Clinical Features and Outcomes of Childhood Dilated Cardiomyopathy
Results From a National Population-Based Study

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Background—Despite considerable mortality, population-based prognostic factors for childhood dilated cardiomyopathy are lacking.

Methods and Results—A population-based cohort study was undertaken of all children in Australia who presented with cardiomyopathy at age 0 to 10 years between January 1, 1987, and December 31, 1996. A single cardiologist analyzed all cardiac investigations, and a single pathologist analyzed histopathological material. There were 184 subjects with dilated cardiomyopathy. Positive viral identification or lymphocytic myocarditis was found in 30 (68.2%) of 44 cases with available early histology and 8 of 9 cases presenting with sudden death. Freedom from death or transplantation comprised age > 5 years at presentation. By proportional hazards regression analysis, risk factors for death or transplantation comprised age > 5 years at presentation (hazard ratio 5.6, 95% CI, 2.6 to 12.0), familial dilated cardiomyopathy (hazard ratio, 2.9; 95% CI, 1.5 to 5.6), lower initial fractional shortening z score (hazard ratio per z-score unit, 0.75; 95% CI, 0.65 to 0.87), and failure to increase fractional shortening z score during follow-up (hazard ratio per unit increase, 0.68; 95% CI, 0.58 to 0.79). At follow-up, 78 (44.6%) of 175 cases diagnosed during life have no symptoms and are not taking any cardiac medication.

Conclusions—Early mortality is high in childhood dilated cardiomyopathy, but the clinical status of long-term survivors is good. This population-based study identifies children at risk of adverse events. (Circulation. 2006;114:2671-2678.)

Key Words cardiomyopathy ■ heart failure ■ myocarditis ■ pediatrics

Dilated cardiomyopathy is the most common childhood cardiomyopathy and is associated with considerable morbidity and mortality. International registry data indicate that dilated cardiomyopathy accounts for > 50% of all cardiac transplantations performed in patients between 1 and 10 years of age. Reported outcomes for childhood dilated cardiomyopathy vary widely and have usually been based on institutional reviews or limited geographic regions. Institutional reviews may not detect children who die soon after presentation, and prognostic variables derived from population-based studies are presently lacking. Some studies have examined outcomes only in relation to patient characteristics at the time of initial evaluation. A better understanding of the spectrum and outcomes of childhood dilated cardiomyopathy would facilitate patient care and permit evaluation of newer therapies. The present study examines the clinical characteristics and risk factors for death and transplantation among children with dilated cardiomyopathy enrolled in the National Australian Childhood Cardiomyopathy Study.

Methods
The National Australian Childhood Cardiomyopathy Study is a population-based cohort study of all children in Australia who presented with cardiomyopathy at 0 to 10 years of age between January 1, 1987, and December 31, 1996. Cases were recruited during a series of site visits undertaken in 1997 to 2000 by the same investigators, who visited all 9 pediatric cardiac centers and an additional 12 hospitals caring for children with heart problems. Cases were also recruited from rural pediatricians, cardiac transplant centers, and cardiologists caring primarily for adults. In each...
location, study subjects were identified from multiple sources, including cardiology and medical record databases and echocardiography logbooks. Children with cardiac dysfunction associated with progressive neuromuscular disorders or inborn errors of metabolism with multiple organ involvement were excluded. The methodology and epidemiological findings have been described previously. Ethics committee approval was obtained from each participating institution.

Cardiomyopathies were categorized according to the current World Health Organization cardiomyopathy classification by a single pediatric cardiologist after review of relevant investigations, including direct visualization and reinterpretation of all available cardiac imaging. The presence of congestive heart failure was based on signs and symptoms recorded by the attending physician. The diagnostic criteria for dilated cardiomyopathy were (1) reduced left ventricular systolic function on any form of cardiac imaging in subjects with symptoms or a family history of dilated cardiomyopathy, (2) a measured left ventricular ejection fraction <45% or a fractional shortening ≤20% in children without symptoms or a positive family history, or (3) pathological evidence of dilated cardiomyopathy at autopsy. Although most subjects had left ventricular dilatation, this was not required for study inclusion, because some subjects with rapidly progressive symptoms had normal left ventricular size at presentation. Subjects with lymphocytic myocarditis and associated left ventricular systolic dysfunction were included because their clinical and echocardiographic findings were frequently indistinguishable from those of other study subjects. A single pediatric pathologist who was unaware of clinical patient details examined all available pathological specimens, including cardiac histology.

Autopsy records were obtained from a computerized index kept by the Australian Bureau of Statistics that used the same diagnostic codes as for hospital records. In this way, information was obtained about subjects who had never had contact with a physician. Prospective clinical and echocardiographic follow-up was arranged for surviving subjects, particularly those not seen within the preceding 24 months.

Specifically designed data forms were used to ascertain and record uniform clinical and epidemiological retrospective information for each enrolled subject from all available hospital and outpatient case records, including the results of all relevant investigations. Data recorded during prospective follow-up were recorded in the same way. Prognostic factors sought included clinical features at presentation and results of relevant investigations (see Appendix in the online Data Supplement). The earliest available ECG within 7 days of presentation was read by a single observer, and measurements were converted to age-appropriate z scores. Serial echocardiographic measurements of left ventricular dimensions, wall thickness, and fractional shortening (in those without regional wall-motion abnormalities), were expressed as z scores based on body surface area (or age, in the case of fractional shortening). These echocardiographic parameters were selected because they were routinely quantified in all subjects who underwent echocardiography and were usually available at presentation, after 3, 6, 12, and 24 months, and at latest follow-up. Among subjects with serial echocardiograms available from the time of presentation, the change in fractional shortening (and fractional shortening z score) at each subsequent occasion of measurement was calculated by subtracting the initial fractional shortening (fractional shortening z score) from the subsequent value.

Familial cardiomyopathy was considered to be present when there was an affected first- or second-degree relative with primary dilated cardiomyopathy identified from the case notes or from prospective screening of other family members. Definite lymphocytic myocarditis was classified according to the Dallas criteria. Routine genetic testing for mutations known to cause dilated cardiomyopathy was not available during the study period.

Statistical Methods
Standard methods of survival analysis were used for the combined end point of death or transplantation. Analysis of prognostic factors excluded 9 subjects whose initial manifestation was sudden death. Important prognostic factors from the univariate analysis (P<0.10) were included in a multivariable Cox proportional hazards model. Lymphocytic myocarditis on endomyocardial biopsy was predictive of survival on univariate analysis but was not entered into the multivariable model because cardiac histology was not available in all subjects. Because echocardiographic measurements were highly interrelated, only fractional shortening z score at presentation and change in fractional shortening z score on subsequent examinations were entered into the multivariable model (as continuous predictors, with the latter a time-dependent covariate defined by the most recent available echocardiographic value). Survival curves were plotted with Kaplan-Meier survival estimates, with accompanying 95% Greenwood confidence bands.

Follow-up data were available at least 2 years after presentation in >90% of surviving subjects. The Wilcoxon rank-sum test was used to compare the distribution of time from diagnosis between subjects with and without lymphocytic myocarditis in those with available myocardial histology. The Fisher exact test was used to examine the association between inotropic support at presentation and the presence or absence of lymphocytic myocarditis in the same subjects.

Analysis was undertaken with Stata software. Ninety-five percent CIs are given for estimated hazard ratios, and all reported probability values are 2-sided.

The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results
The study population included all Australian children diagnosed with dilated cardiomyopathy during the study period, as well as additional subjects identified at autopsy. Table 1 summarizes the characteristics of the study population. The majority of subjects had both left ventricular dilatation and systolic dysfunction at diagnosis.

Presenting Symptoms and Initial Therapy
Congestive heart failure was the presenting symptom in 165 (89.7%) of 184 patients, sudden death in 9 (4.9%), and other symptoms (exercise intolerance or arrhythmias) in 4 (2.2%), whereas 6 cases (3.3%) were detected solely on routine screening of family members. The median age of the 9 cases whose initial symptom was sudden death was 2 months (range 8 days to 11 months). Of the 175 patients who were diagnosed during life, 154 (88%) were hospitalized, and 79 (45.1%) were admitted to an intensive care unit. Established renal failure that required dialysis or specific supportive measures was present in 18 patients (10.3%) at diagnosis, and rhabdomyolysis was present in 2 (1.1%). Assisted mechanical ventilation was administered in 62 patients (35.4%) and inotropic support in 70 (40%). The frequency with which inotropic support was administered at presentation was similar among children with lymphocytic myocarditis (9 of 25 cases, 36%) compared with those with nonspecific histological findings (18 of 45 cases, 40%; P=0.80). Long-term medical therapy for congestive heart failure, including diuretics, digoxin, an afterload-reducing agent (usually an angiotensin-converting enzyme inhibitor), an aldosterone antagonist, or a β-blocker, was initiated at some point in 134 subjects (76.6%), and systemic antiocoagulation was administered in 24 (13.7%). Immune modulating therapy (cyclosporine, steroids, or γ-globulin) was used in 11 of 13 children with lymphocytic myocarditis on endomyocardial biopsy.
Viral Identification and Lymphocytic Myocarditis

**Etiological Considerations**

**Viral Identification and Lymphocytic Myocarditis**

In 41 (22.3%) of 184 subjects, a potentially cardiotoxic virus (most commonly coxsackievirus or adenovirus) was identified from urine, stools, or upper-airway secretions at presentation with polymerase chain reaction or viral culture. Lymphocytic myocarditis was present in 25 (35.7%) of 70 cases with available cardiac histology from any source (endomyocardial biopsy, explantation, or autopsy). There was an inverse relationship between the time from diagnosis to histological examination and the presence of positive histological findings for lymphocytic myocarditis (Table 2; \( P=0.009 \)). Although viral identification from endomyocardial biopsy was not routinely undertaken during the study period, 8 cases had both lymphocytic myocarditis and positive viral identification from at least 1 source. When microbiological and histological investigations were considered together, a potential viral contribution was identified in 58 (31.5%) of 184 cases, including 30 (68.2%) of 44 cases who underwent cardiac histological examination within 7 days of presentation and 6 (66.7%) of 9 whose initial manifestation was sudden death.

**Familial Cardiomyopathy, Metabolic Conditions, and Parental Consanguinity**

Familial dilated cardiomyopathy was identified in 27 subjects (14.7%), 8 of whom did not have symptoms at diagnosis. Three (11.1%) of 27 children with familial cardiomyopathy showed genetic anticipation, with a prior affected family member having onset of cardiomyopathy during adult life. A metabolic or mitochondrial disease (Barth syndrome, carnitine transport defect, fatty acid oxidation defect, or respiratory chain complex deficiency) with predominant cardiac manifestations was diagnosed in 12 (8.9%) of 135 cases who underwent at least 1 metabolic investigation, 8 of whom were aged <12 months. Parental consanguinity was present in 14 (8.8%) of 160 cases in which this variable could be ascertained, including 3 with familial cardiomyopathy.

**Outcomes**

A total of 75 patients (40.8%) have died or undergone transplantation. These included 9 subjects who presented with sudden death and 24 who died during their initial hospitalization at a median of 2 (range, 0 to 18) days after presentation. At latest follow-up, 78 of 184 subjects are taking no regular medication, whereas 31 (16.8%) are receiving long-term medical therapy. Of the 103 patients with known symptomatic status, 94 (91.3%) are without cardiac symptoms.

**Survival Analysis**

Actuarial freedom from death or transplantation was 72% (95% CI, 65% to 78%) 1 year after presentation and 63% (95% CI, 55% to 70%) at 5 years (Figure, panel A). Risk factors showing at least weak evidence (\( P<0.1 \)) of association with risk of death or transplantation are shown in Table 3. There was a clear difference in survival according to age at presentation (Figure, panel B), with a lower fractional shortening \( z \) score at presentation in the 3 youngest age groups, presenting age being dichotomized at 5 years at diagnosis (post hoc 3-group comparison \( P=0.11 \)). Given the weak evidence for differences between the 3 youngest age groups, presenting age was dichotomized at 5 years for entry in the multivariable proportional hazards model. In this model, factors that showed evidence of independent predictive associations included age \( >5 \) years at presentation (Figure, panel B), familial dilated cardiomyopathy (Figure, panel C), a lower fractional shortening \( z \) score at presentation,
and failure to increase fractional shortening z score from presentation.

At 2 years after presentation, 24 (13.7%) of the 175 patients who were diagnosed during life had a measured fractional shortening below 20%. Outcomes for this group were poor. Eleven (45.8%) of the 24 died or underwent transplantation, and all of the remaining subjects continue to have impaired left ventricular function.

**Lymphocytic Myocarditis**

Of 25 children with lymphocytic myocarditis, 12 (48%) were diagnosed at autopsy. Six (24%) of these presented with sudden death, and the other 6 (24%) died within 3 days of presentation. The remaining cases were diagnosed from endomyocardial biopsy. Among 39 children who underwent endomyocardial biopsy, survival among the 13 cases with lymphocytic myocarditis was significantly better than among the 26 who had nonspecific histological findings (Table 2; Figure, panel D). At latest follow-up in children with lymphocytic myocarditis diagnosed from endomyocardial biopsy, the mean (interquartile range) left ventricular end-diastolic dimension and fractional shortening z scores were 0.4 (−0.65, 0.7) and −0.5 (−1.2, 0.8), respectively.

**Discussion**

Population-based studies have provided unique insights into disease severity and outcomes among adults with cardiomyopathy. The National Australian Childhood Cardiomyopathy study is the largest population-based study of childhood cardiomyopathy and therefore provides useful reference data. Consistency of case classification was maintained by having the same observers examine all available cardiac investigations and histopathological material. Although the number of cases with mild unrecognized dilated cardiomyopathy remains unknown, case ascertainment for children already diagnosed is likely to have been effectively complete for the following reason: The majority of children who are diagnosed with dilated cardiomyopathy come to attention in an institutional review. The inverse ascertainment may be due to spurious association with systemic viral illnesses. The present study demonstrates a potential viral contribution in a high proportion of cases, however. This unexpectedly high prevalence may reflect the inclusion of autopsy cases and subjects who would otherwise not have come to attention in an institutional review. The inverse relation between the prevalence of myocarditis and increasing time since presentation is consistent with animal models in which myocardial inflammation disappears within 6 weeks of viral inoculation.

**Symptoms and Causes**

Symptoms were present in most subjects at presentation and were usually severe. Congestive heart failure was the initial symptom in almost 90% of patients, half of whom were admitted to an intensive care unit. Sudden death was the first manifestation of dilated cardiomyopathy in nearly 5%, and a further 13% died during their initial hospitalization. Lymphocytic myocarditis among adults with left ventricular dysfunction occurs in ~10% of cases and may be due to a variety of viral and autoimmune causes. In children with dilated cardiomyopathy, lymphocytic myocarditis is found more frequently and more commonly reflects a viral origin. The results of viral identification from tracheal aspirate by polymerase chain reaction have been shown to correlate well with those obtained from myocardium and the lower respiratory tract. In the present study, positive viral identification or lymphocytic myocarditis was present in 68% of subjects with early available myocardial histology, including 6 of 9 subjects presenting with sudden death. The diagnosis of postviral cardiomyopathy remains problematic, and these findings are open to a number of interpretations. Low ascertainment of viral illness may be due to collection of specimens well after the viremic phase of the initial illness, low utilization of early endomyocardial biopsy, and lack of direct viral testing on myocardial samples, whereas overascertainment may be due to spurious association with systemic viral illnesses. The present study demonstrates a potential viral contribution in a high proportion of cases, however. This unexpectedly high prevalence may reflect the inclusion of autopsy cases and subjects who would otherwise not have come to attention in an institutional review. The inverse relation between the prevalence of myocarditis and increasing time since presentation is consistent with animal models in which myocardial inflammation disappears within 6 weeks of viral inoculation.

**TABLE 2. Frequency of Lymphocytic Myocarditis Among Subjects With Available Cardiac Histology, According to Time Between Diagnosis and Examination of Histological Findings (n=70)**

<table>
<thead>
<tr>
<th>Time From Presentation</th>
<th>0–7 Days</th>
<th>&gt;1–4 Weeks</th>
<th>&gt;4–8 Weeks</th>
<th>&gt;8 Weeks</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic myocarditis</td>
<td>22</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Nonspecific histological findings</td>
<td>22</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>10</td>
<td>8</td>
<td>8</td>
<td>70</td>
</tr>
</tbody>
</table>

P=0.009, Wilcoxon rank-sum test.
been underrecognized, because not all subjects and families were systematically screened.28

Outcomes
Reported outcomes and prognostic factors for childhood dilated cardiomyopathy have varied considerably. Five-year survival rates of 20% to 84% have been described from institutional reviews.3,6,8,10 In 1 study of 24 children presenting at ≤2 years of age4 absence of lymphocytic myocarditis, a spherical left ventricular shape, and more depressed left ventricular function at presentation were associated with worse outcomes. Another review of 25 children aged ≥2 years at presentation reported a 3-year survival of only 20%.6 Some studies have found no relation between late survival and age3,7 or severity of cardiac dysfunction3,6–8 at presentation. Other proposed adverse risk factors include the magnitude of diastolic dysfunction at cardiac catheterization3 or by echocardiography (in adults).29 A single previous national study30 of 62 cases who were diagnosed between 1980 and 1991 reported that right ventricular failure at presentation and requirement for anticoagulant therapy were associated with worse outcomes. The study selection criteria differed from the present study, however, in that subjects with myocarditis and those with self-limiting cardiomyopathies were excluded.30 Few pediatric studies have examined late survival in relation to serial assessment of left ventricular function.

In the present study, independent risk factors for death or transplantation comprised older age at presentation, familial dilated cardiomyopathy, lower initial fractional shortening \( z \) score, and failure to increase fractional shortening \( z \) score during follow-up. Younger patients had a nonsignificant trend to worse survival, which suggests the possibility of a bimodal age distribution for poor outcomes in childhood dilated cardiomyopathy. The impact of each established risk factor was considerable. For example, an increase in fractional shortening \( z \) score over the baseline value measured at presentation was associated with a 32% reduction in hazard ratio per unit \( z \) score. Improvement in left ventricular function among surviving subjects may have been due to supportive medical therapy and, in some cases, resolution of postviral cardiomyopathy. The clinical status of long-term survivors was good, with nearly half of all study subjects having no symptoms and no longer receiving cardiological medications.

Despite a high initial mortality, subjects with lymphocytic myocarditis diagnosed during life had a better survival than those with nonspecific histological findings. This may reflect the rapid evolution of pediatric lymphocytic myocarditis, selection of less critically ill patients for biopsy, a more
favorable natural history of this condition, or the benefits of the various therapies employed. Among adults with lymphocytic myocarditis, fulminant onset is associated with improved outcomes, although there is no evidence that immunosuppressive therapy modifies the natural history. However, there exist numerous reports of favorable outcomes after treatment among both children and subgroups of adults with lymphocytic myocarditis. A separate trial of immune-modulating therapy in children appears warranted to address this issue.

Therapies
The present study took place during a period of rapidly changing medical therapy for subjects with dilated cardiomyopathy. The data supporting the efficacy of medical therapy in children with dilated cardiomyopathy are less robust than in adult subjects, and the present study was not designed to draw conclusions about the benefits of any specific treatment. In adult patients with left ventricular dysfunction, carvedilol reduces mortality and modifies prognostic factors. Retrospective studies in children suggest that β-blockers improve ventricular performance, and a prospective multicenter trial is presently under way. Although mortality and requirement for eventual cardiac transplantation may be reduced by aggressive use of newer medical therapies in children, their impact in the youngest of patients has yet to be defined. The present study identifies children at greatest risk for death or transplantation, who might therefore benefit most from effective early treatment. The long-term limitations of transplantation and the lack of sufficient young donors justify the continuing search for better medical therapy.

Study Limitations
The Dallas criteria are of limited utility in the diagnosis of postviral cardiomyopathy and are subject to considerable interobserver variability. The latter was minimized by having a single pediatric pathologist examine all available myocardial histology. Retrospective data collection, variable diagnostic protocols, and limitations in existing knowledge also restricted the proportion of study subjects with cardiomyopathy of known origin. By comparison with other pediatric studies, however, the proportion of subjects with a known or probable cause remains high. Routine genetic testing for dilated cardiomyopathy was not available during the study period, and the results of the present study cannot be extrapolated to children who have not yet developed left ventricular dysfunction. A more global measure of left ventricular systolic function and routine measurement of diastolic parameters may further increase the predictive value of echocardiography. These were not serially available on all subjects during the study period. The observation that infants may also be at increased risk for worse outcome may be confirmed with a larger study cohort.

Conclusions
Congestive heart failure is severe among children with dilated cardiomyopathy, and lymphocytic myocarditis is an important cause. Although early mortality is high, the clinical status...
of long-term survivors is good. This population-based study identifies children with dilated cardiomyopathy who are at risk for adverse events.

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Disclosures

None.

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Pediatric cardiomyopathies are characterized by heterogeneous origins with varied outcomes. Childhood dilated cardiomyopathy is most common during the first year of life and is associated with significant morbidity and mortality. Most available information is from institutional reviews, which may not detect children who die early and those who do not require hospitalization. Population-based studies of cardiomyopathy in adults have provided valuable insights into disease severity and outcomes. The National Australian Childhood Cardiomyopathy study is a longitudinal cohort study of all children in Australia aged 0 to 10 years who were diagnosed with cardiomyopathy between 1987 and 1996. There were 184 subjects with dilated cardiomyopathy. At presentation, 90% of cases had signs and symptoms of congestive heart failure, and sudden death was the presenting symptom in 4%. Familial cardiomyopathy was identified in 14.7% of subjects, a metabolic or mitochondrial disease in 8.9%, and parental consanguinity, consistent with autosomal recessive inheritance, in 8.8% of cases. A potential viral contribution (lymphocytic myocarditis or positive viral identification) was identified in 68.2% of case subjects who underwent early cardiac histological examination. By multivariate analysis, independent risk factors for death or cardiac transplantation included age >5 years at presentation, familial dilated cardiomyopathy, a lower fractional shortening z score at presentation, and failure to increase fractional shortening z score from presentation. At latest follow-up, 78 of 109 surviving cases had no symptoms and were not taking any cardiac medication. Early mortality is high in childhood dilated cardiomyopathy, and the clinical status of long-term survivors is good. The present population-based study identifies children at risk of adverse outcomes.
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