Comparison of the Clinical Presentation, Treatment, and Outcome of Fulminant and Acute Myocarditis in Children

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Background: Myocarditis (MC) is an important cause of cardiac dysfunction in children. Fulminant MC is sometimes fatal, and sequelae may develop during follow-up. We conducted a nationwide survey to determine the clinico-epidemiological features of MC in Japanese children and adolescents.

Methods and Results: Survey questionnaires were mailed to 627 hospitals, which were asked if they had treated MC patients aged between 1 month and 17 years during the period from January 1997 through December 2002. Responses were collected until December 2005, and data were collected and analyzed until January 2008. A total of 169 patients were reported: 64 fulminant cases, 89 acute cases, and 8 chronic cases. Incidence was 43.5 cases/year and 0.26 cases/100,000. Pathogens were identified in 37 patients; coxsackie virus accounted for 60%. Major cardiovascular manifestations at onset were congestive heart failure, refractory arrhythmia, and syncope in 70, 37, and 17 patients, respectively. Intravenous immunoglobulin was administered to 73 patients. Mechanical support seemed to be effective and life-saving. Among the 169 patients, 123 survived. Cardiovascular sequelae were reported in 49 patients.

Conclusions: The survival rate for children with fulminant MC was disappointing. Overall, two-thirds of survivors had no sequelae. Mechanical support may reduce the mortality and the risk of clinical worsening. (Circ J 2012; 76: 1222–1228)

Key Words: Fulminant; Immunoglobulins; Myocarditis; National survey

Myocarditis (MC) is an inflammation of the myocardium associated with apoptotic degeneration, with or without necrosis of adjacent myocytes. Both direct virus-induced and indirect immune-mediated injuries contribute to the development of myocardial injuries.¹

Fulminant MC is characterized by abrupt onset of cardiogenic shock and systemic collapse, sometimes resulting in death. Postmortem examinations in routine clinical settings suggest that MC is an important cause of acute cardiac death in both pediatric and adult populations.²

Impaired cardiac function, heart failure, or refractory arrhythmias may develop during follow-up for MC. However, the clinical manifestations, diagnosis, treatment, and prognosis of fulminant and acute (nonfulminant) MC in children have not been fully elucidated, as only a few large-scale studies have been conducted.³

A large-scale survey of MC in the pediatric age-group has not been performed in Japan or any other Asian country.⁴ For this reason, the Japanese Society of Pediatric Cardiology and Cardiac Surgery sponsored a nationwide survey to investigate the clinical features of MC in pediatric patients and to collect clinical data that would improve diagnostic tools and treatment options in this population. Herein, we describe the findings of this survey.
Nationwide Survey of Myocarditis in Children

A survey was designed to investigate the nationwide prevalence and clinical characteristics of MC among children and adolescents in Japan. First, survey questionnaires were mailed to 627 teaching hospitals authorized by the Japanese Pediatric Society. The questionnaires requested information on pediatric patients aged between 1 month and 17 years who received a diagnosis of MC and were treated during the period from January 1997 through December 2002. The questionnaire included items regarding clinical manifestations at onset and admission; laboratory data; virus test results; findings on electrocardiography, echocardiography, chest radiography and nuclear cardiac imaging; endomyocardial biopsy findings; treatments; and outcome. The diagnosis of fulminant, acute, or chronic MC was dependent on the diagnostic criteria established by the Japanese Circulation Society’s task force of the guideline of MC. The data collection period was from 2003 through December 2005. Data were confirmed and analyzed between January 2006 and January 2007.

We had permission to research from the Ethical Committee and the Scientific Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (JSPCCS) in 2003.

Data Analysis
Comparisons were performed using Fisher’s exact test and the Statview 4.5 statistical software package. A P value <0.05 was considered statistically significant.

Results
A response was received from 484 (77.2%) of the 627 hospitals contacted. Of these, 111 (22.9%) had treated a child or adolescent with MC. Initially, 261 cases were reported from these 111 hospitals. A total of 151 (57.9%) patients had acute MC, 89 (34.1%) had fulminant MC, and 21 (8.0%) had chronic MC. A second questionnaire was sent to the 111 hospitals to obtain detailed clinical information on their patients. Information on 169 cases from 65 (58.6%) of the 111 hospitals was received. Ultimately, we analyzed data from these 169 patients with MC, which included 64 (37.9%) with fulminant MC, 89 (52.7%) with acute MC, 8 (4.7%) with chronic MC, and 8 (4.7%) with MC of unknown type (Table 1).

Clinical Manifestations at Onset
Regarding initial nonspecific symptoms, fever was observed in only 81 patients (47.9%), including 28 (43.7%) with fulminant MC, and 53 (59.6%) with acute MC. Nausea or vomiting was observed in 51 patients (30.2%), including 29 with fulminant MC and 22 with acute MC. Abdominal pain was observed in 16 patients (9.4%), including 12 with fulminant MC and 4 with acute MC. Diarrhea was observed in 13 patients (7.7%), including 6 with fulminant MC and 6 with acute MC. Cough was observed in 28 patients (16.6%), including 11 with fulminant MC and 17 with acute MC. At onset, gastrointestinal tract symptoms including nausea, vomiting, abdominal pain, and diarrhea (45.3% vs 24.7%, P=0.01) were more frequent than cardiopulmonary symptoms.

Table 1. Number of Patients Reported by Type of MC

<table>
<thead>
<tr>
<th>Type of MC</th>
<th>Total</th>
<th>M/F</th>
<th>Survived</th>
<th>M/F</th>
<th>Died</th>
<th>M/F</th>
<th>Unknown</th>
<th>M/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MC</td>
<td>89</td>
<td>46</td>
<td>86</td>
<td>96</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Fulminant MC</td>
<td>64</td>
<td>25</td>
<td>33</td>
<td>51</td>
<td>6</td>
<td>2</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>Chronic MC</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>62</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>3</td>
<td>6</td>
<td>75</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>169</td>
<td>123</td>
<td>123</td>
<td>72</td>
<td>38</td>
<td>23</td>
<td>8</td>
<td>4.7</td>
</tr>
</tbody>
</table>

*Unknown 5.
MC, myocarditis.

Table 2. Clinical Manifestation at Onset by Type of MC

<table>
<thead>
<tr>
<th></th>
<th>Fulminant MC (n=169)</th>
<th>Acute MC (n=64)</th>
<th>Total (n=89)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonspecific</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>28 (43.8%)</td>
<td>53 (59.6%)</td>
<td>81 (47.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>29 (45.3%)</td>
<td>22 (24.7%)</td>
<td>51 (30.2%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cough</td>
<td>11 (17.2%)</td>
<td>17 (19.1%)</td>
<td>28 (16.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (18.8%)</td>
<td>14 (15.7%)</td>
<td>26 (15.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (9.4%)</td>
<td>7 (7.9%)</td>
<td>13 (7.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>34 (53.1%)</td>
<td>27 (30.3%)</td>
<td>61 (36.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>21 (32.8%)</td>
<td>28 (31.5%)</td>
<td>49 (29.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21 (32.8%)</td>
<td>22 (24.7%)</td>
<td>43 (25.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac shock</td>
<td>18 (28.1%)</td>
<td>4 (4.5%)</td>
<td>22 (13.0%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Cardiomegaly classified as cardiothoracic ratio >0.15.
MC, myocarditis; NS, not significant.

Methods
A survey was designed to investigate the nationwide prevalence and clinical characteristics of MC among children and adolescents in Japan. First, survey questionnaires were mailed to 627 teaching hospitals authorized by the Japanese Pediatric Society. The questionnaires requested information on pediatric patients aged between 1 month and 17 years who received a diagnosis of MC and were treated during the period from January 1997 through December 2002. The questionnaire included items regarding clinical manifestations at onset and admission; laboratory data; virus test results; findings on electrocardiography, echocardiography, chest radiography and nuclear cardiac imaging; endomyocardial biopsy findings; treatments; and outcome. The diagnosis of fulminant, acute, or chronic MC was dependent on the diagnostic criteria established by the Japanese Circulation Society’s task force of the guideline of MC. The data collection period was from 2003 through December 2005. Data were confirmed and analyzed between January 2006 and January 2007.

We had permission to research from the Ethical Committee and the Scientific Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (JSPCCS) in 2003.
with acute MC. Cardiogenic shock was observed in 22 patients (13.0%), including 18 with fulminant MC (11 of whom died) and 4 with acute MC (none of whom died; Table 2), more frequently observed in fulminant MC (28.1% vs. 1.5%, P=0.001).

**Laboratory Data**

We analyzed laboratory data on admission for 64 patients with fulminant MC and 89 patients with acute MC. White blood cell (WBC) counts in peripheral blood and serum creatine kinase (CK) MB fraction did not significantly differ between patients with fulminant MC and those with acute MC. However, plasma troponin-T and plasma myosin light chain (MLC)-1 were significantly higher in patients with fulminant MC than in those with acute MC (P=0.01 for both comparisons). In patients with fulminant MC, there was a significantly higher peak WBC count (P=0.01), and significantly higher levels of plasma CK (P=0.02), plasma CK-MB (P=0.02), and plasma MLC-1 (P=0.01), as compared with patients with acute MC (Table 3).

**Viral Pathogens**

The method used to detect viral pathogens was elevated serum antibody titer in 30 patients, culture and isolation of viruses in 6 patients, detection of viral genome in 2 patients, and unknown in 5 patients. The original samples for viral culture were peripheral blood in 31 patients, nasopharyngeal swab in 6 patients, stool in 2 patients, urine in 1 patient, and an autopsy sample of myocardium (for viral genome) in 1 patient.

Viral pathogens were identified in 37 patients (21.9%); coxsackie virus type A or type B was detected in 15 patients (9 with acute MC, 5 with fulminant MC, 1 with unknown MC type), influenza virus in 10 patients (5 with acute MC, 4 with fulminant MC, 1 with unknown MC type), ECHO virus in 4 patients (2 with acute MC, 1 with fulminant MC, 1 with chronic MC), parvovirus B19 in 2 patients with acute MC, adenovirus in 1 patient with fulminant MC, cytomegalovirus in 1 patient with fulminant MC, and M. pneumoniae in 1 patient with acute MC each. Coxackie virus was found in 9 of 22 patients (40.9%) with acute MC and in 5 of 12 patients (41.7%) with fulminant MC; the difference was not statistically significant (Table 4).

**Echocardiography**

Echocardiographic examination on admission revealed impaired left ventricular (LV) contractility (LVEF <0.5) in 115 patients (68.0%), mitral valve regurgitation in 61 patients (36.1%), pericardial effusion in 29 patients (17.2%), and a thickened ventricular wall in 15 patients (8.9%).

**Nuclear Cardiac Imaging**

To evaluate myocardial damage, necrosis, inflammation and sympathetic denervation, nuclear imaging was performed: 26 of 42 patients (61.9%) who underwent thallium (TI)-201 myocardial scintigraphy had significant perfusion defects; on iodine-123 metaiodobenzylguanidine myocardial scintigraphy, 19 of 23 patients (82.6%) examined had abnormalities; technetium-99m pyrophosphate scanning revealed positive re-
gions of inflammation in 4 of the 5 patients (80%) examined; gallium-67 scintigraphy revealed regions of inflammation in only 1 of the 10 patients examined.

**Endomyocardial Biopsy Findings**

Among the 169 patients, an endomyocardial biopsy was performed in 56 (33.1%). Inflammatory cell infiltration was observed in 43 (77%), myocardial degenerative signs such as liquefaction and swelling in 21 (38%), myocardial necrosis in 13 (23%), and myocardial hypertrophy in 10 patients (18%). Interstitial edema was noted in 15 patients (27%), fibrosis in 22 (40%), and eosinophilic infiltration was observed in 2 patients (4%). Viral genome studies were not performed.

**Treatment**

Intravenous immunoglobulins (IVIG: 1–2 g·kg⁻¹·day⁻¹ IV for 24–48 h) were administered to 73 patients (43.7%). The efficacy of IVIG treatment was classified as effective (based on physician assessment of clinical improvement) in 29 patients (39.7%), ineffective (no clinical improvement or deterioration) in 16 patients (21.9%), and uncertain (not determined) in 28 patients (38.4%). Steroids, such as oral prednisolone (1–2 g·kg⁻¹·day⁻¹, DO or IV) or intravenous methylprednisolone pulse therapy, were classified as effective in 11 patients (22.9%), ineffective in 16 patients (33.3%), and undetectable in 21 patients (43.8%).

Mechanical support systems such as percutaneous cardiopulmonary support (PCPS) were used in 10 patients, intra-aortic balloon pumping in 4 patients, and extracorporeal membrane oxygenation (ECMO) in 4 patients. These supportive procedures were classified as effective in 12 patients (66.7%), ineffective in 1 patient (4.8%), and undetectable in 5 patients (27.8%).

In patients with acute MC, the survival rate at 1 month did not differ between those who received IVIG, steroids, or mechanical support and those who did not receive any of these therapies. In patients with fulminant MC, the survival rate had a tendency to be higher in those receiving either IVIG, steroids, or mechanical support, as compared with those not receiving these therapies; however, the difference was not statistically significant (Table 5). However, there were important limitations because this was not a randomized controlled trial (ie, there were differences in duration of administration, disease severity, and use of monotherapy or combination therapy).

**Cardiovascular Status During Follow-up**

Myocardial function was assessed at hospital discharge in 48 patients (28.4%): 27 (56.2%) had normal cardiac function, 4 (8.3%) had unknown function, and 28 had abnormal cardiac function (58.3%), including reduced LVEF (≤0.5) in 7 patients (14.6%), significant arrhythmias in 10 (20.8%), and significant mitral valve regurgitation (≥grade II) in 4 (8.3%).

After 1 year of follow-up, 87 of the 119 (73.1%) patients followed had normal cardiac function. Abnormal cardiac status was observed in 18 patients (15.1%), including impaired cardiac function in 13 and clinically significant arrhythmias in 9. In 14 patients, complete follow-up data were unavailable.

**Outcome**

Overall, 123 (72.8%) of the 169 patients were alive, 38 patients (22.5%) died, and the status of 8 patients (4.7%) was unknown.

Of the patients with acute MC, 81 (91%) were alive, 3 (3.5%) died, and the status of 4 (4.7%) was unknown. Of the patients with fulminant MC, 31 (48.4%) were alive, 31 (48.4%) died, and the status of 2 was unknown. Among the patients with chronic MC, 4 were alive (50%), 3 (37.5%) died, and the status of 1 patient was unknown. In patients for whom the MC type was unknown, 6 (75.0%) were alive, 1 (12.5%) died, and the status of 1 was unknown.

**Discussion**

Fulminant MC represents approximately 20–30% of MC cases, and can be clinically differentiated from acute MC by the presence of severe hemodynamic deterioration, cardiogenic shock, severe ventricular dysfunction, and/or refractory life-threatening arrhythmias requiring inotropic support or mechanical cardiopulmonary assist devices.\(^1\)

MC is usually caused by a virus. The use of polymerase chain reaction (PCR) to detect viral genomes in myocardial biopsy samples has directly established the critical role of viruses in the pathogenesis of MC. In 1 investigation using PCR, evidence of viral infection was found in 68% of 38 patients with clinically suspected MC.\(^6\) A number of viruses have been associated with MC in humans; however, coxsackie group B (CB) virus is considered the predominant etiological agent.\(^1\)

The CB type 3 virus has a natural tropism for cardiomyocytes, and uses the CB-adenoviral common receptor to gain entry into host cells, resulting in the production of protease 2A, which cleaves the structures of the myocyte skeleton.\(^8\) Adenovirus infection has also been implicated in the pathogenesis of MC. Adenovirus types 2 and 5 (group C adenoviruses) appear to be cardiovirulent serotypes in both children and adults.\(^9\) In most patients, MC is caused by either CB virus or adenovirus.\(^10\)

In a study of 48 children and adolescents, PCR or reverse transcription-PCR detected enteroviruses such as CB type 3 in 72% of patients with dilated cardiomyopathy (DCM) and were more common than adenoviruses in this subgroup; in MC cases, adenoviruses were as frequent as enteroviruses (36%).\(^11\)

Nested PCR analysis of adult and pediatric myocardial samples has demonstrated that the adenoviral genome is more frequent than the enteroviral genome in patients with idiopathic LV dysfunction.\(^12\) Bowles et al reported that group C adenoviruses were detected as frequently as enteroviruses in myocardial samples from children with MC.\(^13\) Although increased expression of the common human CB-adenovirus receptor has also been reported in MC and DCM, the CB-adenovirus receptor was not found to be a major host determinant in the development of MC and DCM.\(^14\)

MC caused by infection with human parvovirus B19 (PV-B19) has been reported in infants with MC,\(^15\) and the PV B19 genome was predominant in patients with unexplained isolated diastolic ventricular dysfunction.\(^16\) PV-B19 is associated

### Table 5. Survival of Patients With Acute or Fulminant MC Who Did or Did Not Receive IVIG, Steroids, or Mechanical Support

<table>
<thead>
<tr>
<th>Group</th>
<th>IVIG (%)</th>
<th>Steroids (%)</th>
<th>Mechanical support (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MC</td>
<td>1/15 (67%)</td>
<td>7/7 (100%)</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Fulminant MC</td>
<td>11/14 (79%)</td>
<td>3/3 (100%)</td>
<td>11/11 (100%)</td>
</tr>
</tbody>
</table>

IVIG, intravenous immunoglobulin. Other abbreviations see in Table 2.
with MC in a small percentage of children and may be a potential contributor to cardiac transplant rejection.17 There is a possibility of multiple viral infections or co-infections, because the prevalence of viral genome was high in the myocardium of patients with idiopathic LV dysfunction.18

Clinical Manifestations

Initial diagnosis of viral MC is based on history, physical examination, and clinical suspicion. In the present survey, most patients presented with nonspecific complaints and a history of viral illness, with manifestations ranging from mild flu-like signs and symptoms of dysrhythmia, shock, and acute death.

To differentiate gastrointestinal tract or flu-like symptoms from cardiopulmonary symptoms can be rather difficult at onset; however, prodromal signs and symptoms have been found a bit earlier initiating cardiopulmonary manifestations in acute MC, but in fulminant MC, prodromal symptoms are usually observed close to the prodromal symptoms.

Electrocardiography typically reveals sinus tachycardia with low-voltage QRS complexes, ST-T wave abnormalities, and some degree of blockage, although a variety of arrhythmias have been described in children with viral MC.19

Echocardiography often shows globally, or sometimes segmentally, reduced wall motion, a mildly dilated ventricular cavity with or without wall thickening, atrioventricular valve regurgitation, wall motion abnormalities, and pleural effusion. Transient ventricular wall thickening is rarely observed on echocardiography in children with acute MC,20 and is reported to be caused by interstitial edema, as indicated in a comparison of the pathological findings of biopsy specimens from patients in the acute or convalescent phase.21 Reversible LV hypertrophy was noted in 15% of patients and typically resolved over a period of several months.22

Nuclear Cardiac Imaging

Noninvasive diagnosis is possible using myocardial imaging for the detection of MC. Techniques include nuclear imaging with gallium-67,23 Tl-201,24,25 and indium-111-labeled antimyosin antibodies, which is not available in Japan.26

Myocardial Biomarkers

Relatively specific markers of myocardial injury include the CK level and its MB fraction, cardiac troponin-T, troponin-I, and other biomarkers released from the myocardium. Although CK and its isoform CK-MB have low predictive value in the diagnosis of MC, the specificities of troponin T and troponin-I are high.27,28 A 4-fold rise in acute and convalescent antibody titers to certain viruses is sufficient for a diagnosis of viral MC.2

Most cardiologists still consider endomyocardial biopsy to be the gold standard for the diagnosis of viral MC. However, the risk of this procedure may be prohibitively high in critically ill children with suspected MC. Perforation of the ventricular wall is considered the worst complication. In a review of 1,000 endomyocardial biopsy procedures, the incidence of this complication was 0.9%.20 The ACC/AHA guidelines for the treatment of heart failure include endomyocardial biopsy as a Class IIb recommendation. In any type of MC, endomyocardial biopsy is quite informative for making an accurate diagnosis, in assessing the use of anti-inflammatory agents, and in predicting prognosis.30,31 Definitive diagnosis of viral MC in biopsy samples requires the use of molecular biological methods to detect viral genome and immunohistochemical staining to reveal myocardial inflammation.32 However, endomyocardial biopsy is indicated only for carefully selected patients, particularly those with rapidly progressive cardiomyopathy or unexplained ventricular dysfunction.33 The risk of a fulminant course of acute MC was shown to be high in patients with elevated C-reactive protein, elevated creatine kinase, decreased EF, and intraventricular conduction disturbances.34

Medical Treatments

A controlled trial of IVIG suggested that for patients with recent-onset DCM, IVIG does not result in further improvement in LVEF. Nevertheless, LVEF significantly improved in those patients during follow-up, and short-term outcomes were favorable.35

In the pediatric population, high-dose IVIG treatment for acute MC is associated with improved recovery of LV function and with a tendency for better survival during the first year after presentation.36

A Cochrane Database review compared IVIG-treated patients and non-IVIG-treated patients and found similar results between groups for the administration of IVIG in adults and children with MC, the incidence of death, the need for heart transplantation, the replacement of an LV assist device in the acute phase, improvement in LVEF, and functional capacity as assessed by peak oxygen consumption after 12 months. They concluded that evidence from 1 trial was insufficient to support the use of IVIG in the management of adults with viral MC.37

Although immunosuppressive therapy has yielded conflicting results in adults, the effects in children with active MC have been favorable.38 In addition, in a randomized trial of 40 adults with chronic DCM, IVIG treatment was associated with marked increases in serum interleukin-10, soluble tumor necrosis factor, and anti-inflammatory cytokines, and with significant improvement in LVEF at 6 months.39,40 However, because these collected data are based on uncontrolled results and on the physician’s impressions, the efficacy and effectiveness of IVIG and steroids remain to be investigated.

There have been no randomized trials in pediatric patients. Further study of the pathophysiological mechanism of MC might lead to improved outcomes, as the long-term effects, benefits, and age-related efficacy of IVIG are unknown.

Mechanical Support Devices

Patients with rapidly progressive CHF and cardiogenic shock are likely to benefit from mechanical circulatory support. Even though the prognosis for MC is not favorable, appropriate mechanical support may improve survival in children.40 In this series, patients with fulminant MC who were treated with mechanical support devices were less likely to show cardiac deterioration during the acute and follow-up periods.

Mechanical circulatory support may be a life-saving measure. In the majority of patients with fulminant MC there appears to be an interval of several days during which ventricular function returns.41 In a series of 15 children with fulminant MC, 80% survived after ECMO and the use of a ventricular assist device. The investigators anticipated recovery of native cardiac function, allowing for weaning from support, and prospects for eventual recovery of full myocardial function were considered excellent.42 A ventricular assist device, PCPS, or ECMO may be required for the aggressive short-term treatment of refractory cardiogenic shock in children.43,44 In a Japanese national survey of fulminant MC in adults, 58% of patients survived and returned to normal social life after treatment with mechanical support devices.45 However, patients who survive the acute phase have a favorable long-term survival rate regardless of whether a mechanical support device
is used.46

The indication of mechanical support for fulminant MC has changed during the 10 years of the present study. However, it is still difficult to decide the appropriate timing for mechanical support in small children.

Outcome

In the majority of patients with MC, the course of the disease is benign and patients recover spontaneously. However, the factors that predispose certain patients to a poor outcome are not clear. Moreover, even in patients who present with severe fulminant MC, the outcome is sometimes favorable. Aggressive management is warranted only when maximal medical therapy does not lead to improvement. In one study, 10 of 11 children with fulminant MC survived after treatment with corticosteroids and IVIG, and were reported to be asymptomatic with normalized LVEF.43 Clinically, one-third of patients with viral MC will spontaneously recover, one-third will have persistent disease, and one-third will deteriorate.43 Viral genome or protein is commonly detected in the myocardium of approximately one-third of patients with DCM.43 Progression of MC to DCM has been documented in 20% of adult cases and is pathologically linked to chronic inflammation and viral persistence.44 In a pediatric study, lymphocytic MC was present in 25 of 70 patients (35.7%) with DCM who underwent cardiac histological examination.3

Our results demonstrated that 15% of recovered patients had impaired cardiac function at 1 year of follow-up, and may be at high risk for progressing to DCM.

Clinical studies have identified relatively few clinical or biological markers that predict myocardial recovery. Neither NYHA functional class, LVEF at presentation, troponin-I, CK, myoglobin, WBC or immunological markers predict LV functional recovery.49

Conclusion

Nationwide surveillance of MC in the Japanese population revealed 261 patients aged between 1 month and 17 years during a 6-year period (43.5 cases/year). The predicted annual incidence of MC is therefore 0.24 cases per 100,000 population. The survival rate for acute MC was 73%; however, fulminant MC was associated with a substantially higher mortality rate, as high as 48%. Two-thirds of survivors had no sequelae during follow-up. On the basis of physician’s assessment, IVIG was effective in 40% of cases and steroids in 23% of cases. Mechanical support devices were life-saving in 67% of patients, especially those with fulminant MC. Randomized trials of IVIG, steroids, and mechanical support devices in children are therefore essential.

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Appendix

Collaborating physicians and institutes are listed in alphabetical order.

Asahi G, Toride Kyodo General Hospital; Baba K, Kurashiki Central Hospital; Ebara E, Osaka City General Hospital; Endo C, Kагагawa Prefectural Central Hospital; Fujimura T, The Jikei University Hospital; Fujiyama J, Yamagata Prefectural Central Hospital; Fukushima T, Kagoshima University Hospital; Fukushima N, Osaka University Hospital; Hamada H, Chiba University Hospital; Hamamoto K, Fukuoka University Hospital; Hagiya N, The Fraternity Memorial Hospital; Haruki S, Fukuoka Prefectural Hospital; Hasegawa K, Toho University Medical Center Omori Hospital; Hashimoto T, Kishiwada Tokushukai Hospital; Himeoka W, Kurume University Hospital; Horigome H, Tsukuba University Hospital; Ishida F, Toyama University Hospital; Ichihashi H, Jichi Medical University Hospital; Inamitsu T, Saga Prefectural Hospital Koseikai; Jouo K, Kyushu Kosei Nenkin Hospital; Katayama A, Japanese Red Cross Society Tottori Tottori Hospital; Katayama H, Osaka Medical College Hospital; Kobayashi T, Gunma Children's Medical Center; Kob E, Kanazawa Medical University Hospital; Kohno T, Iizuka Hospital; Koyama C, Hiraka General Hospital; Kubo M, Ishikawa Prefectural Central Hospital; Maruyama S, Kagoshima University Hospital; Minato T, Toyooka Hospital; Miyashita M, Niho University Hospital; Momoi N, Fukushima Medical University Hospital; Morii K, Tokushima University Hospital; Munakami A, Seirei Hamamatsu General Hospital; Murakami Y, Osaka City General Hospital; Nagai N, Okayama City Hospital; Nakajima H, Chiba Children's Hospital; Nishiguchi T, Miyazaki Prefectural Miyazaki Hospital; Nishihara E, Ogaki Municipal Hospital; Oka T, Gunma Prefectural Hospital; Ohmura K, Chiba Cardiovascular Center; Ohno H, Okayama City Hospital; Oohata K, Koshigaya Municipal Hospital; Ohki H, Tokyo Metropolitan Kiyose Children's Hospital; Otokozawa H, Nago Children's Hospital; Sakakazki N, Hyogo Prefectural Amagasaki Hospital; Satoh J, Funabashi Municipal Medical Center; Scholz R, Ishinomaki Red Cross Hospital; Shimamura Y, Ashikaga Red Cross Hospital; Shiono J, Ibaraki Children's Hospital; Sugimoto H, Osaka City General Hospital; Suzuki H, Yamagata University Hospital; Takahashi K, Koshigaya Municipal Hospital; Takahashi T, Hiroaki University Hospital; Takamuro M, Sapporo Medical University Hospital; Tateno S, Chiba Cardiovascular Center; Tei T, Hyogo Children's Hospital; Tsuji M, Zentsuji National Hospital; Tsukano S, National Cardiovascular Center; Watabe S, Tsuichiura Kyodo General Hospital; Yamada K, Showa University Fujigaoka Hospital; Yamagishi Y, Keio University Hospital; Yamashina M, Chiba Red Cross Hospital; Yamamoto E, Ehime Prefectural Central Hospital; Yu Y, Osaka City General Hospital.