

Treating Children With Idiopathic Dilated Cardiomyopathy (from the Pediatric Cardiomyopathy Registry)

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In 40% of children with symptomatic idiopathic dilated cardiomyopathy (IDC), medical therapy fails within 2 years of diagnosis. Strong evidence-based therapies are not available for these children, and how evidence-based therapies for adults with IDC should be applied to children is unclear. Using data from the National Heart, Lung, and Blood Institute's Pediatric Cardiomyopathy Registry, we compared practice patterns of initial therapies for children with IDC diagnosed from 1990 to 1995 (n = 350) and from 2000 to 2006 (n = 219). At diagnosis, 73% had symptomatic heart failure (HF), and 7% had ≥ 1 family member with IDC. Anti-HF medications were most commonly prescribed initially. Anti-HF medication use was similar across the 2 periods (84% and 87%, respectively), as was angiotensin-converting enzyme inhibitor use (66% and 70%, respectively). These medications were used more commonly in children with greater left ventricular dilation and poorer left ventricular fractional shortening and functional class (p < 0.001). Beta-blocker use was 4% to 18% over the 2 periods. Treatments for pediatric IDC have changed little over the previous 25 years. Anti-HF medications remain the most common treatment, and they are often given to children with asymptomatic left ventricular dysfunction. Children with asymptomatic left ventricular dysfunction are often not offered angiotensin-converting enzyme inhibitors without echocardiographic evidence of advanced disease. In conclusion, therapeutic clinical trials are strongly indicated because practice variation is substantial and medical outcomes in these children have not improved in the previous several decades. © 2009 Elsevier Inc. (Am J Cardiol 2009;104:281–286)

In the absence of evidence-based standards, clinical treatment of children with idiopathic dilated cardiomyopathy (IDC) and heart failure (HF) varies widely. We examined medical therapies offered at presentation to children with IDC who were enrolled in the retrospective arm of the Pediatric Cardiomyopathy Registry (PCMR) database to identify and characterize treatment patterns in managing childhood HF. To examine management trends over time, we compared rates of pharmacologic therapy with a later cohort from the prospective arm of the registry.^{1–11}

Methods

The purpose of the PCMR is to identify epidemiologic characteristics and clinical course of selected cardiomyop-

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athies in children and to promote development of cause-specific prevention and treatment strategies. The design of the PCMR is described elsewhere.¹² The present analysis is based on the retrospective cohort of the PCMR, for which detailed therapeutic data were obtained by standardized chart abstraction on 920 children with cardiomyopathy who presented to a pediatric cardiologist from January 1, 1990, to December 31, 1995. Data were collected at 38 sites in the United States (818 children) and at 1 site in Canada (102 children). A comparison cohort diagnosed from 2000 to 2006 was also analyzed to determine rates of anti-HF medication, angiotensin-converting enzyme inhibitor (ACEI) and β -blocker use. The window for baseline registry data was 1 month after the initial diagnosis of cardiomyopathy; subsequent data were collected annually.

The institutional review board or ethics committee at each participating PCMR site reviewed and approved the protocol. Because there was no direct patient contact and no procurement of medical materials other than written records, written informed consent from individual patients or surrogates was not required.

Children were eligible for inclusion in the registry if they were ≤ 18 years old and were diagnosed with cardiomyopathy on or after January 1, 1990. IDC was diagnosed from echocardiographic evidence, including ≥ 2 left ventricular measurements (decreased fractional shortening, decreased posterior wall thickness, or increased end-diastolic dimension) exceeding 2 SDs for age (fractional shortening) or for

Table 1

Demographic characteristics and clinical status at presentation of 350 children with idiopathic dilated cardiomyopathy diagnosed from 1990 to 1995

Patient Characteristic	Value
Male	180 (51%)
Age (years)	4.9 ± 6
Median age (years)	1.5
Age distribution	
<1 yr	152 (43%)
1 yr–<6 years	81 (23%)
6–<12 years	48 (14%)
12–18 years	69 (20%)
Race/ethnicity	
White	205 (59%)
Black	82 (23%)
Hispanic	40 (11%)
Other	1 (0.3%)
Unknown	5 (1%)
Congestive HF	256 (73%)
Functional class*	
I	100 (28%)
II	47 (13%)
III	86 (25%)
IV	111 (32%)
Unknown	6 (2%)
Echocardiographic left ventricular Z-scores†	
End-systolic dimension (n = 220)	6.29 ± 2.90
End-diastolic dimension (n = 256)	4.46 ± 2.72
Fractional shortening (n = 276)	−8.85 ± 3.58
End-diastolic posterior wall thickness (n = 199)	−0.43 ± 2.39
End-diastolic septal wall thickness (n = 177)	−0.78 ± 2.02

Values are means ± SDs or numbers of patients (percentages).

* Functional class is a composite hierarchical variable based on data in the medical record denoting New York Heart Association congestive HF class, Canadian Consensus (Ross) HF class for children, or objective heart class. Children without congestive HF symptoms at diagnosis were classified as class I.

† Echocardiographic Z-scores are corrected for body surface area (end-diastolic and end-systolic dimensions and end-diastolic posterior and septal wall thicknesses) or for age (fractional shortening). Z-score represents the number of SDs from the mean of healthy children of similar body surface area or age. All mean Z-scores significantly differ ($p < 0.01$) from normal ($Z = 0$).

body surface area (other measurements), a pathologic diagnosis of cardiomyopathy at autopsy or endomyocardial biopsy, or other evidence of clinical cardiomyopathy, as provided by a cardiologist. The 14 clinical exclusion criteria included presence of a congenital heart defect not associated with a malformation syndrome, endocrine disease associated with myocardial injury, chronic arrhythmia, pulmonary or immunologic disease, and chemotherapy-associated cardiac disease.¹²

This report is based on children with pure (not mixed-type) DC for whom the cause was unknown at presentation ($n = 325$) or who also had ≥ 1 family member with DC ($n = 25$). For this report, this entire cohort of 350 children is referred to as having IDC.

Data for the PCMR were collected through on-site abstraction of patient records by a trained outreach team or research staff at the participating site. After patient identification, study personnel confirmed eligibility and enrollment through chart review and assigned a unique study identifier to ensure confidentiality. Supplemental informa-

Table 2

Initial management of 350 children with idiopathic cardiomyopathy (all rates are for children diagnosed from 1990 to 1995, unless otherwise noted)

Therapy	Percentage
Anti-HF	
1990–1995	84
2000–2006*	87
ACEI	
1990–1995	66
2000–2006*	70
Antiarrhythmic	40
β -adrenergic antagonist	5
Calcium channel antagonist	2
Other medication	52
Carnitine supplementation	18
Diet modification	14
Intra-aortic balloon pump	2
ECMO	2
Ventricular assist device	1
Pacemaker	1
Heart transplantation	5
Other procedures	7

* Numbers for 2000 to 2006 diagnoses are 462 for anti-HF therapy and 219 for ACEI therapy.

ECMO = extracorporeal membrane oxygenation.

tion included clinical history, procedures, outcomes, family history, results of laboratory studies, and therapies administered. In addition to demographic and echocardiographic characteristics, functional classifications based on New York Heart Association¹³ classification or, for younger children, the Canadian Consensus (Ross) classification¹⁴ plus objective classification were derived from data in the chart (New York Heart Association classification was used if possible, then Ross, then objective). Children with asymptomatic left ventricular dysfunction were classified as functional class I. Anti-HF therapy was defined as use of digoxin and/or a diuretic.

Left ventricular end-diastolic dimension, end-diastolic posterior wall thickness, and end-diastolic septal thickness were expressed as Z-scores relative to the distribution of these measurements to body surface area in normal children,¹⁵ and left ventricular fractional shortening was expressed as Z-score relative to age.¹⁶ Z-scores are the number of SDs each value lies from the mean value of healthy children of similar body surface area or age. Body surface area was calculated from height and weight.¹⁷

Summary statistics are presented as means ± SDs or medians and interquartile ranges. Echocardiographic Z-scores were compared by therapy status with t tests. Proportions of children receiving a given therapy were compared by cause of cardiomyopathy with chi-square tests and by functional class and by year of diagnosis with a Mantel-Haenszel test for linear trend. Crude and adjusted therapy rates by center were compared using univariate and multivariate logistic regressions. Candidate predictors used in multivariate logistic regression models for therapy included age at diagnosis, center, presence of HF symptoms, cause of IDC, and echocardiographic Z-scores.

Alpha was set at 0.05, and all tests were 2-sided. SAS 9.1 (SAS Institute, Cary, North Carolina) was used for analysis.

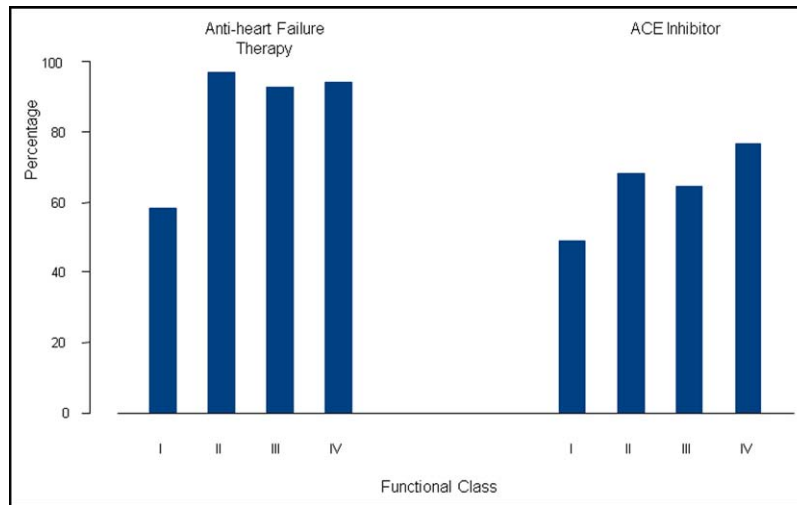


Figure 1. Anti-HF and ACEI use by functional class at diagnosis in 350 children with IDC ($p < 0.001$ for association between each therapy and functional class). See Table 1 footnote for definition of functional class.

Table 3

Left ventricular echocardiographic Z-scores in 350 children with and without antiheart failure and angiotensin-converting enzyme inhibition therapy at diagnosis of cardiomyopathy (1990 to 1995)

Echocardiographic Z-Score*	Therapy	No Therapy	p Value
Anti-HF therapy			
End-diastolic dimension	4.88 ± 2.52	2.66 ± 2.91	<0.001
End-systolic dimension	6.80 ± 2.50	3.69 ± 3.43	<0.001
Fractional shortening	-9.49 ± 2.96	-5.71 ± 4.70	<0.001
End-diastolic posterior wall thickness	-0.35 ± 2.49	-0.82 ± 1.51	0.16
End-diastolic septal wall thickness	-0.72 ± 2.11	-1.19 ± 1.19	0.11
ACEI therapy			
End-diastolic dimension	5.06 ± 2.56	3.48 ± 2.73	<0.001
End-systolic dimension	6.92 ± 2.53	5.17 ± 3.26	<0.001
Fractional shortening	-9.38 ± 3.00	-7.80 ± 4.35	0.002
End-diastolic posterior wall thickness	-0.23 ± 2.55	-0.93 ± 1.81	0.028
End-diastolic septal wall thickness	-0.66 ± 2.13	-1.14 ± 1.70	0.13

Values are means ± SDs.

* Echocardiographic Z-scores are corrected for body surface area (end-diastolic and end-systolic dimensions, end-diastolic posterior and septal wall thicknesses, and left ventricular mass) or for age (fractional shortening). All mean Z-scores significantly differ ($p < 0.05$) from normal ($Z = 0$) except for end-diastolic posterior wall thickness in the therapy group.

Results

The PCMR enrolled 920 children with cardiomyopathy diagnosed from 1990 to 1995, of which of 350 had pure IDC or familial isolated IDC (Table 1). Echocardiographic findings from month of presentation were consistent with IDC. Use of selected medications in this patient group was compared with that in a group of 219 children with pure IDC diagnosed from 2000 to 2006 for whom medication data, other than anti-HF therapy, were collected. Anti-HF therapy data for children diagnosed from 2000 to 2006 were collected for all IDC cases ($n = 462$) in the prospective cohort.

All results that follow are based on the earlier cohort diagnosed from 1990 to 1995, unless otherwise noted. Anti-HF therapy was defined as the use of digoxin and/or furosemide.

Practice variation by center was examined using the 8 largest centers in number of IDC cases (range 15 to 58 per center). After accounting for differences in disease severity (left ventricular fractional shortening Z-score) in the center populations, center-specific rates of anti-HF therapeutic use were similar ($p = 0.07$). However, ACEI use differed significantly among centers, with center-specific rates of 46% to 89%. Antiarrhythmic use also varied significantly, with center-specific rates of 13% to 54%, as did carnitine supplementation (4% to 48%). Differences by center persisted for ACEI use ($p = 0.04$), antiarrhythmic use ($p = 0.01$), and carnitine supplementation ($p = 0.007$), even after adjustment for fractional shortening Z-score.

Anti-HF therapy at diagnosis was the most commonly reported intervention for all children, being reported in 84% (Table 2). Anti-HF administration differed by functional class (Figure 1), being administered to 60% of asymptomatic (class I) children and to 93% of children in class \geq II ($p < 0.001$). Anti-HF agents were also prescribed more frequently in children with echocardiographic evidence of more advanced HF (Table 3). Multivariate modeling ($n = 272$) indicated that HF (odds ratio 6.5, 95% confidence interval 3.0 to 14.0, $p < 0.001$) and left ventricular fractional shortening Z-score (odds ratio 0.8, 95% confidence interval 0.7 to 0.9, $p < 0.001$) were independently associated with anti-HF use. Anti-HF therapy use was similar in the earlier and later cohorts (84% and 87%, respectively).

The second most frequently reported therapy, ACEI, was prescribed for 66% of children during the first month of diagnosis and for 74% within the first year. At presentation, ACEI administration was more common ($p < 0.001$) in children with more advanced HF, as evidenced by larger left ventricular dimension and lower fractional shortening Z-scores (Table 3), and in those with a worse functional class, where 77% of those in class IV received an ACEI (Figure 1). Multivariate modeling ($n = 249$) indicated that left ventricular

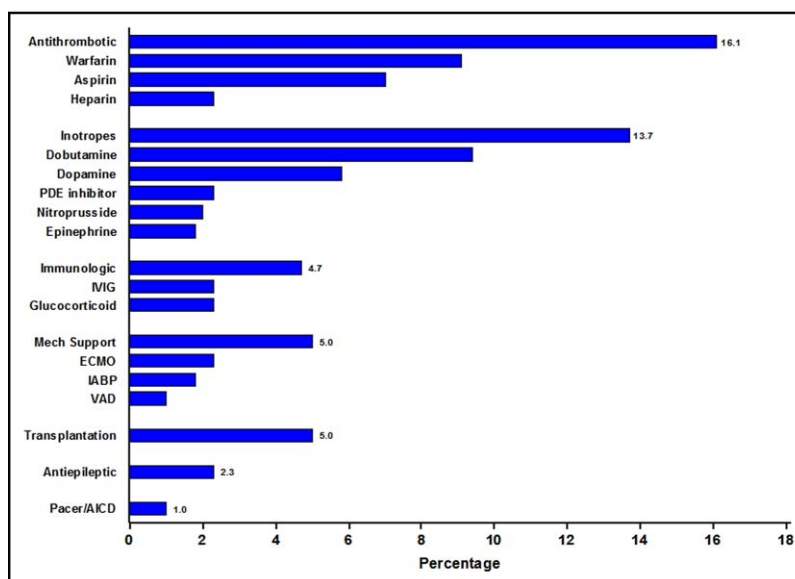


Figure 2. Miscellaneous medical and surgical therapy reported for early treatment of idiopathic dilated cardiomyopathy in 350 children. AICD = automatic implanted cardiac defibrillator; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; IVIG = intravenous immunoglobulin; PDE = phosphodiesterase; VAD = ventricular assist device.

end-diastolic dimension Z-score (odds ratio 1.3, 95% confidence interval 1.1 to 1.4, $p < 0.001$) was independently correlated with ACEI use.

Beta-adrenergic blockade was generally not employed in the earlier cohort, being prescribed for 4% of IDC cases at presentation and 6% within the first year. Rate of ACEI administration at diagnosis did not change significantly over the 6-year (1990 to 1995) diagnostic period (65% vs 69%). In contrast, β -adrenergic blockade use was higher in the later cohort (18%). This difference may be the result, in part, of the fact that some children in the later cohort from several PCMR centers were enrolled in a clinical trial of a β blocker.¹⁸

Dietary modification (mainly salt restriction) was infrequently reported (14%), but nevertheless was associated with functional class ($p = 0.01$), being used in 5% of children in class I and in 14% to 19% of symptomatic (classes II through IV) children. Carnitine supplementation was prescribed in 18%. Use of this therapy varied by center.

Calcium channel blockers (2%) and pacemakers or automatic implanted cardiac defibrillators (1%) were generally not used as initial therapy. Mechanical support was instituted in 17 children (5%) in the first 30 days after presentation. Mechanical support was provided using extracorporeal membrane oxygenation in 8 children, intra-aortic balloon pumps in 6, and ventricular assist devices in 3. Within 1 month after diagnosis, 17 children (5%) underwent cardiac transplantation.

The PCMR specifically recorded medical and surgical interventions as discussed earlier and as presented in Table 2. Medical records were further scrutinized for other medications. A majority (52%) of children received a variety of other medications during treatment of their cardiomyopathy (Figure 2). Antithrombotic agents were prescribed to 16% of the overall sample. Warfarin was the most widely used anticoagulant (9%), followed by aspirin and unfractionated heparin. Children treated with warfarin or heparin were

older at diagnosis (median 9.5 vs 1.2 years) and more often had HF (91% vs 71%, $p = 0.003$). However, antithrombotic use was independent of left ventricular size and function.

Children treated with intravenous inotropic infusions at presentation (16%) were more symptomatic than those not receiving them (HF was present in 86% vs 71%, $p < 0.001$). However, as was the case with antithrombotic use, children treated and those not treated with inotropic infusions did not differ with regard to their echocardiographic profiles. Immunomodulatory treatment was recorded in 5% of children and was reported as intravenous immunoglobulins and/or glucocorticoids in nearly equal proportions (Figure 2).

Discussion

Childhood IDC is a rare but highly debilitating disease of multiple causes with profound morbidity and mortality.^{5,8,19} The disease most often affects very young children, and indeed, presentation during infancy was noted in 43% of the children reported in this study. The 1- and 5-year rates for death or transplantation for children with IDC enrolled in the PCMR are 39% and 53%, respectively, illustrating the relative inadequacy of current medical therapy.⁵ In this study, we found little change in practice patterns over the previous several decades. Our pharmacologic options have not greatly increased in the most recent decades. Among new options, ACEI use lags far behind expert recommendations.¹⁰

For adults with HF, numerous clinical trials have led to standardized practices that have improved length and quality of life. Practice guidelines for treating IDC and HF in adults have been published jointly by the American College of Cardiology and the American Heart Association as evidenced-based standards of care.⁶ Pediatric HF experts have also examined potentially relevant adult and limited pediatric data to suggest management protocols for children

with IDC and HF.¹⁰ In the absence of evidence-based pediatric studies, such guidelines cannot be considered definitive standards of care, but nevertheless do represent a reasonable basis to compare management strategies over time. These recommendations for children begin by suggesting a thorough causative evaluation, including screening of all first-degree relatives. However, published data indicate that this evaluation rarely occurs.^{2,5}

ACEI therapy is recommended for nearly all children with asymptomatic left ventricular dysfunction (unless they have a drug reaction) and with symptomatic HF, except in the initial management of decompensated disease.^{10,11} However, in our study, ACEI was used only in 53% of children with asymptomatic left ventricular dysfunction (functional class I disease). However, we did identify increased left ventricular end-diastolic dimension Z-score at presentation as an independent correlate of ACEI use. It appears that many cardiologists wait until children have echocardiographic evidence of more advanced disease before initiating ACEI therapy. If recommendations for universal use had been followed, this association with markers of disease severity (increased left ventricular end-diastolic dimension Z-score at presentation) would probably not have been found.

Diuretics are recommended in children with HF to achieve euvolemia and to minimize congestive symptoms. Addition of digoxin is then recommended if the child remains symptomatic. Digoxin is specifically not recommended for children with asymptomatic left ventricular dysfunction because its use has not been associated with increased survival in large adult trials. We found that anti-HF medications were often used in asymptomatic children. Although the rate of anti-HF use correlated positively with increase in functional class, 60% of children with asymptomatic left ventricular dysfunction (functional class I) received these agents.

Beta-adrenergic blockade was generally not employed; only 5% of children received such therapy at presentation. Pending new pediatric-specific data, there are no current recommendations for routine use of β -adrenergic blockade in children with HF, other than to warn that it is not appropriate for treating end-stage, decompensated HF.¹⁰ Of note, 18% of children in the prospective cohort (diagnosed in 2000 and later) were treated with β -adrenergic blockade, often in the setting of an ongoing clinical trial.

Sixteen percent of children with newly diagnosed HF received concurrent warfarin or heparin, indicating a concern in practitioners for potential thromboembolic complications of childhood IDC. Few data exist to guide anticoagulation in these children. Patient selection, risk stratification, and drug selection vary in the absence of evidence-derived data, making this a topic for further study.

This inventory of therapies offered to children enrolled in the PCMR has some limitations. First, children in the earlier cohort (1990 to 1995) were enrolled voluntarily by pediatric cardiologists across the United States and Canada, making it difficult to ensure complete patient capture and to avoid potential selection bias. Most practitioners enrolled all their patients with cardiomyopathy, but total patient capture was neither ensured nor controlled for. Nevertheless, outcomes of the

PCMR retrospective and prospective cohorts in children with IDC overlap, suggesting no marked bias.⁵

Second, the later cohort used to determine current therapies was derived from a subset of children for whom detailed therapeutic data had been collected. ACEI data were available for 219 of 462 children in the dataset. These data were included to assess usage in the previous decade. The database structure, designed in 1995, did not allow for detailed analysis of all variables. For example, coding of anti-HF therapy as use of digoxin or furosemide limited a closer examination of these medications. Third, observational registry data cannot determine the causal impact of any specific therapy on patient outcomes.

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