study (31) in children with IDCM who recovered LV function demonstrated recurrence of LV dysfunction when drug therapy was withdrawn.

Limitations of the study

Since the inception of data collection within the PCMR in the early 1990s, the clinical entity of "fulminant myocarditis" has been identified (24) and been found to be associated with high rates of resolution of abnormalities in LV size and function. The timing of this discovery precluded incorporation of the diagnostic criteria for fulminant myocarditis in the analysis of outcomes for myocarditis in subjects in the PCMR. However, our findings confirm that the echocardiographic phenotype of fulminant myocarditis observed in adults (reduced LV function with normal LV chamber size) (23) was also associated with a very high (nearly 80%) rate of echocardiographic normalization in PCMR subjects with myocarditis.

We have estimated the time to echocardiographic normalization based on data from the most recent echocardiogram in each annual reporting period. For many patients, surveillance is indeed comprised of only an annual exam. Therefore, the estimated times to normalization presented here are an upper limit, since normalization may have occurred at some time prior to the time of the echocardiogram.

Information about specific viral etiologies for myocarditis is limited in the PCMR database. The technologies for detecting viral genomes in the myocardium largely evolved after the inception of the PCMR (26,27,35,37). Viruses such as adenovirus, parvovirus B19, and human herpes virus 6 were not considered common viral agents for pediatric myocarditis at the inception of the PCMR. Although there is some evidence that certain viruses may be associated with poorer outcomes than others (27), the

presence of viral genome (or histopathologic findings as in the Dallas criteria) was not associated with outcome in a recent study of adult myocarditis (26).

The Australian registry (5) has identified failure to increase LVFS at follow-up as a risk factor for death or heart transplantation in children with a new-onset dilated cardiomyopathy phenotype. In that study, echocardiographic data are recorded, if available, quarterly in the first year after presentation, compared to annually in the PCMR. As a large number of outcome events occurred within the first year of presentation in this study, the availability of only annual echocardiographic data in the PCMR precludes assessment of changes in LVFS as an outcomes marker in this study.

Multivariable analyses in our study found no association of IVIG or corticosteroids with survival or LV normalization. These findings are similar those of the Children's Hospital of Pittsburgh (8), previous adult and pediatric systematic reviews (38,39), and randomized trials in adults (40,41). Recent pediatric studies using various regimens of IVIG and immunosuppression have reported somewhat higher rates of LV recovery than we did (9-12). The power of our assessment of the effects of IVIG and steroids on outcome is limited by capture of therapeutic information in only a subset of patients, and may be biased by the lack of random assignment to these treatments. Thus, our findings do not necessarily mean that IVIG and steroids do not have a role in the treatment of myocarditis in children.

The PCMR database did not collect information on patient status at the time of listing or performance of heart transplantation. However, many PCMR centers also participate in the Pediatric Heart Transplant Study (PHTS) where this information is collected and where myocarditis and IDCM are specifically identified subgroups for patients listed with a dilated cardiomyopathy phenotype. A recent PHTS study (42) found 77% of patients with such a phenotype were listed while on inotropic, mechanical ventilatory, and/or mechanical circulatory support, and 85% of such patients were transplanted while on such support. These findings suggest that children listed for transplantation with a dilated cardiomyopathy phenotype, including those with myocarditis, are severely ill and few have been transplanted who do not require high levels of support.

Conclusions

Although our findings must be considered in the context of coming from a retrospective registry with incomplete data capture, they support the concept that children having a dilated cardiomyopathy phenotype who are diagnosed with myocarditis have better outcomes than those in whom no cause can be found, regardless of endomyocardial biopsy findings. Endomyocardial biopsy may still be helpful to determine etiology in an otherwise idiopathic dilated cardiomyopathy phenotype in a child, or to exclude rare conditions in children, such as giant cell or hypersensitivity myocarditis, as suggested in recently developed guidelines (43). Any biopsy findings need to be interpreted in the context of the entire clinical picture. Other diagnostic modalities such as cardiac magnetic resonance imaging (44) may further refine the non-invasive diagnosis of myocarditis but their efficacy remains to be defined in children.

The fact that we found no differences in outcomes in patients treated with IVIG or corticosteroids does not mean that these drugs have no benefit, especially in patients showing evidence of autoimmunity (45). However, the generally high rate of LV normalization observed in our patients suggests that randomized studies with very large patient sample sizes would be necessary to answer this question definitively. The good chance for echocardiographic normalization in pediatric myocarditis argues against heart transplantation for children who do not require high levels of cardiac support, as continued echocardiographic normalization can occur even after 3 years.

When to abandon high levels of support for cardiac replacement therapy is not clear-cut, but our findings suggest that this decision might be deferred for a longer period in those patients who present with a normal chamber size than in those who present with LV dilatation. As they become increasingly available, ventricular assist devices, such as the Berlin Heart for infants and children (46), may possibly be used as a bridge to recovery, as well as a bridge to heart transplantation, in children with myocarditis.

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Table. Demographic and Clinical Characteristics of 1495 Children with Cardiomyopathies at Diagnosis and within 1 Month of Diagnosis

Characteristic	Biopsy-Confirmed Myocarditis [n]*	Probable Myocarditis [n]*	Idiopathic Dilated CM [n]*	P‡
Characteristics at Diagnosis				
Male, %	47.1 [119]	49.8 [253]	49.2 [1,123]	0.88
Median age (Q1,Q3), y	1.6 (1.0, 7.4) [119]	1.9 (0.6, 10.4) [253]	1.2 (0.3, 9.8) [1,123]	**0.002**
Age < 1 year, %	25.2 [119]	33.2 [253]	46.9 [1,123]	**<0.001**
Retrospective cohort, %	58.0 [119]	25.3 [253]	24.8 [1,123]	**<0.001**†
Race/Ethnicity, %				0.73
White	52.1 [117]	56.0 [250]	52.6 [1,099]	
Black	27.4 [117]	20.8 [250]	22.8 [1,099]	
Hispanic	16.2 [117]	16.0 [250]	17.3 [1,099]	
Other	4.3 [117]	7.2 [250]	7.3 [1,099]	
Congestive Heart Failure, %	86.4 [118]	77.3 [251]	75.0 [1,118]	**0.02** †
Hospitalized, %	96.6 [88]	80.0 [130]	75.5 [490]	**<0.001**†
Admitted to ICU, %	81.7 [71]	52.4 [82]	46.1 [358]	**<0.001**†

Characteristics within 30 Days of Diagnosis				
Listed for Transplant, %	10.3 [117]	13.1 [252]	17.0 [1,120]	0.07
Congestive Heart Failure therapy, %	94.1 [118]	85.1 [241]	84.2 [1,071]	**0.02**†
ECMO, %	3.4 [88]	6.9 [130]	2.6 [492]	0.06
Balloon pump, %	0.0 [88]	2.3 [130]	1.0 [492]	0.26
Ventricular assist device, %	2.3 [88]	2.3 [130]	0.8 [492]	0.27
IVIG therapy, %	23.0 [87]	8.6 [128]	3.6 [469]	**<0.001**†
Steroids, %	29.9 [87]	15.6 [128]	3.4 [469]	**<0.001**†
IVIG or Steroids, %	47.1 [87]	24.2 [128]	6.6 [469]	**<0.001**†
LV Z-Scores at Diagnosis				
Mean EDD (SD)	3.83 (2.43) [102]	3.42 (2.67) [193]	4.77 (2.64) [896]	**<0.001**
EDD z-score > 2, %	75.5 [102]	68.4 [193]	86.3 [896]	**<0.001**
Mean ESD (SD)	5.58 (2.78) [87]	5.24 (3.69) [162]	6.54 (2.94) [748]	**<0.001**
Median FS (Q1,Q3)	-9.10 (-11.0, -6.7) [103]	-8.56 (-11.01, 5.46) [202]	-9.68(-11.47, -9.40) [903]	**0.001**
FS z-score < -2, %	92.2 [103]	93.1 [202]	96.4 [903]	**0.03**
Median PWT (Q1,Q3)	0.16 (-1.47, 1.84) [87]	-0.34 (-1.65, 1.01) [141]	-0.64 (-1.82, 0.87) [684]	**0.005**
Median SWT (Q1,Q3)	0.02 (-1.31, 0.91) [75]	-0.39 (-1.35, 0.39) [128]	-0.87 (-1.96, 0.14) [623]	**<0.001**
Median Mass (Q1,Q3)	3.08 (1.07, 4.16) [86]	1.92 (0.55, 3.61) [136]	2.56 (0.86, 4.24) [671]	**0.03**†

Median PWT:EDD Ratio (Q1,Q3)	0.14 (0.11, 0.17) [89]	0.14 (0.11, 0.18) [150]	0.12 [742]	**<0.001**

CM, cardiomyopathy; EDD, end-diastolic dimension; ESD, end-systolic dimension; FS, fractional shortening; ICU, intensive care unit; IVIG, gamma globulin therapy; LV, left ventricular; PWT, posterior wall thickness; SWT, septal wall thickness; (Q1,Q3), interquartile range, defined here as the 25th to 75th percentile

* "n" refers to the total available sample size for the variable specified

† Pairwise comparison between biopsy-confirmed and probable myocarditis groups significant at ≤ 0.05

‡ P-value is from analysis of variance where means are presented and Kruskal-Wallis test where medians are presented.

Figure Legends

Figure 1. Crude cumulative incidence rates of echocardiographic normalization, cardiac transplantation and death among children with a) biopsy-confirmed myocarditis (BCM) [1A], b) probable myocarditis (PM) [1B], and c) idiopathic dilated cardiomyopathy (IDCM) [1C]. Event rates did not differ for the outcomes between the BCM and PM groups ($P \geq 0.5$), but they all differed when compared to those for IDCM ($P < 0.01$). Curves are truncated at 8 years, except for 1C, which is truncated at 10 years due to some late events.

Figure 2. Crude cumulative incidences of echocardiographic normalization, cardiac transplantation and death among children with myocarditis (combined BCM and PM groups) and abnormal function at presentation with LV end-diastolic dilation at diagnosis [2A] or no LV end-diastolic dilation at diagnosis [2B]. The two groups differed in the incidence of cardiac transplant ($P = 0.02$) and echocardiographic normalization rates ($P < 0.001$), but not mortality ($P = 0.45$). Curves are truncated at 8 years.