Dilated cardiomyopathy (DCM) is the most common childhood cardiomyopathy and is associated with considerable early morbidity and mortality. International registry data indicate that DCM accounts for 76% of all pediatric patients undergoing transplantation for cardiomyopathy. Epidemiological studies from the National Australian Childhood Cardiomyopathy Study (NACCS) and the North American Pediatric Cardiomyopathy Registry (PCMR) determined the incidence of newly diagnosed DCM to be between 0.57 cases per 100,000 population per year for children 0 to 18 years of age and 0.73 cases per 100,000 population per year for ages 0 to 10 years of age. In particular, the registries demonstrated a higher incidence in infants and Australian indigenous and black populations. In these studies, freedom from death or transplantation was between 69% and 72% at 1 year and 54% and 63% at 5 years after diagnosis. The primary study end point included time to the combined outcome of death or cardiac transplantation. There were 175 patients 0 to <10 years of age at the time of diagnosis. Survival free from death or transplantation was 74% (95% confidence interval, 67–80) 1 year after diagnosis, 62% (95% confidence interval, 55–69) at 10 years, and 56% (95% confidence interval, 46–65) at 20 years. In multivariable analysis, age at diagnosis <4 weeks or >5 years, familial cardiomyopathy, and lower baseline left ventricular fractional shortening Z score were associated with increased risk of death or transplantation, as was lower left ventricular fractional shortening Z score during follow-up. At 15 years after diagnosis, echocardiographic normalization had occurred in 69% of surviving study subjects. Normalization was related to higher baseline left ventricular fractional shortening Z score, higher left ventricular fractional shortening Z score during follow-up, and greater improvement in left ventricular fractional shortening Z score. Children with lymphocytic myocarditis had better survival and a higher rate of echocardiographic normalization. At the latest follow-up, 100 of 104 of survivors (96%) were free of cardiac symptoms, and 83 (80%) were no longer receiving pharmacotherapy. Risk factors for death or transplantation include age at diagnosis, familial cardiomyopathy, and severity of left ventricular dysfunction. The majority of surviving subjects are well and free of cardiac medication. (Circulation. 2013;128:2039-2046.)

Diluted cardiomyopathy (DCM) is the most common childhood cardiomyopathy and is associated with considerable early morbidity and mortality. Epidemiological studies from the National Australian Childhood Cardiomyopathy Study (NACCS) and the North American Pediatric Cardiomyopathy Registry (PCMR) determined the incidence of newly diagnosed DCM to be between 0.57 cases per 100,000 population per year for children 0 to 18 years of age and 0.73 cases per 100,000 population per year for ages 0 to 10 years of age. In particular, the registries demonstrated a higher incidence in infants and Australian indigenous and black populations. In these studies, freedom from death or transplantation was between 69% and 72% at 1 year and 54% and 63% at 5 years after diagnosis. In the
PCMR cohort, risk factors for death or transplantation differed according to the etiology of DCM.3

Although population-based registries have provided valuable insights into the incidence, risk factors, and short-term outcomes of DCM, late survival and the symptomatic status for children with DCM remain uncertain. Better information about long-term outcomes would facilitate decisions about medical care, including the role of cardiac transplantation. The present study examines late outcomes for children with DCM enrolled in NACCS.

Methods

NACCS is a population-based cohort study of all children in Australia diagnosed with primary cardiomyopathy at 0 to 10 years of age between January 1, 1987, and December 31, 1996. Local institutional review board approval was obtained from participating centers. The methodology and epidemiological findings of NACCS have been described previously.3

Cardiomyopathies were categorized by a single pediatric cardiologist (R.G.W.) after review of relevant investigations, including reinterpretation of all available cardiac imaging. The presence of congestive cardiac failure was based on signs and symptoms recorded by the attending physician. The diagnostic criteria for DCM have previously been described.1

Endomyocardial biopsies were performed at the discretion of the attending physician. A single pediatric pathologist, blinded to patient clinical details, examined all available pathological specimens. The diagnosis of lymphocytic myocarditis was based on the Dallas criteria.7

Data forms were designed to ascertain uniform clinical and epidemiological information for each enrolled subject from available hospital and outpatient case records, including clinical features at diagnosis and the results of all relevant investigations during follow-up. Local clinical and echocardiographic data were collected and verified by the primary investigator at each center. Prospective follow-up was arranged for any subjects not undergoing regular medical review.

Survival Analysis

Survival time is presented through the use of Kaplan-Meier survival curves, summarized as the proportion surviving and 95% confidence intervals (CIs) at 1, 3, 5, 10, 15, and 20 years after diagnosis. Survival time was calculated in days; hence, participation ceased at the time of death or transplantation, with a median follow-up of 15.1 years (quartiles 1 and 3, 13.0 and 17.3 years) for surviving subjects. A competing risk analysis was performed for the outcomes of normalization of LV function and the combined end point of death or transplantation. A separate competing-risk analysis was performed in the subgroup of patients with myocardial histological findings available from endomyocardial biopsy. Prognostic factors for normalization of LV function were also explored by use of the 2-stage approach described above. All analyses were undertaken with Stata Release 11.10

Results

Table 1 summarizes the characteristics of the study population. The majority of patients (64%) presented before 12 months of age. Familial cardiomyopathy and consanguinity were present in 15% and 9% of the population, respectively. Congestive heart failure was present in 163 of patients (93%) at diagnosis and in 19 of 27 patients (70%) with familial DCM. During follow-up, a total of 71 patients (41%) reached the combined end point of death or transplantation, with a median follow-up time of 15.1 years (quartiles 1 and 3, 13.0 and 17.3 years) for surviving subjects.

Table 1. Characteristics of the Patients Studied (n=175)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>76 (43)</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td>3.9 (2.5, 4.3)</td>
</tr>
<tr>
<td>Consanguinity*</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Congestive heart failure at diagnosis</td>
<td>163 (93)</td>
</tr>
<tr>
<td>Lymphocytic myocarditis on endomyocardial biopsy†</td>
<td>13 (40)</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter Z score at diagnosis (n=153), median (Q1, Q3)</td>
<td>4.4 (2.5, 6.3)</td>
</tr>
<tr>
<td>Left ventricular fractional shortening Z score at diagnosis (n=154), median (Q1, Q3)</td>
<td>−0.105 (−12.1, −8.6)</td>
</tr>
<tr>
<td>Follow-up from diagnosis for all patients (n=175), median (Q1, Q3), y</td>
<td>12.5 (6.0, 15.9)</td>
</tr>
<tr>
<td>Follow-up from diagnosis for surviving patients (n=104), median (Q1, Q3), y</td>
<td>15.1 (13.0, 17.3)</td>
</tr>
<tr>
<td>Most recent left ventricular end-diastolic diameter Z score (n=150), median (Q1, Q3)</td>
<td>1.64 (0.38, 4.62)</td>
</tr>
<tr>
<td>Most recent left ventricular fractional shortening Z score (n=153), median (Q1, Q3)</td>
<td>−2.35 (−9.5, 0.01)</td>
</tr>
<tr>
<td>Death/transplantation, n (%)†</td>
<td>71 (41)</td>
</tr>
</tbody>
</table>

*Percentage of those with data available.
†Includes 3 subjects who died within 24 hours of diagnosis.
years, 62% (95% CI, 55–69) at 10 years, and 56% (95% CI, 46–65) at 20 years (Figure 1).

Table 2 shows factors associated with the risk of death or transplantation. LV end-diastolic dimension and LVFS Z scores were found to be highly interrelated, and LVFS Z score was chosen for multivariable modeling. Age at diagnosis (Figure 2A), family history of cardiomyopathy (Figure 2B), and lower LVFS Z score at diagnosis were all independently associated with a higher hazard of death or transplantation. In particular, children >5 years of age at diagnosis and those diagnosed during the first 4 weeks of life had an increased hazard of death or transplantation compared with those diagnosed at other ages (Table 2 and Figure 2A). In addition to these baseline predictors, rate of change in LVFS Z score during follow-up was weakly associated with survival. When the latest LVFS Z score was included in the model, rate of change in LVFS Z score was not independently associated with survival, but the results of the analysis were otherwise unchanged (Table 2).

Of the 40 subjects who underwent endomyocardial biopsy, 13 had diagnostic features of lymphocytic myocarditis on histopathological examination, and the remaining 27 had nonspecific histological findings. Transplantation-free survival was better for patients with histologically confirmed myocarditis compared with those with nonspecific histologic findings (P<0.01; Figure 2C). The presence of myocarditis was not included in the multivariable model because myocardial histology was not available for all study subjects.

Normalization of LV Function, Symptoms, and Medical Therapy
Figure 3A shows a competing-risk analysis for the outcomes of echocardiographic evidence of LV function normalization, ongoing LV dysfunction, and death or transplantation for all study subjects. During follow-up, 104 participants (60%) remained free from transplantation, of whom 72 (69%) achieved normalization of LV function. Of 104 surviving patients, 100 (96%) were free of cardiac symptoms, 83 (80%) were not receiving long-term medical therapy, and 4 (4%) had an implantable cardioverter-defibrillator. Of the 21 children receiving medical therapy at the latest follow-up, 16 were receiving an angiotensin-converting enzyme inhibitor, 9 were on a β-adrenoceptor antagonist (β-blocker), 6 were on digoxin, 2 were taking spironolactone, 1 was taking carnitine, 1 was receiving Coenzyme Q10, and 3 were taking warfarin or an antiplatelet agent. Children with persisting echocardiographic abnormalities were more likely than those who had reached normalization of LV function to have cardiac symptoms (12% versus 1%; P=0.03) and ongoing use of medical therapy (47% versus 9%; P<0.001). Of note, no patients had a clinical relapse of heart failure after having attained echocardiographic normalization.

Table 3 shows factors associated with LV function normalization. A higher LVFS Z score at diagnosis was the only baseline variable associated with an increased chance of normalization. In addition to the baseline predictors, both higher most recent LVFS Z score and increased rate of change of LVFS Z score were associated with an increased chance of normalization.

Finally, Figure 3B shows competing-risk analysis of LV function normalization and death or transplantation for patients with biopsy-proven lymphocytic myocarditis, and Figure 3C shows the same information for those with nonspecific histological findings. During follow-up, echocardiographic normalization of LV function had occurred in 92% of patients with histologically confirmed lymphocytic myocarditis compared with 36% of those with nonspecific histologic findings.

Discussion
Population-based studies have provided insights into disease severity and outcomes among adults, and, more recently, children with cardiomyopathy. NACCS is unique in representing the longest and most complete longitudinal cohort study of childhood DCM, with a median follow-up among surviving subjects now exceeding 15 years. Consistency of case classification was maintained in NACCS by having 2 observers independently review all available diagnostic and histological material, respectively; recruitment was maximized by the centralized system of Australian tertiary health care. Prospective follow-up of this cohort now provides novel long-term information about outcomes for this serious disease.

Survival and Risk Factors for Death or Transplantation
Short-term survival of 40% to 80% for children with DCM has been reported in single-center reviews, with a more recent study reporting 1-year and 5-year survival of 90% and 83%, respectively, with the use of cardiac transplantation. Two large registries of pediatric cardiomyopathy patients, NACCS and PCMR, with clear inclusion criteria and prospective follow-up revealed strikingly similar outcomes for survival free from cardiac transplantation at 1 and 5 years after diagnosis. We now report long-term outcomes of children with DCM enrolled in NACCS, with freedom from death or transplantation being 74% at 1 year, 65% at 5 years, 62% at 10 years, and 56% at 20 years. Our study demonstrates that the highest-risk period for children with DCM is the first year after diagnosis, with 26% of patients achieving the combined end point of death or transplantation by 1 year compared with an average of ~1% per year in subsequent years.
Table 2. Predictors of Death or Transplantation*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects, n</th>
<th>Univariable Survival Analysis</th>
<th>Baseline Multivariable Survival Analysis</th>
<th>Full Multivariable Survival Analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>Hazard Ratio (95% CI)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Male sex</td>
<td>172</td>
<td>0.86 (0.53—1.38)</td>
<td>3.69 (1.75—7.80)</td>
<td>0.64 (0.55—0.74)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>172</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>≤4 wk</td>
<td></td>
<td>1.66 (0.91—3.02)</td>
<td>3.69 (1.75—7.80)</td>
<td></td>
</tr>
<tr>
<td>&gt;4 wk–≤1 y‡</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;1–≤5 y</td>
<td></td>
<td>0.62 (0.31—1.26)</td>
<td>1.60 (0.72—3.52)</td>
<td></td>
</tr>
<tr>
<td>&gt;5 y</td>
<td></td>
<td>3.42 (1.74–6.70)</td>
<td>11.2 (4.72–26.4)</td>
<td></td>
</tr>
<tr>
<td>Familial cardiomyopathy</td>
<td>172</td>
<td>2.04 (1.16–3.58)</td>
<td>3.22 (1.66–6.24)</td>
<td>0.001</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>172</td>
<td>1.43 (0.65–3.14)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Congestive cardiac failure at diagnosis</td>
<td>172</td>
<td>2.94 (0.72–12.0)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>LVFS Z score at diagnosis</td>
<td>153</td>
<td>0.86 (0.77—0.96)</td>
<td>0.75 (0.66–0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Most recent LVFS Z score†</td>
<td>151</td>
<td>0.64 (0.55–0.74)</td>
<td>&lt;0.001</td>
<td>0.64 (0.55–0.74)</td>
</tr>
<tr>
<td>Rate of change of LVFS Z score (per year)‡§</td>
<td>136</td>
<td>0.95 (0.89–1.01)</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

The results presented are hazard ratios from Cox proportional hazards analysis of time to death or transplantation. Results in the univariable survival analysis column represent unadjusted hazard ratios from separate models including just the predictor of interest, except for the most recent LVFS Z score and rate of change of LVFS Z score, for which the factor of interest has been added to the model shown in the Baseline Multivariable Survival Analysis column. Results in the Baseline Multivariable Survival Analysis column and the Full Multivariable Survival Analysis column are from a single Cox proportional hazards model including all of the factors. CI indicates confidence interval; and LVFS, left ventricular fractional shortening.

*Model based on n=153 participants.
†Time-dependent variables added to the multivariable model containing the baseline predictors.
‡Reference category.
§Per unit Z-score, at any time during follow-up.

Previous studies have produced conflicting data about risk factors for death or transplantation in children with DCM, particularly in terms of age at diagnosis and severity of cardiac dysfunction. Multicenter registries have demonstrated a more consistent pattern of disease over the first 5 years after diagnosis, with similar risk factors for death and transplantation. In the present study, age at diagnosis, family history of cardiomyopathy, and baseline LVFS Z scores were all associated with survival. There was a complex interaction between age at diagnosis and transplantation-free survival, with patients diagnosed <4 weeks and those diagnosed >5 years having a higher risk of death or transplantation. In addition to these baseline factors, the risk of death or transplantation was higher for those with worse LVFS Z scores and those who failed to have improved LVFS Z scores during follow-up.

In the present study, subjects with biopsy-confirmed lymphocytic myocarditis had better survival than those with non-specific histological findings. This is consistent with results of multiple single-center case series and a recent multicenter study from PCMR, which demonstrated that in children with biopsy-confirmed or clinically diagnosed lymphocytic myocarditis, freedom from death or transplantation was 75% 3 years after diagnosis and was better than for children with idiopathic DCM. In a single-center contemporaneous series, 97% of patients with active lymphocytic myocarditis on myocardial biopsy survived to a median follow-up of 13 years compared with 32% of those without features of lymphocytic myocarditis on biopsy.

Advances in genetics have shed light on the molecular basis of familial DCM, which includes mutations in sarcomeric, cytoskeletal, and nuclear proteins. In the present study, outcomes for children with familial DCM were worse than those for children with no familial DCM, despite a lower incidence of congestive heart failure at diagnosis. Other studies that have shown longer survival for subjects with familial DCM may have included older subjects with less severe cardiac dysfunction who came to attention as a result of routine screening.

Normalization of Cardiac Function

Our study provides novel information on long-term reverse cardiac remodeling in children with DCM. This occurred in 33% of all subjects and 69% of all transplantation-free survivors during follow-up, with a continuing proportion of subjects attaining normalization >10 years after diagnosis. Factors associated with normalization of LV function, which was defined by both LV size and systolic function, included a higher LVFS Z score at diagnosis and improvement in LVFS Z score during follow-up. Possible explanations for improvement in LV function in some patients may include the use of supportive medical therapy or recovery from post–viral myocarditis, even in those without diagnostic histopathology. Although the usefulness of Dallas criteria for the diagnosis of post–viral lymphocytic myocarditis has been questioned, there are several reports on differential outcomes between patients with active lymphocytic myocarditis on biopsy compared with other patients. In a single-center study of...
>100 new DCM patients, LV normalization occurred in 79% of patients with active lymphocytic myocarditis compared with 54% of patients with borderline lymphocytic myocarditis and only 36% of patients with noninflammatory DCM. An analysis of outcomes from >1000 patients in PCMR found that LV normalization rates were equivalent among patients with clinical or histopathological diagnosis of lymphocytic myocarditis (54%) compared with 21% of children with idiopathic DCM. In our study, echocardiographic normalization of LV function for patients with biopsy-confirmed lymphocytic myocarditis occurred more commonly (92%) than in those with nonspecific histologic findings (36%).

Relevance of This Cohort Study to Patients Diagnosed in the Current Era

Although the classification of cardiomyopathies has recently been revised, the diagnostic criteria for DCM in patients with established cardiac dysfunction have remained unchanged since the enrollment of patients in NACCS. Available pharmacotherapy for pediatric patients has been driven by...
significant advances in the treatment of adult DCM. Survival benefit in adults with congestive heart failure has been demonstrated with angiotensin-converting enzyme inhibitors, β-blockers, and the targeted use of implantable cardioverter-defibrillators, biventricular pacing, and mechanical circulatory support. Outcomes of adult heart failure have improved as a result, and new recommendations for heart transplantation referral have been developed.

Despite early encouraging reports on the benefits of medical therapy in children with DCM, a recent multicenter, randomized, controlled pediatric study showed no significant improvement in heart failure outcomes over the use of placebo. In a recent retrospective single-center review, no difference in transplantation-free survival could be demonstrated between patients receiving previous-era care and those receiving current-era care. Our study was not designed to assess the impact of medical therapy on heart failure symptoms and outcomes; however, there is currently little evidence to indicate that outcomes in children with DCM are modified by medical therapy. The long-term outcomes of the NACCS cohort remain relevant and applicable to patients diagnosed in the current era.

### Study Limitations

The present study is subject to the usual limitations of a retrospectively ascertained patient cohort. Genetic testing was not routinely available throughout the study period, potentially restricting the number of cases detected before the onset of symptoms. Our findings may not apply to those children who are found to have a causal genetic mutation but who have not yet developed a DCM phenotype or to patients with neuromuscular and multisystem metabolic diseases, who were excluded from this study because of potential death resulting from noncardiac causes. Options for circulatory support were limited in the early years of the study, when mortality was highest and cardiac transplantation was not universally available. There were insufficient numbers in the later group for a separate risk factor analysis. Measurement of LVFS has inherent limitations, and a more global measure of LV systolic function might add to the predictive value of echocardiography but was not available for all subjects during the study period. Reliance on histologic criteria may have led to underestimation of the proportion of subjects with post–viral myocarditis. This was unavoidable because polymerase chain reaction analysis for common viral pathogens was not routinely available for all subjects during the study period. Although similar limitations apply to the published PCMR cohort, outcomes for both groups have been strikingly similar.

### Conclusions

The highest-risk period for children with DCM was in the first year after diagnosis, with 26% of patients achieving the end point of death or transplantation compared with ~1% per year in subsequent years. Survival was worse for subjects diagnosed at <4 weeks and >5 years of age, those...
with familial cardiomyopathy, and those with a lower baseline LVFS Z score at diagnosis. In addition, lower LVFS Z score during follow-up was associated with worse survival. Echocardiographic normalization of LV function occurred in 33% of all patients by 15 years after diagnosis. Higher LVFS Z score at diagnosis, higher LVFS Z score during follow-up, and greater improvement in LVFS Z score were all predictive of an increased likelihood of normalization. Late outcomes among surviving subjects were good, with a low rate of symptoms, medical therapy, and implantable cardioverter-defibrillator use. This population-based study identifies long-term outcomes in children with DCM.

Sources of Funding

This study was supported by grant 98001 from the Royal Children’s Hospital Research Foundation; grants G 98M 0159, G 04M 1586, G 05M 2151, and G 07M 3180 from the National Heart Foundation of Australia; an NACCs grant from the Australia and New Zealand Children’s Heart Research Centre; and an NACCs grant from Heartkids Australia. Dr Daubney is supported by the Biomedical Research Unit at the Royal Brompton Hospital.

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Dilated cardiomyopathy is the most common childhood cardiomyopathy and is associated with significant morbidity and mortality. Better information about long-term outcomes would facilitate decisions about medical care, including the role of cardiac transplantation. The National Australian Childhood Cardiomyopathy Study is unique in representing the longest and most complete longitudinal national cohort study of childhood dilated cardiomyopathy, with a median follow-up among surviving subjects of 15 years. The highest-risk period for children with dilated cardiomyopathy was in the first year following diagnosis, with 26% of patients achieving the end point of death or transplantation compared with ~1% per year in subsequent years. Survival was worse for subjects diagnosed before 4 weeks and after 5 years of age, those who failed to improve left ventricular fractional shortening Z score, and those with worse left ventricular fractional shortening Z score during follow-up. Echocardiographic normalization of left ventricular function occurred in 33% of all patients by 15 years after diagnosis. Both survival and echocardiographic normalization were more common in children with biopsy-confirmed myocarditis. Late outcomes among surviving subjects were good with a low rate of symptoms, medical therapy, and implantable cardioverter-defibrillator use. This population-based study identifies long-term outcomes in children with dilated cardiomyopathy.

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Long-Term Outcomes of Dilated Cardiomyopathy Diagnosed During Childhood: Results From a National Population-Based Study of Childhood Cardiomyopathy


for the National Australian Childhood Cardiomyopathy Study

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