Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy in children and the most common indication (64%) for heart transplantation in children over the age of 5 years. It also represents a common indication for transplant in infants (31%).1 With an annual incidence of 0.34 to 1.13 per 1,000,000 children, the etiology of DCM is varied.2 Nearly two thirds of cases of DCM in children are idiopathic; the remainder are secondary to numerous factors, including familial, myocarditis, metabolic, or neuromuscular disease and malformation syndromes.3 Unfortunately, despite the introduction of diuretics, ACE-inhibitors, and β-blockers, the prognosis of this disease remains poor, and organ survival in children with DCM has changed little in the last 20 years.4 Cardiac transplantation is currently the only effective treatment for end stage heart failure associated with DCM.

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Despite improved strategies for outpatient management, hospital admission for DCM is common. The initial hospitalization for heart failure is often accompanied by an extensive evaluation, including echocardiography, serum studies, and cardiac catheterization. Adult studies, including the Seattle Heart Failure Study, have attempted to use this data to predict death or urgent transplantation in patients with heart failure, and studies in pediatric populations have attempted to validate this model in children.5,6 In 2010, Patel et al reported that percent lymphocytes, sodium, and creatinine were predictive of death or transplant for children hospitalized with heart failure. In their study of 99 patients, however, only 58 children had DCM, while the remainder (41; 41%) had heart failure of varied etiology, including congenital heart disease. The present study, limited to patients with DCM exclusively, with data collection beginning at the time of their first hospitalization, provides a more homogeneous cohort normalized to an easily recognized entry time point.

We hypothesized that the first hospitalization for DCM represents a sentinel event predictive of poor 1-year freedom from death or transplantation. Echocardiographic function and hemodynamic and serum measurements may aid in predicting outcomes. Despite medical management, most patients will be rehospitalized and/or require cardiac transplantation within 1 year of admission. (Circ Heart Fail. 2012;5:437-443.)

Key Words: cardiomyopathy ■ heart failure ■ hospitalization ■ outcomes ■ pediatrics
freedom from death or transplantation during the index hospitalization and at 1 year of follow-up. To our knowledge, this contemporary and homogenous cohort is the largest single-institution experience reported for hospitalized pediatric patients with DCM published to date.

Methods

Study Cohort and Data Source

We identified and performed a retrospective chart review on 83 patients with DCM who had at least 1 hospitalization at Lucile Packard Children’s Hospital at the time of, or subsequent to, their diagnosis between January 1, 2004, and December 31, 2009, of which 71 had reached the end point of death, transplantation, or had at least 1 year of follow-up. The diagnosis of DCM was based on the echocardiographic appearance of left ventricular dilatation and reduced left ventricular ejection fraction (LVEF), consistent with the approach taken in large pediatric registries. Secondary diagnoses included DCM identified as primary idiopathic/familial or secondary to myocarditis, anthracycline toxicity, arrhythmias leading to heart failure, or genetic, neuromuscular, metabolic, or autoimmune disease. DCM was defined as idiopathic if no specific etiology of DCM was discovered and there were no affected family members. Myocarditis was either biopsy-proven or diagnosed presumptively by the history of fever with or without the presence of upper respiratory infection symptoms or a known concomitant viral illness. Familial DCM was diagnosed if no specific etiology was discovered but there was at least 1 first-degree relative with the same or similar phenotype. Left ventricular noncompaction was diagnosed echocardiographically by the presence of a spongy appearance to the left ventricular endocardial surface and only included in the study cohort if the characteristic echocardiographic findings of DCM were also present. Anthracycline toxicity was diagnosed when the characteristic features of DCM were discovered following the exposure to at least 150 g/m² of anthracycline drugs. Neuromuscular and metabolic disorders were defined either by the presence of a known genetic mutation and/or by the presence of characteristic comorbidities.

Patients were excluded from the study if their primary diagnosis was hypertrophic cardiomyopathy, restrictive cardiomyopathy, or if they had a history of congenital heart disease. Hospitalizations for cardiac or noncardiac indications were included, however, scheduled admissions for routine procedures such as cardiac catheterization or electrophysiological study, as well as those lasting <24 hours, were excluded. This study was approved by the Stanford University institutional review board.

Clinical Data Collection

Baseline demographics, including age, gender, race, and primary/secondary diagnoses were obtained from the electronic medical record. Outside hospital data, including length of stay, level of care, and total intubation days were obtained from outside hospital records incorporated into the patient’s Lucile Packard Children’s Hospital Medical record. The first set of laboratory studies reported in the medical record was recorded, unless they occurred beyond the seventh hospital day, in which case they were excluded. Qualitative and quantitative data from the first echocardiogram was collected for all patients, except those already on ventricular assist devices or extracorporeal membrane oxygenator.

Analysis

The primary measure studied was death or transplantation during the first hospitalization. Measures of severity of disease, including laboratory, echocardiographic, and catheterization data, duration of intubation and/or intensive care unit stay, and the need for inotropic support were analyzed as risk factors for the primary outcome. Cardiac function was reported in 2 ways: (1) by the qualitative interpretation by the echocardiographer as reported in the clinical echocardiogram report (normal, mildly reduced, moderately reduced, or severely reduced); and (2) by the calculated fractional shortening (FS) or LVEF derived from m-mode measurements. Quantitative LVEF was considered normal if >55% and severely reduced if <35%. Only the quantitative measurements were used in univariate and multivariable analysis.

Follow-up outcomes data, including cardiac transplantation, death, and rehospitalization were collected for 1 year following admission. Univariate analysis was performed using χ² testing for categorical variables and unpaired t tests for continuous variables and was used to compare patients who experienced death or transplantation in the first hospitalization with those who survived to discharge without transplantation. Similar analysis was performed using the end point of death or transplantation within 1 year of the index admission date for all patients, regardless of their initial hospitalization outcome. Multivariable analysis was conducted using logistic regression taking into consideration those variables that demonstrated significance at P<0.05 in univariate analysis. Owing to a large number of missing values, we excluded patients with missing values for variables with >50% missing data.
cases in the catheterization data, an imputed value equal to the group mean was substituted for all missing values of mixed venous saturation.

Data were collected using REDCap (Version 3.4.1, Vanderbilt University), a web-based application designed to support data capture for research studies. All statistical analysis, including a Kaplan–Meier curve for 1-year freedom from death or transplantation was conducted using STATA (Version 10; STATA Corp). For Kaplan–Meier analysis, patients who did not experience one of the specified outcomes were censored at the time of their most recent clinical encounter.

**Results**

Between January 1, 2004, and December 31, 2009, 83 patients with DCM were admitted to Lucile Packard Children’s Hospital. Baseline characteristics are described in Table 1. Forty-two percent were female (35 patients), and the median age at first admission was 7 years (range 0 to 22 years). Thirty-seven (45%) identified as Caucasian; 3 (4%), African-American; 23 (28%), Hispanic/Latino; and 17 (20%), Asian/Pacific Islander. In 64 patients (77%), the diagnosis of DCM was made at the time of hospital admission. Fifty patients (60%) were transferred from another hospital. Forty-two patients (51%) were transferred directly from an outside intensive care unit. The majority of patients (66 patients; 80%) were critically ill as defined by direct admission to our intensive care unit.

The underlying diagnosis was idiopathic or familial DCM in 32 (39%) patients; the other 51 patients had DCM associated with various arrhythmic, genetic, infectious, neuromuscular, rheumatologic, or other disease processes (Table 2). The majority of patients (79/83; 96%) presented with symptoms (Table 3). Only 4 patients were discovered incidentally to have DCM on surveillance echocardiogram.

Laboratory and clinical measurements at the time of admission are summarized in Table 4. Although the mean serum sodium level was within the normal range, many patients presented with hyponatremia, with 21/83 (25%) patients presenting with a sodium <125 mmol/L. Mean serum creatinine was only mildly elevated at 1.0±1.7 mg/dL. Mean N-terminal B-type natriuretic peptide was markedly elevated at 9384±8714 pg/mL but was measured in a comparatively small number of patients (n=19).

Of the 80 patients who had echocardiograms performed on admission, the mean LVEF was 28±15%, indicating severely reduced systolic function. Qualitative interpretation yielded similar results, in that 64 (80%) subjects had moderately to severely reduced left ventricular function as described in the echo report. Fifty-seven patients (69%) received inotropic support within the first week of admission. Endotracheal intubation was performed in 37 patients (45%), including 24 (29%) who were already intubated at the time of admission. Median stay in the intensive care unit was 22.5 days (range 1 to 250 days), with median hospitalization duration of 33.8 days (range 1 to 284 days). Fifteen patients (18%) underwent heart transplantation, and 5 patients (6%) died during the initial hospitalization. Follow-up was complete at 1 year for 71 patients, of whom, 27 (38%) were transplanted and 11 (15%) had died. (Figure)

Univariate analysis for clinical, laboratory, echocardiographic, and catheterization data comparing those who experienced death or transplantation (organ death) during the initial hospitalization versus those who survived to discharge without transplantation (organ survival) is summarized in Table 5. LVEF (20% for organ death versus 31% for

| Table 4. Laboratory Indices of Patients Admitted with DCM |
|-----------------|-------|-----------------|-----------------|-----------------|
| Variable       | Mean  | SD              | Median          | Range           |
| Serum Sodium (n=83) | 137   | 4.7             | 137             | 121–155         |
| NT-BNP (n=20)  | 9384  | 8714            | 6389            | 1187–30 000     |
| Creatinine (n=82) | 1     | 1.7             | 0.6             | 0.1–14.11 (Age-dependent) |
| Hemoglobin (n=79) | 12.1  | 2.1             | 12.3            | 7.8–17.2        |
| RDW (n=78)     | 14.7  | 3.2             | 14              | 10.7–32.8       |
| Systolic BP (n=80) | 95    | 19              | 95              | 50–154         |
| Heart rate (n=81) | 125   | 33              | 122             | 65–252         |
| Uric acid (n=79) | 6.9   | 3.5             | 6               | 2–16.5         |
| Cholesterol (n=79) | 117   | 45              | 112             | 47–303         |
| Triglycerides (n=79) | 109   | 82              | 85              | 30–488         |
| Ejection fraction (n=74) | 28    | 15              | 27              | 2–53           |

DCM indicates dilated cardiomyopathy; NT-BNP, N-terminal B-type natriuretic peptide; RDW, red cell distribution width; BP, blood pressure.

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survivors; $P=0.006$) and FS (9% versus 16%; $P=0.004$) calculated on the first echocardiogram achieved the most statistical significance. Serum cholesterol levels were significantly lower (97 versus 122 mg/dL; $P=0.03$) and serum uric acid levels were significantly higher (8.7 versus 6.3 mg/dL; $P=0.01$) in patients who experienced organ death during the initial hospitalization. Of the 31 patients who underwent cardiac catheterization during the first hospitalization, mixed venous saturation was significantly lower in patients who experienced organ death during the index hospitalization (53% versus 67%; $P=0.004$). Right atrial and pulmonary capillary wedge pressures were also predictive of organ death during the first hospitalization ($P=0.02$ and $P=0.04$, respectively).

Twenty-one patients underwent right ventricular endomyocardial biopsy as part of their catheterization. Of these, 17 (81%) showed fibrosis, 1 (5%) was consistent with anthracycline toxicity, 1 (5%) showed lymphocytic infiltrate consistent with acute myocarditis as well as fibrosis, and 2 (10%) were read as normal. Biopsy data were not associated with hospital outcome.

In multivariable analysis of hospital outcome data, FS and uric acid achieved significance. For the outcome variable of organ death at 1 year from index admission, univariate analysis for clinical, laboratory, echocardiographic, and catheterization data are summarized in Table 6. Only the LVEF calculated on initial echocardiogram was significantly lower in patients who experienced organ death within 1 year of the index admission (22% versus 32%; $P=0.001$).

### Discussion

We found that children with DCM who require hospital admission are at very high risk for death or transplantation.
during their first hospitalization and in the first year following hospital admission. Twenty-four percent of patients with DCM died or were transplanted during the index hospitalization. FS, LVEF, serum cholesterol, uric acid, mixed venous saturation, and atrial filling pressures were all predictive of hospital outcome. Fifty-four percent of patients died or were transplanted within 1 year of the index admission, with LVEF being predictive of 1-year outcome. Hospital readmission for nontransplanted survivors was common.

When compared with outcomes studies of pediatric patients with DCM as a whole, the results of the current study suggest that first-time hospitalized patients are at heightened risk for death or transplantation. Tsirka et al reported a 70% 1-year freedom from death or transplantation in 91 children following diagnosis of DCM. Using data from the Pediatric Cardiomyopathy Registry, Trowin et al reported that the freedom from death or transplantation in pediatric patients with cardiomyopathy was 69% at 1 year from diagnosis, somewhat more favorable than our finding of 49% for hospitalized patients. In their cohort (excluding those with neuromuscular disease), older age at diagnosis, cause, congestive heart failure (CHF), and FS z-score were all predictive of death or transplantation. Furthermore, patients with CHF were 4 times more likely to experience death or transplantation within 1 year of diagnosis. Those with CHF are likely similar to our study cohort, given that all of our patients were hospitalized for CHF at the study entry point. Moreover, their finding that FS was an independent risk factor for poor outcome is consistent with ours.

Several clinical, serological, and echocardiographic parameters have been used for prognostic modeling for mortality and/or rehospitalization in adults with heart failure. The Seattle Heart Failure study has recently offered a predictive model that includes New York Heart Association class, ischemic etiology, medications, blood pressure, as well as several serological indices, including percent lymphocytes, uric acid, and cholesterol to predict 1-, 2-, and 3-year survival in adults with CHF; and a separate model has also been offered to predict 30-day and 1-year mortality among adults hospitalized for heart failure. Nevertheless, risk stratification remains a serious challenge, and prognostic models for adult populations have not been reliable when applied to pediatric patients. Patel and colleagues recently developed a model that incorporates percent lymphocytes, serum creatinine, and serum sodium to predict death or the need for transplant for pediatric patients hospitalized for heart failure; however, they did not extrapolate their data to include rehospitalization or 1-year outcomes.

In their study included a heterogeneous population of patients with cardiomyopathies as well as congenital heart disease. As it is not known whether these groups behave similarly, interpretation of this model is challenging.

We found that specific echocardiographic and serological indices were predictive of outcome in children hospitalized with DCM. Both quantitative and qualitative LVEF and FS were strongly predictive of outcome for the initial hospitalization, and LVEF was strongly predictive of 1-year outcome. LVEF has been identified previously as a predictor for death, transplantation, or rehospitalization in pediatric patients with DCM.

Low serum cholesterol and high serum uric acid were also predictive of death/transplant during the first hospitalization, which has been previously reported in adult populations but has not been demonstrated in children. Uric acid is elevated with oxidative stress, leads to the production of free radicals via the xanthine oxidase system, is elevated in states of cytokine-activated inflammation, and is a general marker for cell death. Low serum cholesterol may represent depletions in metabolic reserve, as well as poor nutritional status, both of which may serve as markers of either long-standing or severe CHF; and the body’s reduced capacity to resist the natural progression of the disease. Serum sodium has been identified as a predictor for hospital length of stay, in-hospital mortality, and 60-day mortality and/or rehospitalization in adults with heart failure. Although mean N-terminal B-type natriuretic peptide was also markedly elevated, and prior studies have suggested that it may be a predictor of adverse outcomes in children with heart failure, the current study had too few observations to detect a difference between groups. Our finding that red cell distribution width was not predictive of freedom from death...
or transplantation during the initial hospitalization contrasts prior reports identifying elevated red cell distribution width as an independent predictor of morbidity and mortality in adults with symptomatic heart failure.16

Of our 83 patients, 79 presented with common symptoms, including fatigue, shortness of breath, or gastrointestinal upset, with no patients presenting with syncope and only 7 presenting with cardiac arrest. The incidental discovery of DCM was uncommon. Conversely, patients were usually quite ill at the time of admission, with the majority requiring inotropic medications and nearly half requiring endotracheal intubation, although this effect may have been influenced by the fact that the majority of our patients were transferred from another hospital (60%), often specifically for an escalation in care.

Although cardiac catheterization is not necessarily a component of the initial evaluation for patients hospitalized with DCM, 31/83 (37%) patients underwent catheterization during the initial hospitalization, either as part of a pretransplant work-up, diagnostic biopsy (21/31), or left atrial decompression after extracorporeal membrane oxygenation cannulation. The timing of the catheterization was therefore variable and did not necessarily occur at the beginning of the hospitalization. Mixed venous saturation was predictive of death/transplant during the initial hospitalization, likely secondary to increased tissue oxygen extraction in the low cardiac output state. Right atrial and pulmonary capillary wedge pressures were also elevated, indicating diastolic dysfunction. Reports from earlier smaller series are mixed as to whether hemodynamic data collected during cardiac catheterization is useful in predicting hospital outcomes in children with heart failure.29,30

Biopsy data, although useful to confirm the diagnosis, was of little prognostic value.

The current study was limited by its retrospective nature, and it is possible that we did not capture every patient with DCM who had been hospitalized at our institution. Additionally, data collected during the initial hospitalization was not collected at uniform times. Lastly, although we limited our study to patients with DCM, our study population was heterogeneous with regard to the etiologies of DCM. Only 32/83 (39%) of patients had idiopathic or familial forms of DCM, the remainder presented with a variety of diagnoses, including neuromuscular/metabolic defects, infections, autoimmune disease, and primary arrhythmias. Unfortunately, there were too few patients in each subgroup to allow subgroup analysis, and differences in outcomes have been shown to differ depending on the etiology of DCM.31,32

The current study demonstrates that children with DCM are at particular risk for death or the need for cardiac transplantation during the initial hospitalization and within 1 year following the index admission. FS/LVEF, serum cholesterol, uric acid, and hemodynamic data may be predictive of outcome. Data on this clinically homogeneous, contemporary patient population at a uniform and easily recognizable study entry point has not been previously reported. For nontransplanted hospital survivors, there is a high incidence of rehospitalization, death, or transplantation within 1 year. Patients with significant risk factors may benefit from closer outpatient observation and, perhaps, earlier consideration for cardiac transplantation.

Disclosures
We thank Esther Liu, RN, FNP, and Aileen Lin, RN, FNP, for assistance with data collection for this manuscript.

References
Dilated cardiomyopathy (DCM) in children is a heterogeneous disease with a variable clinical course. Whereas some patients with DCM can remain relatively clinically stable for several years, others show a more precipitous decline, leading to death or requiring heart transplantation within 1 to 2 years following diagnosis. We hypothesized that the first hospitalization for DCM represents an inflection point in a patient’s disease trajectory for which death or the need for cardiac transplantation within 1 year was likely. Furthermore, we hypothesized that certain clinical, laboratory, and echocardiographic findings at the time of presentation may aid in predicting outcomes. The results of this study demonstrate that the first hospitalization for DCM marks a period of high risk for clinical decline, end stage heart failure, and the need for cardiac transplantation when compared with studies of pediatric patients with DCM using time of diagnosis as the study entry point, and that fractional shortening, left ventricular ejection fraction, uric acid, mixed venous saturation, and atrial filling pressures may aid in predicting outcomes. The results of this study may aid practitioners to identify at-risk patients who may benefit from closer outpatient observation, and, perhaps, earlier consideration for cardiac transplantation.