Demographics, Trends, and Outcomes in Pediatric Acute Myocarditis in the United States, 2006 to 2011

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Background—There is a lack of clear diagnostic and management guidelines for acute myocarditis in the pediatric population. We used a multi-institutional database to characterize demographics, practice variability, and outcomes in this population.

Methods and Results—Patients with acute myocarditis (n=514) were identified from April 2006 to March 2011 using the Pediatric Health Information System database, and regional variations in management and outcomes were analyzed. Ninety-seven patients (18.9%) received extracorporeal membrane oxygenation, 22 (4.3%) received ventricular assist device, 21 (4.1%) received heart transplantation, and 37 (7.2%) died. Of the 104 patients who received extracorporeal membrane oxygenation or ventricular assist device, 17 (16.3%) had heart transplantation, 25 (24%) died, and 62 (59.6%) showed recovery of myocardial function. There was a decrease in the use of endomyocardial biopsy and an increase in the use of magnetic resonance imaging (P<0.01) over the study period. Although the use of medications and procedures varied between different regions, the occurrence of death or heart transplantation showed no significant regional associations. The use of extracorporeal membrane oxygenation (odds ratio, 5.8; 95% confidence interval, 2.9–11.4; P<0.01), ventricular assist device (odds ratio, 8.2; 95% confidence interval, 2.7–24.9; P<0.01), and vasoactive medications (odds ratio, 5.7; 95% confidence interval, 1.2–26.1; P=0.03) was independently associated with death/transplantation.

Conclusions—There is significant temporal and regional variation in the diagnostic modalities and management used for pediatric myocarditis, which continues to have high morbidity and mortality. Extracorporeal membrane oxygenation, ventricular assist device, and vasoactive medications are independently associated with increased mortality/transplantation. (Circ Cardiovasc Qual Outcomes. 2012;5:622-627.)

Key Words: myocarditis • pediatrics • outcome • regional variation

Myocarditis is an important cause of cardiovascular morbidity and mortality in children and adults. There is substantial published literature on its management in the adult population; however, large pediatric studies are lacking. Although children commonly present with acute disease, pediatric myocarditis has a wide spectrum of presentation from mild asymptomatic disease to acute fulminant disease and even sudden death. There is no universally accepted clinical definition of acute myocarditis, and its exact prevalence is not known. Overall, myocarditis accounts for approximately 0.05% of pediatric hospital discharges in the United States. Because of the heterogeneous presentation, the diagnosis of myocarditis is difficult, and there is significant variation in its management. The use of endomyocardial biopsy, cardiac magnetic resonance imaging (MRI), immunosuppression, mechanical circulatory support (extracorporeal membrane oxygenation [ECMO] or ventricular assist device [VAD]), and heart transplantation all demonstrate variable clinical outcomes.

The broad spectrum of presentation, lack of clear diagnostic criteria, and practice variation make it difficult to establish a consensus on diagnosis and management. We analyzed 5 years of data using the Pediatric Health Information System (PHIS) database with the following objectives: (1) describe the demographics of pediatric acute myocarditis in the United States, (2) identify patient-related characteristics that may be associated with transplantation or death, and (3) describe temporal and regional trends in diagnostic and therapeutic modalities for pediatric myocarditis.

Methods

Study Design

We performed a retrospective database review and subsequent outcomes analysis. The institutional review board at the Children’s National Medical Center reviewed and approved this study.

Data Source

Data for this study were obtained from PHIS, an administrative database that contains inpatient, emergency department, ambulatory surgery, and observation data from 42 nonprofit, tertiary care centers.
WHAT IS KNOWN

- Pediatric acute myocarditis has a heterogeneous clinical presentation, and its accurate diagnosis is difficult.
- There is lack of sufficient evidence-based diagnostic and treatment guidelines for management of pediatric acute myocarditis.

WHAT THE STUDY ADDS

- There is significant regional variability and temporal changes in treatments used for pediatric myocarditis during the past 5 years in the United States.
- Myocarditis continues to have significant morbidity and mortality, with a large percentage of patients requiring mechanical cardiovascular support.

pediatric hospitals in the United States. These hospitals are affiliated with the Child Health Corporation of America (Shawnee Mission, KS), a business alliance of children’s hospitals. Data quality and reliability are assured through a joint effort between the Child Health Corporation of America and participating hospitals. The data warehouse function for the PHIS database is managed by Thomson Reuters (Ann Arbor, MI). For the purposes of external benchmarking, participating hospitals provide discharge/encounter data, including demographics, diagnoses, and procedures. These hospitals also submit resource utilization data (eg pharmaceuticals, imaging, and laboratory). Data are deidentified at the time of data submission, and data are subjected to several reliability and validity checks before being included in the database.

Data Checks

The participating hospitals submit discharge-level data on a quarterly basis from their internal data systems, using a standardized discharge abstract. These data include the hospital identifier, medical record number, admission and discharge dates, age, race, sex, payor, pharmacy and procedure information, and up to 21 diagnoses. The medical record numbers, billing numbers, physician identifications, and zip codes are encrypted to protect the identity of the patients and assure compliance with federal regulations. These data are then subjected to several reliability and validity checks before being processed. During the study period, all data from each of the participating institutions met the reliability and validity thresholds and were included for analysis.

Subjects and Definitions

All consecutive subjects discharged between April 1, 2006 and March 31, 2011 were included. The following principal diagnoses (International Classification of Diseases, Ninth Revision codes) were initially populated: coxsackie myocarditis (7423), acute rheumatic myocarditis (3912), acute myocarditis, unspecified (42290), idiopathic myocarditis (42291), septic myocarditis (42292), toxic myocarditis (42293), and other acute myocarditis (42294). Acute rheumatic, toxic, and septic myocarditis were excluded from further analysis because they may benefit from therapies that are not applicable to viral myocarditis and might change outcome variables. From the available data points in PHIS database, the following variables were collected: patient age, sex, ethnicity, geographic region (Northeast, North Central, South and West), dates of admission and discharge, diagnostic procedures (endomyocardial biopsy, cardiac MRI), medications (methylprednisolone, intravenous immunoglobulin, and inotropes), ECMO, VAD, and heart transplantation. The study period was divided into 5 study year groups: year 1 spanned from April 2006 to March 2007, year 2 from April 2007 to March 2008, year 3 from April 2008 to March 2009, year 4 from April 2009 to March 2010, and year 5 from April 2010 to March 2011.

Data Analysis

The aims of our analysis were as follows: (1) provide a description of demographic parameters of pediatric patients with acute myocarditis in the United States, (2) identify characteristics that may be associated with transplantation or death, and (3) identify diagnostic and therapeutic modalities that show significant increasing or decreasing trend temporally or regional variability in utilization. Data are summarized as mean and SD when normally distributed and as medians with interquartile ranges when nonparametric. Proportions were compared using χ² or Fisher exact tests and are presented as odds ratios with 95% confidence intervals (CI) with P values. Temporal trends were assessed using the Mantel-Haenszel test for trend, which generated a linear-by-linear association statistic. Multivariable logistic regression analyses were conducted to adjust for differences in case mix among myocarditis patients and to determine their association with outcome of death/heart transplantation. Type 1 error was set at 0.05. All calculations were performed using SPSS Statistics 17 for Windows (IBM Corporation, Armonk, NY) or Open Office Calc (www.openoffice.org v3.3.0 Oracle Inc, Redwood City, CA).

Results

A total of 540 patient encounters were identified for 528 patients. For the 12 patients who were readmitted during the study period, only the initial admissions were analyzed. Fourteen patients with the following diagnoses were excluded: septic (9 patients), rheumatic (4 patients), and toxic (1 patient) myocarditis; the final study population composed of 514 patients. The mean age of the study population was 9.2 years (SD 6.8 years), and the median length of stay was 7 days (interquartile range 3–19 days). There was a bimodal age distribution with a peak in infancy and a similar peak in mid-teenage years (Figure 1). Non-Hispanic whites accounted for 41.4% of the patient population, blacks 22.4%, and Hispanics 17.7%. Males accounted for 64% of the entire study population; 49.1% of patients <12 years of age (n=273) and 80.9% of patients >12 years of age (n=241; P<0.01). There was a 50% increase in the number of patients diagnosed with myocarditis in the final 2 years of the study period compared with the first 2 years (248 versus 166). The International Classification of Diseases, Ninth Revision code for idiopathic myocarditis accounted for 70% of the cases, acute unspecified for 19.3%, and acute other myocarditis for 5.4% of identified cases. Coxsackie myocarditis was billed as the primary diagnosis in 5.3% of patients.

Four hundred thirteen (80.4%) patients were admitted to the intensive care unit, 228 (44.4%) were mechanically ventilated, 97 (18.9%) received ECMO, 22 (4.3%) received VAD, and 15 (2.9%) received both ECMO and VAD. Of the 97 subjects who received ECMO, 25 of 97 (25.8%) died and 13 of 97 (13.4%) underwent heart transplantation. Of the 22 VAD patients, 6 of 22 (27.3%) died and 9 of 22 (40.9%) underwent heart transplantation. Of the 104 patients who received ECMO or VAD, 17 (16.3%) had heart transplantation, 25 (24%) died, and 62 (59.6%) showed recovery of myocardial function. Overall, there were 37 deaths (7.2%) and 21 (4.1%) patients received heart transplantation, all of whom survived to discharge. Patients were compared based on outcome of death or heart transplantation (Table 1). On univariable comparisons, the use of ECMO, epinephrine, norepinephrine, dopamine, milrinone, dobutamine, and methylprednisolone were all associated with increased mortality or transplantation. In addition, endomyocardial biopsy was associated with higher
mortality/transplantation, whereas MRI was associated with lower mortality/transplantation. There was no association between intravenous immunoglobulin use, sex, or ethnicity and mortality/transplantation.

Patients were further stratified into 2 groups based on age: <12 years age and >12 years age. The overall mortality or transplantation rate was higher (16.1%) in children <12 years of age than it was in children >12 years of age (5.8%; \( P < 0.01 \)). Univariable comparisons in both of these groups revealed statistical significance for the same variables as that of the entire group; however, unlike the entire group, in patients <12 years of age, the use of MRI, myocardial biopsy, and milrinone was not significantly associated with death/transplantation.

Adjusting for age, methylprednisolone use, cardiac biopsy, and MRI use, logistic regression analysis revealed that the use

| Table 1. Characteristics of Patients Hospitalized With Myocarditis Stratified by Survival |
|-----------------------------------------------|------------------------------------------|---------------------------------|-----------------|-----------------|
| Characteristic                 | Transplant-Free Survival (n=456) | Death or Transplant (n=58) | OR   | Lower | Upper | \( P \) Value |
| Male sex                      | 297 (65.1) | 32 (55.2) | 1.5  | 0.9   | 2.6   | 0.14          |
| Ethnicity                     | | | | | | |
| White                         | 191 (41.9) | 22 (37.9) | 0.36 | | | |
| Black                         | 95 (20.8)  | 20 (34.5) | | | | |
| Hispanic                      | 84 (18.4)  | 7 (12.1)  | | | | |
| Asian                         | 12 (2.6)   | 1 (1.7)   | | | | |
| American Indian               | 3 (0.7)    | 0         | | | | |
| Pacific Islander              | 3 (0.7)    | 0         | | | | |
| Other/Unknown                 | 68 (14.9)  | 8 (13.8)  | | | | |
| MRI                            | 78 (17.1)  | 1 (1.7)   | 0.1  | 0.01  | 0.6   | <0.01         |
| Myocardial biopsy             | 108 (23.7) | 23 (39.7) | 2.1  | 1.2   | 3.7   | 0.01          |
| ECMO                           | 59 (12.9)  | 38 (65.5) | 12.8 | 7     | 23.4  | <0.01         |
| VAD                            | 7 (1.5)    | 15 (25.9) | 22.4 | 8.6   | 57.9  | <0.01         |
| Medications                   | | | | | | |
| IVIG                           | 317 (69.5) | 42 (72.4) | 1.2  | 0.6   | 2.1   | 0.65          |
| Epinephrine                   | 175 (38.4) | 53 (91.4) | 17   | 6.7   | 43.4  | <0.01         |
| Norepinephrine                | 18 (3.9)   | 16 (27.6) | 9.3  | 4.4   | 19.5  | <0.01         |
| Dopamine                      | 143 (31.4) | 43 (74.1) | 6.3  | 3.4   | 11.7  | <0.01         |
| Milrinone                     | 243 (53.3) | 50 (86.2) | 5.5  | 2.5   | 11.8  | <0.01         |
| Dobutamine                    | 61 (13.4)  | 21 (36.2) | 3.7  | 2     | 6.7   | <0.01         |
| Methylprednisolone            | 107 (23.5) | 31 (53.4) | 3.7  | 2.1   | 6.6   | <0.01         |

OR indicates odds ratio; CI, confidence interval. MRI, magnetic resonance imaging; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device; IVIG, intravenous immunoglobulin.
of ECMO (odds ratio, 5.8; 95% CI, 2.9–11.4; P<0.01), VAD (odds ratio, 8.2; 95% CI, 2.7–24.9; P<0.01), and vasoactive medications (odds ratio, 5.7; 95% CI, 1.2–26.1; P=0.03) was independently associated with death/transplantation.

Temporal trends in medication use, procedures, and outcomes are shown in Figure 2. There was a decrease in the use of dobutamine over the study period, whereas other medications did not show a significant trend. The use of endomyocardial biopsies decreased during the study (24.7% in year 1 to 14.0% in year 5; P=0.03), whereas the use of cardiac MRI increased (5.2% in year 1 to 28.1% in year 5; P<0.01).

The data were also analyzed by geographic region; there were 11 hospitals in the North central region, 6 in the Northeast, 15 in the South, and 10 in the West region. Regional variation in management is presented in Table 2. The use of medications and procedures varied between regions; however, the occurrence of death or heart transplantation showed no significant regional associations.

**Discussion**

In this large cohort of children with myocarditis, there were significant temporal changes in the management of pediatric myocarditis from 2006 to 2011, with increasing use of MRI and decreasing use of endomyocardial biopsy and dobutamine. Although the use of ECMO, VAD, and vasoactive medications was independently associated with increased mortality, 76% of these high-risk patients on VAD or ECMO improved or survived to transplant and hospital discharge, suggesting that these are successful strategies for supporting patients.

Patients with myocarditis in this cohort continue to have significant morbidity and mortality. The majority (80.4%) of our subjects were admitted to an intensive care unit, and a substantial number received mechanical ventilation (44.4%) and mechanical circulatory support (23.2%). Current literature supports the use of VAD as a bridge to transplantation; however, the reported frequency of myocardial recovery is low.11,12 Similar to these reports, in this study myocardial recovery was seen in only 59.6% patients who received ECMO or VAD, whereas 16.3% were successfully bridged to transplantation with 100% survival to discharge. The overall mortality rate was 7.3%. Previous pediatric reports report overall mortality rates in myocarditis of ≈15%, and patients with fulminant myocarditis and those requiring mechanical cardiovascular support have worse outcomes.8,10,13,14 Multiple reasons may account for the relatively low mortality in this study. We analyzed all patients in the PHIS database with the diagnosis of acute myocarditis, irrespective of morbidity, and our mortality analysis is limited to a single hospitalization. Part of the lower mortality may also be attributed to improved supportive care in the recent years; however, our study period is too brief to identify the impact of such a change.

There was a 5-fold increase in the use of cardiac MRI from 5.2% to 28.1% during the study period. MRI in acute myocarditis is characterized by relative edema, relative enhancement, and late enhancement.15 Along with the increase in MRI use, we noted a significant decline in endomyocardial biopsy rate from 24.7% to 14.0%. Although endomyocardial biopsy in acute myocarditis is relatively safe with experienced providers, accurate interpretation remains a challenge, and there is a risk of arrhythmia, right ventricular perforation, and tamponade.16 On univariable analysis, MRI was associated with lower mortality/transplantation and endomyocardial biopsy with higher mortality/transplantation; however, there was a lack of independent association. Several factors, including the severity of a patient’s condition, might impact the decision to perform these tests and hence this finding. Nevertheless, the use of MRI in pediatric myocarditis is likely to continue to increase, given its diagnostic strengths as well as the opportunity to avoid the potential adverse events associated with biopsy.

The use of dobutamine decreased significantly during the study period, whereas intravenous immunoglobulin and methylprednisolone use remained consistently high, despite lack of consensus in the literature regarding the benefit of immunosuppressive therapies in acute myocarditis.17–19 The continued use of immunosuppression in this disease is likely multifactorial and reflects the variability in diagnosis and management. The ongoing use of both intravenous immunoglobulin and methylprednisolone, despite limited evidence of improved outcome, highlights the need for a prospective randomized trial in pediatrics; however, establishing consensus on the definition and diagnostic criteria for the disease remains challenging.

As evident in Table 2, there were regional differences in diagnostic and treatment modalities for pediatric myocarditis.
Despite these differences, mortality or transplantation showed no significant associations with specific regions as defined in this PHIS data set. The number of patients varied widely between regions—the West with the smallest number of patients (98) and the South region with the largest (176). Some of this variability likely reflects the diagnostic challenge of myocarditis.

In our population, there was a bimodal age distribution, and compared with girls of similar age, acute myocarditis was 4 times more common in boys <12 years of age. The exact reasons for these findings are not clear, but given the heterogeneity in etiological agents, multiple host and agent-related factors likely play a role. Age- and sex-dependent susceptibility to specific viral strains has been experimentally observed in mice.20–22 Sex-based predilections in experimental animals are thought to be related to hormone levels, and although these experiments have not been replicated in humans, it is possible that the second peak and male preponderance of acute myocarditis in mid-teenage years is related to hormonal changes of puberty.23 Recently, Costantini et al24 reported a syndrome of a myocarditis-like illness almost exclusive to men, which presents with flu-like symptoms, seasonal trends, elevated troponin levels, and evidence of enterovirus infection in some of their patients, leading the authors to suspect a viral etiology.

This study has several limitations. Most importantly, we used an administrative database, and as a result, our study population might not be a true representation of the entire population. Because it is difficult to establish a consensus on the definition and diagnostic criteria for the disease, different institutions may have differing criteria to make the diagnosis, which is a problem for database studies. Because of the lack of specific International Classification of Diseases codes and the administrative nature of the PHIS database, specific culture results are not available. There was a 50% increase in the number of patients from the initial 2 study years to the last 2 years. However, this only reflects an increase in myocarditis hospitalizations at the participating hospitals and cannot be interpreted as a true increase in incidence. Changes in physician practice and coding may be partly responsible for this increase; however, it is not possible to estimate its impact based on available data in PHIS. Last, because of the nature of the database, a longitudinal follow-up of patients was not possible, limiting our analysis to a single hospitalization.

**Conclusions**

This is the largest description of trends in diagnosis and regional variation in outcomes and management of pediatric acute myocarditis in the United States. ECMO, VAD, and vasoactive medications are independently associated with increased mortality/transplantation. Mechanical circulatory support with ECMO or VAD may be successful strategies in supporting patients until resolution of cardiac dysfunction or as a bridge to transplant, because 76% of this high-risk cohort were successfully bridged to transplant or recovery. Increased diagnostic utilization of MRI may demonstrate benefits over endomyocardial biopsy and should be considered in high-risk patients. These data further highlight the need for additional multicenter studies to improve diagnosis, management, and outcome for patients with this challenging diagnosis.
Disclosures

None.

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