Incidence, Causes, and Outcomes of Dilated Cardiomyopathy in Children

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Context Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy and cause of cardiac transplantation in children. However, the epidemiology and clinical course of DCM in children are not well established.

Objective To provide a detailed description of the incidence, causes, outcomes, and related risk factors for DCM in children.

Design and Setting Longitudinal study based on a population-based, prospective cohort of children diagnosed as having DCM since January 1, 1996, at 89 pediatric cardiac centers and a retrospectively collected cohort of patients seen primarily at large tertiary care centers in North America and who had diagnoses between January 1, 1990, and December 31, 1995, and were enrolled through February 2003.

Participants A total of 1426 children from the United States and Canada diagnosed as having DCM at younger than 18 years. Primary DCM was determined by strict echocardiographic and/or pathologic criteria. Patients with disease due to endocrine, immunologic, drug toxicity, and other causes were excluded.

Main Outcome Measures Annual incidence per 100 000 children; mortality; cardiac transplantation.

Results The annual incidence of DCM in children younger than 18 years was 0.57 cases per 100 000 per year overall. The annual incidence was higher in boys than in girls (0.66 vs 0.47 cases per 100 000; $P<.001$), in blacks than in whites (0.98 vs 0.46 cases per 100 000; $P<.001$), and in infants (<1 year) than in children (4.40 vs 0.34 cases per 100 000; $P<.001$). The majority of children (66%) had idiopathic disease. The most common known causes were myocarditis (46%) and neuromuscular disease (26%). The 1- and 5-year rates of death or transplantation were 31% and 46%, respectively. Independent risk factors at DCM diagnosis for subsequent death or transplantation were older age, congestive heart failure, lower left ventricular fractional shortening *Z* score, and cause of DCM ($P<.001$ for all).

Conclusions In children, DCM is a diverse disorder with outcomes that depend largely on cause, age, and heart failure status at presentation. Race, sex, and age affect the incidence of disease. Most children do not have a known cause of DCM, which limits the potential for disease-specific therapies.

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CARDIOMYOPATHIES ARE HEART muscle disorders that affect ventricular systolic function, diastolic function, or both. They are classified by the World Health Organization as (1) dilated cardiomyopathy (DCM), (2) hypertrophic cardiomyopathy, (3) restrictive cardiomyopathy, and (4) arrhythmogenic right ventricular dysplasia-cardiomyopathy.[1] Most patients have "pure" forms of these disorders that fulfill strict diagnostic criteria, although some have overlapping disorders with mixed forms of disease. Despite long-standing interest in these high-impact disorders, the demographics and underlying causes have been difficult to ascertain, particularly in children.

Dilated cardiomyopathy, a myocardial disorder characterized by a dilated left ventricular (LV) chamber and systolic dysfunction that commonly results in congestive heart failure (CHF),[1,2] is the most common form of cardiomyopathy and reason for cardiac transplantation in adults and children.[3,4] In some cases, right ventricular dysfunction is also noted and may add to the clinical severity of disease. The estimated cost of caring for patients with this disorder is $4 billion to $10 billion annually in the United States alone.[5,6] In adults, the incidence of DCM has been reported to be 5.5 cases per 100 000 population per year, with a prevalence of 36 cases per 100 000 population.[7,8] The underlying

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cause in adults[2] is usually coronary artery disease, but other causes are also seen, including inflammatory heart disease, myocardial toxins, and genetic defects.[9,10] Approximately 30% to 35% of patients are reported to have a genetic form of DCM.[11-14] Infants and older children, however, appear to have a wider spectrum of causes,[9,15-17] although identifying these causes has been difficult.

Relatively little information on the incidence of cardiomyopathies in childhood has been published.[18-20] Arola et al[20] reported an incidence of DCM of 0.34 cases per 100 000 children per year and a prevalence of 2.6 cases per 100 000 children in Finland, a racially homogeneous population. A large percentage of cases occurred in infants (<1 year of age; 3.8 per 100 000 cases per year). Recently, our group, the Pediatric Cardiomyopathy Registry (PCMR), reported the incidence of pediatric cardiomyopathy in 2 regions of the United States, New England and the central Southwest.[21] A total of 467 cases of childhood cardiomyopathy were reported, yielding an annual incidence of 1.13 per 100 000 infants and children overall, with differences by race, sex, and region. These data are supported by similar findings in Australia.[22] The PCMR report defines the overall incidence of all forms of childhood cardiomyopathy but has limited details regarding the causes, risks, and outcomes of specific forms of cardiomyopathy. However, more detailed information focusing on particular forms of cardiomyopathy is required for clinicians to understand the clinical disorders of individual patients.

The current report provides the most up-to-date estimates of the incidence of DCM in patients younger than 18 years living in 2 regions of the United States, as well as a detailed description of the causes, outcomes, and related risk factors for DCM in children.

METHODS

Study Design

Two PCMR cohorts were established. The first is a population-based, prospective cohort of patients younger than 18 years who have been diagnosed as having DCM between January 1, 1996, and February 25, 2003, at 98 pediatric cardiac centers and is based on identification at the time of diagnosis by a pediatric cardiologist. For this cohort, comprehensive patient enrollment was conducted in 2 geographically distinct regions of the United States (New England and the central Southwest).[21] In addition, a retrospective cohort of patients seen primarily at 39 tertiary care centers in North America and who had diagnoses between January 1, 1990, and December 31, 1995, was identified by chart review. Both groups are followed up using annual chart review, and enrollment of newly diagnosed cases is ongoing. All participating PCMR centers obtained institutional review board or ethics committee approval with a waiver of consent authorization. The participating centers and associated investigators representing the PCMR Study Group are detailed by Grenier et al.[23]

Eligibility Criteria

All patients with cardiomyopathy were identified by clinical presentation to a pediatric cardiologist with signs and symptoms of heart failure, sudden death or aborted sudden death, or evaluation for possible cardiomyopathy because of familial inheritance. In addition, autopsy reports were evaluated in a retrospective case review. Sudden death was captured by review of the cardiology and pathology medical records. A variety of diagnostic exclusion criteria[23] were used, including endocrine disorders or immunologic diseases known to cause heart muscle disease, treatment with doxorubicin, and inflammation caused by human immunodeficiency virus (HIV) infection (or birth to an HIV-positive mother) or by Kawasaki disease.

A patient is eligible for the PCMR if he/she is younger than 18 years, strict quantitative echocardiographic criteria of LV dilation and systolic dysfunction are met, the pattern of cardiomyopathy conforms to a defined semiquantitative pattern, the diagnosis is confirmed by autopsy or tissue analysis, or the investigator has other compelling evidence of cardiomyopathy.

This analysis focuses on pure DCM, defined as the presence of DCM at diagnosis, excluding any additional overlapping cardiac phenotype (n=1426). Cases of mixed functional DCM, including a combination of DCM with hypertrophic, restrictive, arrhythmogenic, noncompaction without gene mapping, or other functional types of cardiac disorder, were excluded. A sufficient number of significant differences in characteristics at diagnosis were found between patients in these 2 categories, and genetic and clinical studies indicate that mixed functional types of DCM have different causes than pure DCM and therefore are not representative of DCM as a classification. In addition, classification schemes for cardiomyopathy were developed on the basis of pure DCM.[1,2]

Data Collection

Following patient identification, confirmation of eligibility and enrollment are established by chart review performed by study personnel using a unique study identifier to ensure confidentiality. Supplemental information on clinical history, procedures, and outcomes is obtained annually for all patients, and information on family history, results of laboratory studies, and therapies administered is additionally collected for retrospective cohort patients. All patients are seen by their primary pediatric cardiologist in follow-up, and data reported are based on comprehensive chart review of each patient visit.

Statistical Methods

The clinical components of this report include all patients who were enrolled in the PCMR as of February 25, 2003, and the incidence rates are based on all cardiomyopathy diagnoses in the New England and central Southwest regions between January 1, 1996, and December 31, 2002. The retrospective co-

hort cannot be confirmed to include all cases and, therefore, was not used for incidence estimates. Population denominators used for incidence rate calculations were obtained from the state-specific US census counts for 1996 through 2002.

Race/ethnicity was assessed to create a subgroup factor for incidence rates and clinical outcomes. As a result of differences between race/ethnicity definitions in the US Census and the PCMR, both an upper and a lower estimate for incidence rates are given for white, black, and Hispanic children. The PCMR data on race/ethnicity consist of a single question with choices of white, black, Hispanic, Native American, Asian/Pacific Islander, or other. However, the census data on race/ethnicity cross-tabulates Hispanic status by racial category. Therefore, we calculated both lower-bound and upper-bound estimates of race-specific incidence rates. The lower-bound estimate includes all white Hispanics and black Hispanics in the white and black population counts, respectively, and the upper bound includes none of the white Hispanics and black Hispanics in the white and black population counts, respectively. The lower-bound estimate for the Hispanic rate includes all Hispanics of any race (white, black, or other race) in the population count, and the upper-bound estimate for the Hispanic rate includes only Hispanics with a racial background not classified as white or black in the population count.[23]

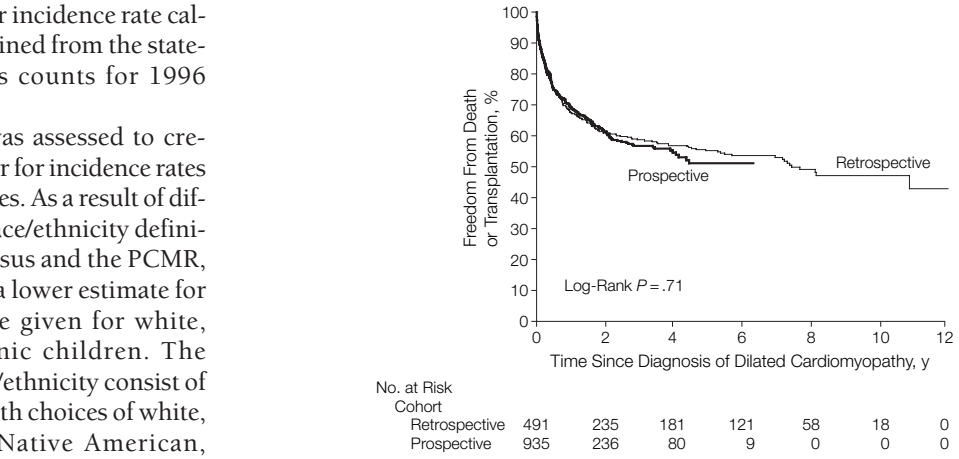
Descriptive statistics are presented as percentages or means and standard deviations, with skewed continuous data summarized as medians and interquartile ranges. The distributions of categorical variables were compared using the Fisher exact test, except for comparisons by cause, for which the χ^2 statistic was used. Two groups of normally distributed variables were compared using the *t* test, and analysis of variance was used to compare more than 2 groups. Skewed data were analyzed using the Wilcoxon rank-sum test and the Kruskal-Wallis test. The Mantel-Haenszel test for linear trend was used to examine age at diagnosis of cardiomyopathy grouped categorically by cause.

Left ventricular end-diastolic dimension, posterior wall thickness, septal thickness, and mass were measured and expressed conditional on body surface area.[22,24-26] Fractional shortening is a measure of LV contractility and is defined by the ratio of the difference between the end-diastolic dimension (LVEDD) and end-systolic dimension (LVESD) to the LVEDD, expressed as fractional shortening = (LVEDD − LVESD)/LVEDD × 100. Quantitative right ventricular structure and function data were not collected.

Outcome measures were death, cardiac transplantation, and the composite end point of death or transplantation. Because of varying amounts of follow-up, survival figures and estimates were calculated using the Kaplan-Meier method and were compared with the log-rank test, with time from DCM diagnosis as the origin. Cox regression modeling was used to find predictors of death or transplantation in patients with pure DCM, excluding those with neuromuscular disease and inborn errors of metabolism.

To control for the large number of subgroup analyses as well as multiple comparisons, only $P<.01$ was considered to be statistically significant. All analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, NC) and S-Plus version 6.1 (Insightful Corp, Seattle, Wash).

Figure 1. Estimated Freedom From Death or Transplantation for Patients With Pure Dilated Cardiomyopathy by Cohort



Retrospective: diagnosed 1990 to 1995, 491 patients; prospective: diagnosed 1996 to 2002, 935 patients.

RESULTS

Registry Characteristics

A total of 1426 patients with pure DCM were enrolled as of February 25, 2003, including 491 (34%) enrolled retrospectively and 935 (66%) enrolled prospectively. These patients resided in New England (n = 195 [14%]), the central Southwest (n = 397 [28%]), and the remainder of North America (n = 834 [58%]) at the time of diagnosis.

Cohort Differences

The retrospective and prospective cohorts are similar with respect to sex, age, region, cause, presence of CHF at diagnosis, and outcome (FIGURE 1). Therefore, although there were statistical differences according to race (slightly more white children were enrolled in the retrospective cohort: 61% [298/485] vs 54% [497/918]) and rate of idiopathic disease (67% [331/491] vs 76% [710/934] for retrospective vs prospective), these 2 cohorts were combined for all other analyses.

Table 1. Pediatric Cardiomyopathy Registry Annual Incidence of Pure Dilated Cardiomyopathy in 422 Patients Diagnosed Between 1996 and 2002 in the New England and Central Southwest Regions of the United States*

Characteristics	No. of Patients	Annual Incidence per 100 000 Children (95% Confidence Interval)	P Value
Total	422	0.57 (0.52-0.63)†	
Region‡			
New England	146	0.64 (0.54-0.75)	.09
Central Southwest	276	0.54 (0.48-0.60)	
Sex			
Male	252	0.66 (0.58-0.75)	<.001
Female	170	0.47 (0.40-0.55)	
Race/ethnicity§			
White, lower/upper	207	0.33/0.46 (0.29-0.38/0.40-0.53)	<.001
Black, lower/upper	87	0.98/1.05 (0.78-1.21/0.84-1.30)	
Hispanic, lower/upper	109	0.58/32.99 (0.48-0.70/27.08-39.79)	
Age group, y			
<1	181	4.40 (3.78-5.09)	<.001
1 to <18	241	0.34 (0.30-0.39)	

*The registry aim was complete capture of cases in these 2 regions, representing a subset of the overall registry sample.
†The population denominator was obtained from state-specific US census estimates for 1999-2006 and totals 74 212 292 children younger than 18 years across the 7-year period.
‡New England: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont; central Southwest: Arkansas, Oklahoma, Texas.
§See "Methods" section of text for description of race/ethnicity data collection. Lower and upper bounds were estimated for incidence rates by racial/ethnic subgroup. The *P* value compares the upper white to lower black estimated incidence rates (ie, the most conservative comparison).

Annual Incidence of DCM

Incidence rates were based on 422 cases of DCM diagnosed from 1996 to 2002 in 2 regions of the United States. The overall rate of pure DCM in childhood was 0.57 cases per 100 000 per year. The incidence was higher in boys than in girls (0.66 vs 0.47 per 100 000 per year; $P=.006$), in blacks than in whites (0.98-1.05 vs 0.33-0.46 per 100 000 per year; $P<.001$), and in infants (<1 year) than in older children (4.40 vs 0.34 per 100 000 per year; $P<.001$) (TABLE 1).

Clinical Presentation

Clinical findings, therapy, and outcomes are based on the entire cohort of 1426 patients with pure DCM unless otherwise specified. The median age at diagnosis was 1.5 years (interquartile range, 0.3-11.3 years) (TABLE 2). Age younger than 1 year was the most common age at diagnosis of DCM (n=591 [41%]). The 6- to younger than 12-year-old age group was the least common (n=194 [14%]) age at initial diagnosis. The majority of patients had clinical evidence of CHF at diagnosis (71% [999/1415]), with 27% (261/967) overall classified as having class IV heart failure.[21,23,27,28]

Echocardiogram results were available for 97% of patients (1378/1419). The mean LVEDD *Z* score was 4.17 (SD, 2.70), whereas the mean LVESD *Z* score was 5.96 (SD, 2.86) (Table 2). Left ventricular fractional shortening was severely depressed, with a median *Z* score of –9.16 (interquartile range, –11.08 to –6.10). Left ventricular end-diastolic posterior wall thickness and septal wall thickness were, on average, normal, but LV mass was mildly abnormal, with a mean *Z* score of 2.34 (SD, 2.89).

Causes of DCM

The cause of DCM was identified in 34% of patients (Table 2). Of the 485 patients with a known cause, the most common causes were myocarditis (46% [222/485]) and neuromuscular disease (26% [125/485]). Half of myocarditis cases (52% [116/222]) met strict Dallas histopathologic criteria. Specific viral or other causes were known for very few cases because cultures and polymerase chain reaction information were not available in most cases. The majority of children with neuromuscular disorders had Duchenne (80% [100/125]) or Becker (10% [12/125]) muscular dystrophy, both caused by mutations in dystrophin. Three children (2%) had Emery-Dreifuss muscular dystrophy.

The majority of patients with familial DCM (14% [66/485]) had autosomal dominant inheritance (68% [45/66]), and 24% (16/66) had autosomal recessive inheritance. The remainder had X-linked inheritance (2% [1/66]) or the complex phenotype of LV noncompaction with gene mapping (6% [4/66]). An additional 48 cases had LV noncompaction that was identified as the cause of DCM; of these, 45 remained idiopathic and 2 had unspecified chromosomal defects and 1 had Barth syndrome as the primary cause of DCM. Causative gene abnormalities were identified in 4 families with autosomal dominant disease, including mutations in δ-sarcoglycan in 2 families and ZASP (Z-band alternatively spliced PDZ domain protein) in 2 families. In addition, mutations in 2 families with LV noncompaction (ZASP) and in 2 with X-linked disease (dystrophin mutation in 1 and tafazzin mutation in 1) were also identified.[29-32]

Among the 54 patients with inborn errors of metabolism, the largest subgroups were mitochondrial disorders (46% [20/54]), Barth syndrome (24% [13/54]), and primary or systemic carnitine deficiency (11% [7/54]). Malformation syndromes were the least common cause of DCM, and these disorders affected 15 patients, with Alström syndrome occurring in 5 cases (33%) and a chromosomal defect occurring in 7 cases (47%).

Therapy

At the time of diagnosis of DCM, 82% of patients (1120/1370) were prescribed an anticongestive agent and 64% (307/478) an angiotensin-converting enzyme inhibitor, with 38% (182/478) receiving an antiarrhythmic agent, 15% (67/458) using L-carnitine supplementation, and 13% (65/487) having other dietary modification. Antithrombotic therapy was prescribed in 19% of cases and inotropes in 16%. There was low use of calcium channel blockers (3% [12/473]) and β-blockers (4% [17/474]).

Pacemaker and balloon pump use at diagnosis was rare (1% each [7/480 and 7/486, respectively]), as was use of an (left or right ventricular) assist device (2% [9/486]) and extracorporeal membrane oxygenation (3% [13/486]).

Clinical Outcomes

The median age of the patients at the time of diagnosis was 1.5 years (TABLE 3), the median age at listing for transplantation was 4.0 years, and the median age at transplantation was 4.8 years. Death occurred (for all patients who died) at a median age of 3.0 years. Median follow-up time from diagnosis of DCM among survivors who did not undergo transplantation was 1.6 years, with 25% having more than 4 years of follow-up.

Kaplan-Meier analysis of survival after DCM diagnosis revealed 1-year survival of 87%, 2-year survival of 83%, 5-year survival of 77%, and 10-year survival of 70% (Table 3). Similarly, the rate of freedom from transplantation at 1, 2, 5, and 10 years was 79%, 74%, 70%, and 66%, respectively. Freedom from death or transplantation was 69% at 1 year, 61% at 2 years, 54% at 5 years, and 46% at 10 years.

Kaplan-Meier estimates showed significant differences in survival, freedom from transplantation, and the

Table 2. Characteristics at Diagnosis of 1426 Patients With Pure DCM From the Pediatric Cardiomyopathy Registry, by Cause*

Characteristics at DCM Diagnosis	All Patients (N=1426)	Idiopathic DCM (n=941 [66%])	Myocarditis (n=222 [16%])	Neuromuscular Disorders (n=125 [9%])	Familial DCM (n=66 [5%])	Inborn Errors of Metabolism (n=54 [4%])	Malformation Syndrome (n=15 [1%])	*P* Value†
Region, No. (%)								
New England	195 (14)	87 (9)	51 (23)	25 (20)	11 (17)	17 (31)	4 (27)	<.001
Central Southwest	397 (28)	248 (26)	74 (33)	39 (31)	17 (26)	12 (22)	6 (40)	
Other	834 (58)	606 (64)	97 (44)	61 (49)	38 (58)	25 (46)	5 (33)	
Male, No. (%)	769 (54)	465 (49)	102 (46)	121 (97)	36 (55)	39 (72)	6 (40)	<.001
Age at diagnosis, No. (%), y								
<1	591 (41)	460 (49)	65 (29)	2 (2)	26 (39)	28 (52)	10 (67)	<.001
1 to <6	314 (22)	197 (21)	91 (41)	1 (1)	9 (14)	13 (24)	3 (20)	
6 to <12	194 (14)	116 (12)	32 (14)	23 (18)	14 (21)	8 (15)	1 (7)	
12 to <18	327 (23)	168 (18)	34 (15)	99 (79)	17 (26)	5 (9)	1 (7)	
Age at diagnosis, median (IQR), y	1.54 (0.35 to 11.28)	1.07 (0.29 to 9.13)	1.59 (0.93 to 8.61)	14.14 (12.82 to 15.77)	4.04 (0.22 to 13.45)	0.89 (0.07 to 5.61)	0.61 (0.17 to 1.81)	<.001
Race/ethnicity, No. (%)								
White	795 (57)	490 (53)	120 (55)	91 (73)	43 (65)	38 (72)	13 (93)	<.001
Black	282 (20)	202 (22)	55 (25)	15 (12)	8 (12)	1 (2)	0	
Hispanic	235 (17)	166 (18)	29 (13)	15 (12)	12 (18)	10 (19)	1 (7)	
Other	91 (6)	67 (7)	14 (6)	3 (2)	3 (5)	4 (8)	0	
Congestive heart failure present at diagnosis, No. (%)	999 (71)	693 (74)	184 (84)	43 (35)	35 (53)	32 (60)	10 (67)	<.001
Family history at diagnosis, No. (%)‡								
Cardiomyopathy	180 (19)	92 (14)	7 (6)	12 (18)	60 (92)	6 (19)	3 (30)	<.001
Sudden death	85 (9)	36 (5)	11 (8)	2 (3)	24 (44)	9 (24)	3 (27)	<.001
Congenital structural heart disease	32 (4)	22 (4)	3 (2)	0	4 (9)	0	3 (33)	<.001
Arrhythmia	27 (3)	17 (3)	1 (1)	3 (5)	6 (13)	0	0	.001
Genetic syndromes	68 (7)	24 (4)	2 (1)	25 (32)	6 (13)	7 (20)	4 (44)	<.001
LV echocardiographic *Z* scores at diagnosis§								
ED dimension, mean (SD)	4.17 (2.70)	4.65 (2.65)	3.87 (2.59)	1.89 (1.87)	3.28 (2.68)	3.42 (2.28)	2.32 (2.55)	<.001
ES dimension, mean (SD)	5.96 (2.86)	6.45 (2.80)	5.89 (2.66)	3.46 (2.28)	4.84 (2.91)	5.19 (2.39)	3.90 (2.68)	<.001
Fractional shortening, median (IQR)	–9.16 (–11.08 to –6.10)	–9.62 (–11.42 to –7.16)	–9.11 (–11.05 to –6.67)	–5.88 (–8.02 to –3.32)	–7.07 (–9.63 to –3.68)	–8.94 (–10.30 to –5.33)	–5.95 (–9.49 to –5.10)	<.001
ED posterior wall thickness, median (IQR)	–0.56 (–1.84 to 0.96)	–0.63 (–1.80 to 0.95)	0.21 (–1.22 to 1.84)	–1.62 (–2.88 to –0.09)	–0.75 (–2.07 to 0.87)	–0.05 (–1.33 to 1.51)	–0.88 (–1.33 to 1.30)	<.001
ED septal wall thickness, median (IQR)	–0.74 (–1.77 to 0.29)	–0.80 (–1.86 to 0.20)	–0.26 (–1.12 to 0.62)	–1.34 (–2.27 to –0.26)	–0.74 (–1.87 to 0.29)	–0.20 (–0.91 to 1.24)	–1.18 (–2.28 to –0.15)	<.001
Mass, mean (SD)	2.34 (2.89)	2.58 (2.92)	2.70 (2.26)	0.17 (2.90)	2.07 (3.33)	2.30 (2.27)	1.22 (2.19)	<.001
ED posterior wall thickness to ED dimension, ratio at diagnosis, median (IQR)	0.13 (0.10 to 0.16)	0.12 (0.10 to 0.15)	0.14 (0.11 to 0.17)	0.13 (0.11 to 0.16)	0.14 (0.11 to 0.17)	0.15 (0.13 to 0.17)	0.16 (0.14 to 0.19)	<.001

Abbreviations: DCM, dilated cardiomyopathy; ED, end-diastolic; ES, end-systolic; IQR, interquartile range; LV, left ventricular.
*Causes of DCM were determined from all available follow-up information. Three patients had causes (1 lupus and 2 postpartum cardiomyopathy) that could not be categorized into any of the 5 subgroups but that are included in the overall analysis.
†*P* values represent the overall comparison of idiopathic DCM vs myocarditis vs neuromuscular disorder vs familial DCM vs inborn error of metabolism vs malformation syndrome. *P* values are based on analysis of variance or the Kruskal-Wallis test with the exception of age, for which the Mantel-Haenszel test for linear trend was used.
‡Family history information was unavailable for more than one third of cases.
§A *Z* score of zero represents the mean for healthy children of similar age or body surface area.

composite end point of freedom from death or transplantation by cause (Table 3 and FIGURE 2 and FIGURE 3). Patients with neuromuscular disorders had the worst long-term outcome, with 57% survival at 5 years after diagnosis of DCM. Familial DCM had the best survival, with 94% at 5 years after diagnosis. Patients with myocarditis (92% survival at 1 year and 90% at 2 and 5 years) and inborn errors of metabolism (86% with 1- and 2-year survival and 83% with 5-year survival) had plateaued curves.

Estimation of freedom from transplantation by cause revealed that patients with idiopathic or familial DCM had the worst outcomes (62% freedom from transplantation at 5 years after diagnosis). Individuals with myocarditis had a 5-year rate of freedom from transplantation of 81%. Freedom from death or transplantation by 5 years was disappointing for all diagnostic categories, particularly for those with idiopathic disease (47%), neuromuscular disorders (52%), and familial DCM (59%). Patients with myocarditis, malformation syndrome, or inborn errors of metabolism had the best 5-year composite outcomes (73%, 76%, and 78% freedom from death or transplantation, respectively).

Predictors of Clinical Outcome

Risk factors for the composite end point of death or transplantation (TABLE 4) were identified after excluding cases caused by neuromuscular disease and inborn errors of metabolism because transplantation is not typically considered a treatment option for these groups. The final multivariate model included age at diagnosis, cause, CHF at diagnosis, and fractional shortening *Z* score ($P<.001$ for all). Children with diagnoses after age 6 years were at a 2-fold greater risk of an event, and those with idiopathic disease had a 2-fold worse outcome than those with myocarditis. Patients with CHF at diagnosis had a 4-fold hazard of death or transplantation in the first year after diagnosis compared with those without CHF ($P<.001$); however, there was no additional risk for patients with CHF after 1 year (hazard ratio, 1.12) relative to those without CHF present at diagnosis. A higher fractional shortening *Z* score was associated with better outcome; risk decreased 0.9 times for each unit increase in *Z* score. All echocardiographic measures examined were univariately associated with DCM outcome except for septal and posterior wall thickness, but fractional shortening was the only independent echocardiographic risk factor.

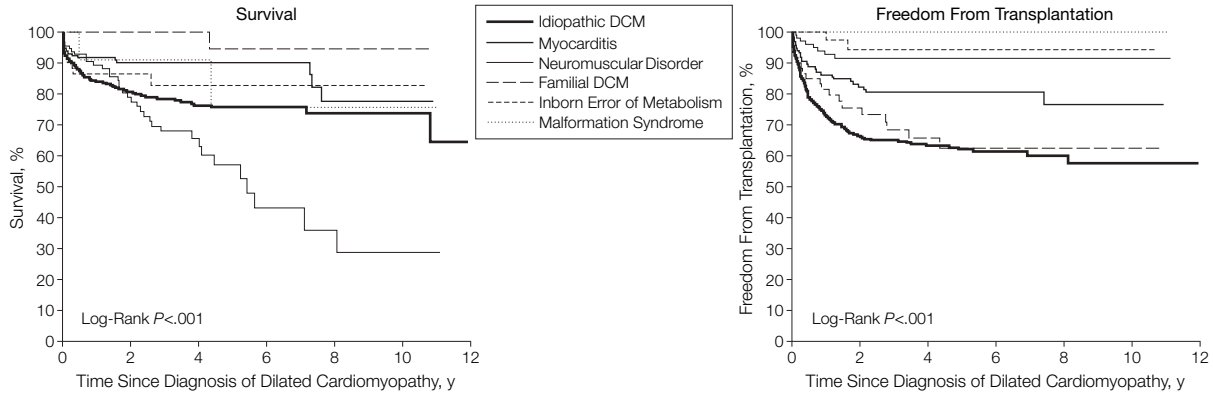
Based on our multivariable model, a patient presenting with DCM and a moderate degree of LV dysfunction with a LV fractional shortening of –8 SD (fractional shortening, 20%) has a risk of death or cardiac transplantation increased by 2.2 times (hazard ratio, 2.19; 95% confidence interval, 1.55-3.08) compared with a patient with normal LV function (LV fractional shortening *Z* score, 0 SD [fractional shortening, 32%]) associated with LV dilation (as seen in familial DCM, treated myocarditis, or other primary heart muscle disease).

Table 3. Age at Diagnosis and Outcomes in 1426 Patients With Pure DCM From the Pediatric Cardiomyopathy Registry, by Cause*

	All Patients (N=1426)	Idiopathic DCM (n=941)	Myocarditis (n=222)	Neuromuscular Disorders (n=125)	Familial DCM (n=66)	Inborn Errors of Metabolism (n=54)	Malformation Syndrome (n=15)
Age at DCM diagnosis, median (IQR), y	1.54 (0.35-11.28)	1.07 (0.29-9.13)	1.59 (0.93-8.61)	14.14 (12.82-15.77)	4.04 (0.22-13.45)	0.89 (0.07-5.61)	0.61 (0.17-1.81)
No. of deaths	206	139	21	35	1	8	2
Survival rate, % (95% CI), y†							
1	87 (85-89)	84 (81-87)	92 (88-96)	89 (83-95)	100	86 (77-96)	91 (74-100)
2	83 (81-86)	80 (77-84)	90 (86-95)	79 (70-88)	100	86 (77-96)	91 (74-100)
5	77 (74-80)	76 (71-80)	90 (86-95)	57 (44-70)	94 (84-100)	83 (71-94)	76 (45-100)
10	70 (64-75)	74 (68-79)	78 (64-91)	29 (9-49)	94 (84-100)	83 (71-94)	76 (45-100)
No. of cardiac transplantations	292	231	32	8	19	2	0
Transplantation-free rate, % (95% CI), y†							
1	79 (76-81)	73 (70-76)	86 (81-91)	93 (88-98)	81 (72-91)	97 (92-100)	100
2	74 (71-76)	66 (62-70)	82 (77-88)	91 (86-97)	76 (64-87)	94 (87-100)	100
5	70 (66-73)	62 (58-66)	81 (74-87)	91 (86-97)	62 (48-76)	94 (87-100)	100
10	66 (61-71)	58 (51-64)	77 (67-86)	91 (86-97)	62 (48-76)	94 (87-100)	100
No. of end-point events (deaths and cardiac transplantations)	498	370	53	43	20	10	2
End-point event–free rate, % (95% CI), y†							
1	69 (66-71)	61 (58-65)	79 (74-85)	83 (76-90)	81 (72-91)	84 (74-94)	91 (74-100)
2	61 (58-64)	53 (50-57)	74 (68-81)	72 (63-81)	76 (64-87)	81 (70-92)	91 (74-100)
5	54 (50-57)	47 (43-51)	73 (66-79)	52 (40-65)	59 (44-74)	78 (65-90)	76 (45-100)
10	46 (41-51)	42 (37-48)	60 (47-72)	26 (8-44)	59 (44-74)	78 (65-90)	76 (45-100)

Abbreviations: CI, confidence interval; DCM, dilated cardiomyopathy.
*Causes of DCM were determined from all available follow-up information. Event rates are based on Kaplan-Meier estimates at 1, 2, 5, and 10 years following diagnosis of DCM. Three patients had causes (1 lupus and 2 postpartum cardiomyopathy) that could not be categorized into any of the 5 subgroups but are included in the overall analysis.
†The Greenwood formula was used for estimation of standard error with no transformation to the survivor function.

Figure 2. Estimated Survival and Freedom From Transplantation for Patients With Pure Dilated Cardiomyopathy (DCM), by Cause



No. at Risk

Cohort							
Idiopathic DCM	941	252	132	68	30	13	0
Myocarditis	222	95	55	32	12	1	0
Neuromuscular Disorder	125	56	25	8	5	1	0
Familial DCM	66	33	21	11	4	1	0
Inborn Error of Metabolism	54	27	20	8	1	0	0
Malformation Syndrome	15	6	6	2	2	1	0

No. at Risk

Cohort							
Idiopathic DCM	941	252	132	68	30	13	0
Myocarditis	222	95	55	32	12	1	0
Neuromuscular Disorder	125	56	25	8	5	1	0
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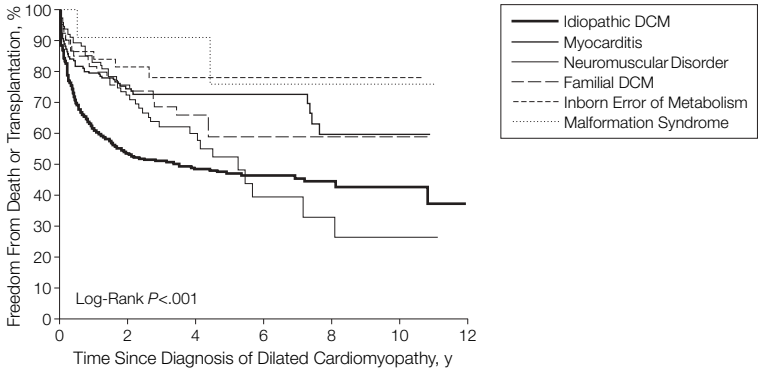
Inborn Error of Metabolism	54	27	12	8	5	1	0
Malformation Syndrome	15	6	6	2	2	1	0

COMMENT

Dilated cardiomyopathy in childhood is a diverse disorder with outcomes that depend on cause and age at presentation, as well as heart failure status. We previously reported that early failure of medical management, high mortality rates, and progressive deterioration are found regardless of etiology.[3]

The incidence of DCM was 0.56 cases per 100 000 per year, 10-fold lower than in adults.[21,22] This may relate to fewer chronic health habit–associated risk factors, a longer latency period for clinical expression of the effects of genetic and environmental factors on the heart, and the wider age span of adulthood compared with childhood, giving adults more opportunity to develop DCM. When study differences are accounted for, the incidence of pediatric DCM in the United States is similar to that reported in Finland (0.65 per 100 000 aged ≤20 years) and, after accounting for age, Australia (1.09 per 100 000 aged ≤10 years).[20-22] Boys have a higher DCM incidence than girls related to X-linked genetic causes and neuromuscular disorders. Black children have higher rates of DCM and different causes of DCM than do white children.

Figure 3. Freedom From Death or Transplantation for Patients With Pure Dilated Cardiomyopathy (DCM)



No. at Risk

Cohort							
Idiopathic DCM	941	252	132	68	30	13	0
Myocarditis	222	95	55	32	12	1	0
Neuromuscular Disorder	125	56	25	8	5	1	0
Familial DCM	66	33	21	11	4	1	0
Inborn Error of Metabolism	54	27	20	8	5	1	0
Malformation Syndrome	15	6	6	2	2	1	0

Dilated cardiomyopathy is significantly more likely to present in the first year of life than at older pediatric ages. Infants had more than 13 times the in-

cidence of older children. The most common causes of infantile DCM include idiopathic, inborn errors of metabolism, and malformation syndromes. However, DCM presenting at older pediatric ages is, in general, associated with worse outcomes. In addition to older age, worse ventricular dysfunction at presentation and more advanced CHF at presentation were associated with worse outcomes. Congestive heart failure was present in 71% of patients presenting with DCM and was more common in myocarditis and idiopathic DCM and less common in those presenting with neuromuscular, familial, or inborn errors of metabolism–associated DCM. Most mortality or transplantation occurs early, within 2 years of DCM presentation, except with neuromuscular etiologies.

The cause of DCM was an independent predictor of the composite outcome of death or transplantation. Outcomes by cause varied widely from 57% to 94% survival at 5 years, suggesting the need to establish an etiology to de-

Table 4. Cox Regression Modeling Results for Death or Transplantation, Excluding Cases With Neuromuscular Disorders and Inborn Errors of Metabolism*

		Univariate Analysis		Final Multivariate Model	
Covariates	No.	Hazard Ratio for Death or Transplantation (95% CI)	*P* Value†	Hazard Ratio for Death or Transplantation (95% CI)	*P* Value†
Age at diagnosis of DCM (3 *df*)	1244		<.001		<.001
1 to <6 vs <1 y		0.95 (0.74-1.22)	.67	1.20 (0.89-1.63)	.23
6 to <12 vs <1 y		1.43 (1.09-1.87)	.01	2.31 (1.67-3.20)	<.001
12 to <18 vs <1 y		1.48 (1.15-1.89)	.002	2.40 (1.75-3.30)	<.001
Sex (male vs female)	1244	1.17 (0.97-1.40)	.11		
Race/ethnicity (white vs Hispanic vs black vs other race) (3 *df*)	1223		.16		
Region (New England vs central Southwest vs other) (2 *df*)	1244		<.001		
Central Southwest vs New England		1.73 (1.17-2.54)	.006		
Other vs New England		2.02 (1.41-2.90)	<.001		
Cohort (prospective vs retrospective)	1244	1.08 (0.89-1.32)	.42		
Etiology (idiopathic vs known)	1244	2.01 (1.57-2.58)	<.001		
Cause of DCM (3 *df*)	1244		<.001		<.001
Idiopathic vs malformation syndrome		4.06 (1.01-16.32)	.05	1.81 (0.45-7.30)	.41
Idiopathic vs familial		1.76 (1.12-2.77)	.01	1.65 (0.96-2.84)	.07
Idiopathic vs myocarditis		2.03 (1.52-2.70)	<.001	2.06 (1.47-2.87)	<.001
Family history (present vs absent)					
Cardiomyopathy	846	1.04 (0.79-1.36)	.81		
Sudden death	868	1.06 (0.73-1.54)	.75		
Congenital heart disease	794	1.24 (0.74-2.09)	.41		
Arrhythmia	787	0.60 (0.28-1.26)	.18		
Genetic syndromes	822	1.02 (0.60-1.75)	.94		
CHF at diagnosis (present vs absent) (2 *df*)	1235				
Risk at <1 y after diagnosis		3.03 (2.19-4.20)	<.001	3.67 (2.40-5.60)	<.001
Risk at ≥1 y after diagnosis		1.30 (0.83-2.05)	.25	1.12 (0.66-1.91)	.67
LV ED dimension *Z* score (per SD increase)	941	1.14 (1.10-1.20)	<.001		
LV ES dimension *Z* score (per SD increase)	830	1.16 (1.11-1.22)	<.001		
LV fractional shortening *Z* score (per SD increase)	998	0.91 (0.88-0.94)	<.001	0.90 (0.87-0.94)	<.001
LV ED posterior wall thickness *Z* score quartiles (3 *df*)‡	756		.78		
LV ED septal wall thickness *Z* score quartiles (3 *df*)‡	691		.48		
LV mass *Z* score (per SD increase)	748	1.07 (1.03-1.11)	.001		
Ratio of LV ED posterior wall thickness to LV ED dimension quartiles (3 *df*)‡	826		<.001		
First vs second		1.43 (1.04-1.96)	.03		
First vs third		1.87 (1.33-2.64)	<.001		
First vs fourth		1.76 (1.25-2.48)	.001		

Abbreviations: CI, confidence interval; DCM, dilated cardiomyopathy; *df*, degrees of freedom; ED, end-diastolic; ES, end-systolic; LV, left ventricular.
*Data are from 1244 patients with pure DCM from the Pediatric Cardiomyopathy Registry. Multivariate modeling is based on 990 patients in whom 282 transplantations and 163 deaths occurred. Three additional patients had causes (1 lupus and 2 postpartum cardiomyopathy) that could not be categorized into any of the 5 etiologic subgroups and, therefore, are not included in modeling analyses.
†Raw (unadjusted) *P* values are presented for pairwise comparisons of subgroups where an omnibus difference is detected.
‡Left ventricular ED posterior wall thickness and LV ED septal wall thickness *Z* scores as well as ratio of LV ED posterior wall thickness to LV ED dimension were categorized by quartiles because of nonlinear effects.

termine the subsequent optimal management and to more accurately predict prognosis. However, understanding the cause of DCM remains difficult, with only 34% of pediatric patients having an identifiable cause. The spectrum of disease etiologies in childhood is quite different than that reported in adults. In pure DCM, myocarditis and neuromuscular disorders are the most common causes during childhood, with familial DCM, inborn errors of metabolism, and malformation syndromes less common. In adults, coronary artery disease is a common cause of DCM, which is rare in childhood, and explains some differences between incidence rates in childhood vs adulthood.

Mortality and cardiac transplantation rates did not match for specific causes of pediatric DCM. There was lower mortality but a higher rate of cardiac transplantation for familial DCM compared with idiopathic DCM. Idiopathic DCM had high rates of both death and cardiac transplantation. This raises questions about optimal cardiac transplantation management. One conclusion would be that patients with idiopathic DCM are not undergoing transplantation as often as they should, since mortality remains elevated, or that more needs to be done to establish etiologies for idiopathic DCM in pediatric patients. Similar questions are raised for myocarditis, in which deaths continue to occur years after presentation. The continuing mortality risk contradicts the previously held belief of a high recovery rate in this population. Familial DCM has high early transplantation rates and lower mortality compared with other causes, suggesting that families and their care providers may be more prepared to allow transplantation in these young patients early.

There are limitations to this study. First, subclinical cases of DCM are, by definition, not completely captured by the methods used in this study. For this reason, the incidence of DCM is probably underestimated and disease severity is possibly overestimated. In addition, the large percentage of infants and children with no known etiology reduces the predictability of etiology-based outcomes. The regions captured may not be fully representative of the United States, and potential endemic outbreaks or genetic or acquired factors might be overlooked. Finally, the observational nature of the study plus the fact that detailed treatment data were only collected from the retrospective cohort preclude reliable conclusions regarding potential associations between therapy and outcomes in this cohort. However, therapies have not been shown to affect outcomes dramatically.[21,33]

Despite the billions of dollars used to care for these patients, develop new therapies, and perform genetics-based studies, survival is still poor. New methods for early diagnosis[34] and risk stratification, as well as new therapies, need to be developed for infants and children with DCM to avoid transplantation and premature death.[3,35] The identification of patient characteristics and underlying diseases with the worst and best outcomes should enable focused investigations regarding these issues.

Author Contributions: Drs Towbin and Sleeper had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Towbin, Colan, Lurie, Lipshultz.
Acquisition of data: Towbin, Colan, Clunie, Messere, Hsu, Canter, Lipshultz.
Analysis and interpretation of data: Towbin, Lowe, Colan, Sleeper, Orav, Cox, Lurie, Hsu, Canter, Wilkinson, Lipshultz.
Drafting of the manuscript: Towbin, Lowe, Colan, Sleeper, Lipshultz.
Critical revision of the manuscript for important intellectual content: Lowe, Colan, Sleeper, Orav, Clunie, Messere, Cox, Lurie, Hsu, Canter, Wilkinson, Lipshultz.
Statistical analysis: Lowe, Sleeper, Orav, Lipshultz.
Obtained funding: Towbin, Colan, Lurie, Lipshultz.
Administrative, technical, or material support: Colan, Clunie, Messere, Wilkinson, Lipshultz.
Study supervision: Towbin, Colan, Sleeper, Lipshultz.
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Role of the Sponsors: The NHLBI provided oversight of the study with an independent observational study monitoring board, but neither the NHLBI nor any other funders had any role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.
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