Table 3. Laboratory data and physical findings for study patients at presentation*.

Variable	Group 1 ≤2			Group 2 3–7			Group 3 8–14			Group 4 >14			P value**
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
WBC ($10^3/\mu L$)†	20	8.19	5.13	101	6.62	3.39	73	7.32	3.99	29	7.89	4.12	0.212
Neutrophil count ($10^3/\mu L$)	17	5.45	4.53	70	4.67	3.07	45	5.51	4.37	24	4.70	2.73	0.596
Lymphocytes count ($10^3/\mu L$)	17	0.81	0.51	70	1.12	0.76	45	1.25	0.84	24	1.27	1.11	0.264
RBC ($10^6/\mu L$)‡	16	5.04	0.63	68	4.80	0.62	44	4.76	0.54	22	4.58	0.72	0.161
Hemoglobin (g/dL)	18	14.9	1.42	85	14.06	2.08	63	13.97	1.77	26	13.55	2.26	0.161
Platelets ($10^3/\mu L$)	19	200.9	48.6	86	186.8	85.4	72	232.9	116.5	29	228.9	107.4	0.021
Albumin (d/dL)	14	4.29	0.46	59	3.86	0.50	41	3.65	0.48	18	3.50	0.72	<0.001
Sodium (mEq/L)	19	137.6	4.5	80	136.5	3.5	62	138.4	4.1	25	138.2	3.9	0.020
Body temperature (°C)	69	37.7	1.0	157	37.4	1.0	75	37.1	0.9	28	37.3	0.9	0.007
Respiratory rate	76	23.1	5.9	171	24.4	7.3	89	25.7	10.2	32	25.6	8.5	0.178
SpO_2§	80	92.3	4.3	182	90.0	7.1	82	85.8	9.6	32	86.1	12.1	<0.001

Grouping of patients was based on the number of days from symptom onset to oseltamivir administration: Group 1, ≤2 days; Group 2, 3–7 days; Group 3, 8–14 days; Group 4, >14 days.
†WBC: white blood cell count,
‡RBC: red blood cell count,
§SpO_2: oxygen saturation measured by pulse oximetry in room air.
*Normal ranges are as follows: WBC, 4000–10 000; neutrophil count, 2200–8250; lymphocyte count, 1500–4000; RBC, 3.8–6.5; hemoglobin, 11.5–17.0; platelets, 150–400; albumin, 2.30–3.50; sodium, 138–150; respiratory rate, 12–20 per min in adults; SpO_2, 92–98% at sea level.
**One-way ANOVA.
SD denotes standard deviation.
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values were summarized, and the linearity of incidence of each symptom according to the number of days to oseltamivir administration was analyzed using Cochran-Armitage test. The severity of the respiratory features was analyzed using Jonckheere's test. Severe pneumonia, mild to moderate pneumonia, and upper respiratory tract involvement without pneumonia were handled as ordinal variables and were analyzed using proportional odds models with the time-interval from the symptom onset to the oseltamivir administration as the explanatory and continuous variable [11]. A graph of the probability of severe pneumonia and the probability of mild to severe (any severity) pneumonia, which were estimated by varying the number of days from the symptom onset from 0 to 50 days with the estimated regression coefficient, was depicted. The calculation formula was provided in the figure legend. The multivariate analysis using a proportional odds model was performed to identify profound factors that affected the severity of respiratory features. The explanatory variables were Groups 1 through 4, the socioeconomic background, gender, age and comorbidities.

The cumulative rate of hospital discharge for Groups 1 through 4 was calculated by Kaplan-Meier's method using mortality data as censored data and then comparatively analyzed using Tarone's test.

Data analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). For all analyses, significance levels were two tailed, and a P value of <0.05 was considered significant.

Results

Characteristics of the study patients

Among patients suspected of having pandemic H1N1 2009 virus infection and admitted to the INER during the study period,

Table 4. Severity of respiratory features in each group.

Variable	Oseltamivir administration				Total
Days from symptom onset until oseltamivir administration	Group 1 ≤2	Group 2 3–7	Group 3 8–14	Group 4 >14	
No. of patients (% of total patients)	n = 92 (20.8%)	n = 213 (48.2%)	n = 101 (22.9%)	n = 36 (8.1%)	n = 442
Severe pneumonia* (% of group)	2 (2.2)	31 (14.6)	26 (25.7)	12 (33.3)	71 (16.1)
Moderate/mild pneumonia† (% of group)	21 (22.8)	90 (42.3)	58 (57.4)	22 (61.1)	191 (43.2)
Upper respiratory tract infection‡ (% of group)	69 (75)	92 (43.2)	17 (16.8)	2 (5.6)	180 (40.7)

(P<0.001, Jonckheere's test).
Grouping of patients was based on the number of days from symptom onset to oseltamivir administration: Group 1, ≤2 days; Group 2, 3–7 days; Group 3, 8–14 days; Group 4, >14 days.
*Severe pneumonia: abnormal shadows on chest radiographs and required mechanical ventilation.
†Moderate/mild pneumonia: abnormal shadows on chest radiographs but did not require mechanical ventilation.
‡Upper respiratory tract infection: absence of pneumonia.
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528 were confirmed to have pandemic H1N1 2009 virus infection by RT-PCR. There were no resistant viral strains involved in this study. Of these 528 patients, 442 received oseltamivir treatment during either ambulatory care (45.5%) or hospitalization (54.5%), these included 24 individuals who died. The 442 patients comprised the study subjects from whom clinical data were collected. Their characteristics are shown in Table 1. Data were obtained at the time of patients' presentation to the INER before oseltamivir administration. Median days from symptoms onset to oseltamivir administration was 5.0 (range, 0–43). Groups 1, 2, 3, and 4 comprised 92 (20.8%), 213 (48.2%), 101 (22.9%), and 36 (8.1%) patients, respectively.

Median age of study patients (193 females and 249 males) was 36 years with a range of 4 months to 85 years. Of the 442 study patients, 75 (17%) were aged <18 years, and 292 (66.1%) were aged 18 to 50 years. A total of 399 (90.3%) earned less than $15 US per day (<level 2). Only 11 (2.5%) had a history of vaccination for seasonal influenza in 2008 and/or 2009. The number of hospitalized patients ($P<0.001$), mortality ($P=0.004$), older age ($P=0.01$), and lower socioeconomic level ($P=0.001$) were associated with the Groups. The presence of comorbidities was not associated with the Groups; however, smoking ($P<0.05$), drug dependency ($P=0.002$), and alcohol dependency ($P<0.04$) were associated.

Symptoms of the study patients were shown in Table 2. The main symptoms were cough (76.9%), arthralgia (52.0%), dyspnea (50.7%), myalgia (50.0%), purulent sputum (19.0%), cyanosis (17.0%), and sore throat(15.4%). A total of 59% of study patients had pneumonia with abnormal shadows on chest radiographs, and 16% required mechanical ventilation.

Clinical symptoms and findings that increased significantly with time to oseltamivir administration ($P<0.05$) were included abnormal respiratory sounds; hemoptysis; abnormal pulmonary shadows, pneumothorax and pleurisy on chest radiographs; dyspnea; cyanosis; and need for intubation. On the other hand, incidence of nasal obstruction, sore throat, and conjunctivitis decreased as the time to oseltamivir administration increased.

Among the laboratory findings (Table 3), oxygen saturation (SpO_2) measured by pulse oximetry decreased significantly as the time to oseltamivir administration increased. Although within the normal range, serum albumin decreased significantly, and serum sodium, platelets, and body temperature differed significantly among the Groups.

Severity of respiratory features

Severe pneumonia was present in 71 (16.1%) patients. Mild to moderate pneumonia was present in 191 (43.2%), and upper respiratory tract involvement without pneumonia was present in 180 (40.7%) (Table 4).

The proportions of patients with severe pneumonia or mild to moderate pneumonia increased from Groups 1 to 4 (Table 4). By the contrast, the proportions of patients with upper respiratory tract infection without pneumonia decreased from Groups 1 to 4. These results indicated that the severity of respiratory features reflected the time to oseltamivir administration ($P<0.001$, Jonckheere's test).

The results obtained by the multivariate analysis using a proportional odds model indicated that severity of respiratory features was also affected by socioeconomic level, gender, hypertension, obesity, asthma and smoking (Table 5). The proportional odds ratios for severities of respiratory features for Groups 2–4 were 5.17, 15.02, and 20.40 times higher, respectively, than that for Group 1. The grouping, which indicated days to oseltamivir administration, showed a high level of significance in terms of the severity of respiratory features.

Table 5. Multivariate analysis of the severity of respiratory features using a proportional odds model.

Parameter	Regression coefficient	Standard error	$\chi 2$	P value	Reference group	Odds ratio and 95% confidence interval
Intercept 1	4.42	1.62				
Intercept 2	7.39	1.66				
Group 2* 3–7	1.64	0.30	29.49	<0.001	vs Group 1*	5.17 (2.86–9.37)
Group 3* 8–14	2.70	0.35	59.59	<0.001	vs Group 1*	15.02 (7.55–29.89)
Group 4* >14	3.01	0.44	45.33	<0.001	vs Group 1*	20.40 (8.48–49.10)
Socioeconomic category†	−0.49	0.12	15.91	<0.001	-†	0.60 (0.47–0.77)
Gender (female)	0.80	0.21	14.03	<0.001	vs male	2.23 (1.46–3.40)
AGE 2‡	0.37	0.29	1.60	0.205	vs AGE 1‡	1.45 (0.81–2.59)
AGE 3‡	0.94	0.37	6.35	0.011	vs AGE 1‡	2.57 (1.23–5.38)
Diabetes§	−0.34	0.43	0.64	0.424	vs present	0.70 (0.30–1.65)
Hypertension§	−0.85	0.36	5.37	0.020	vs present	0.42 (0.20–0.87)
Obesity§	−1.76	0.32	29.52	<0.001	vs present	0.17 (0.09–0.32)
Asthma§	−1.04	0.34	8.99	0.002	vs present	0.35 (0.17–0.69)
Smoking§	−0.73	0.24	9.16	0.002	vs present	0.47 (0.29–0.77)
Alcoholism§	0.22	0.34	0.42	0.515	vs present	1.25 (0.63–2.44)

*Grouping of patients was based on the number of days from symptom onset to oseltamivir administration: Group 1, ≤2 days; Group 2, 3–7 days; Group 3, 8–14 days; Group 4, >14 days.

†The odds ratio of socioeconomic level was presented when the level was upped by one unit as a continuous variable.

‡AGE 1 (age <18 y), AGE 2 (age 18–50 y), AGE 3 (≥50 y).

§Comorbidities are compared between present and absent.

$\chi 2$: Chi-square test.

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Occurrence of pneumonia

The number of patients who developed radiographic pneumonia was 262 (59.3%). The probability of pneumonia occurrence was estimated in relation to time from symptom onset using a proportional odds model (Figure 1). Figure 1 shows the time to occurrence of pneumonia. Both the probability of any severity of pneumonia and the probability of severe pneumonia increased gradually with the time from symptom onset to oseltamivir administration. The 50% probability for occurrence of any severity of pneumonia and that of severe pneumonia in patients who would develop pneumonia reached at approximately 3.4 and 21 days, respectively, after symptom onset.

Duration of hospitalization

Of the 442 patients evaluated, 241 (54.5%) were hospitalized. The numbers of hospitalized patients in each group are shown in Table 1. The cumulative discharge rate in each group on a Kaplan-Meier's curve using death data as censored data is shown in Figure 2. Patients with a shorter time to oseltamivir administration were discharged earlier from the hospital ($p<0.001$, Tarone's test).

Discussion

Severe pneumonia caused by pandemic H1N1 2009 has been frequently found [1,3,7,8,9,12,13]. Severity of pneumonia can be assumed to be a main indicator of overall disease severity. We hypothesized that the number of days to oseltamivir administration from symptom onset was one of the primary factors affecting the severity of pneumonia due to pandemic H1N1 2009.

Patients with pandemic H1N1 2009 infection in the INER had various time-intervals between the symptom onset and oseltamivir administration. Median days from symptom onset to oseltamivir administration was 5.0 (range 0–43) (Table 1), even though 92.5% of study patients was administered oseltamivir within one day after admission (median 0, range 0–12).

The study findings indicated that the following symptoms and clinical findings, associated with the severity of illness, increased significantly with the number of days to oseltamivir administration: abnormal respiratory sounds; hemoptysis; pulmonary infiltrative shadows, pneumothorax and pleurisy on chest radiographs; dyspnea; cyanosis; and need for intubation (Table 2). Conversely, SpO_2 decreased with time to oseltamivir administration, as did the incidence of upper respiratory tract symptoms, including nasal

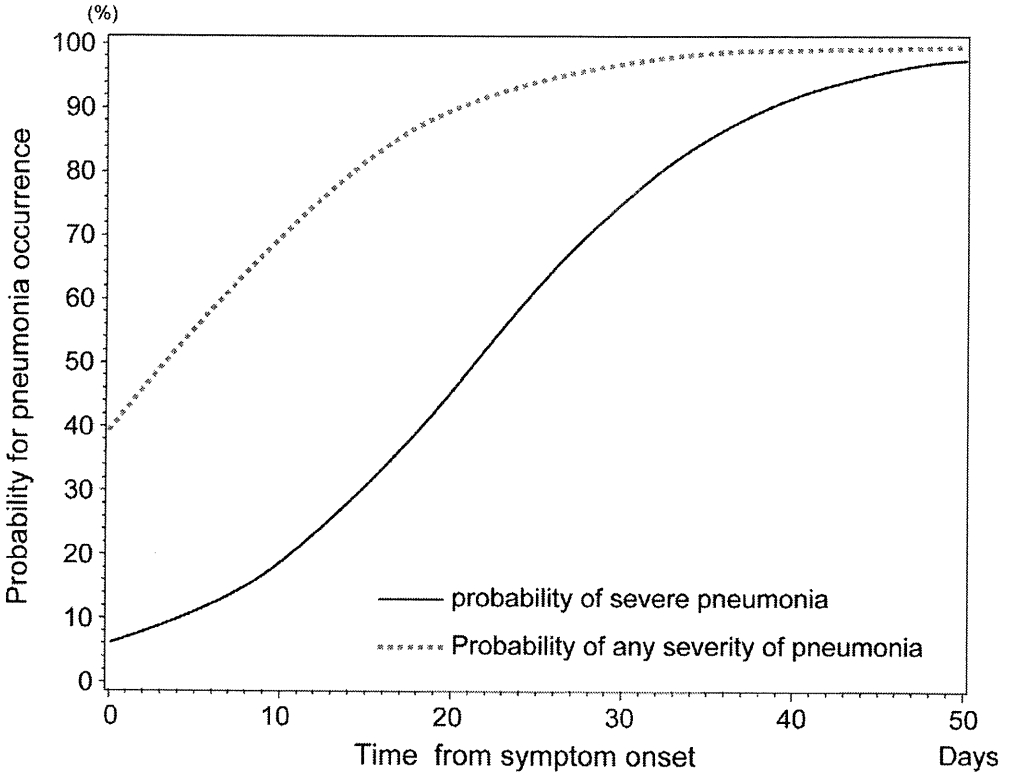

Figure 1. Model of the probability of occurrence of pneumonia. The probability of developing pneumonia is depicted using a proportional odds model. p_1, the probability of severe pneumonia; p_2, the probability of mild/moderate pneumonia; x, time until oseltamivir administration from symptom onset.

$$p_1 = exp(-2.7313+0.1281\ x)/(1+exp(-2.7313+0.128\ x))$$
$$p_1+p_2 = exp(-0.4301+0.1281\ x)/(1+exp(-0.4301+0.1281\ x))$$

Parameter, estimated value (standard error) : intercept 1, −2,7313 (0.2047); intercept 2, −0.4301 (0.11449); slope of x, 0.1281 (0.0179). [χ^2 value $=51.41$, $p<0.001$].

The solid line indicates the probability of occurrence of severe pneumonia (p_1). The dotted line indicates the probability of occurrence of any severity of pneumonia (mild to severe pneumonia, p_1+p_2).

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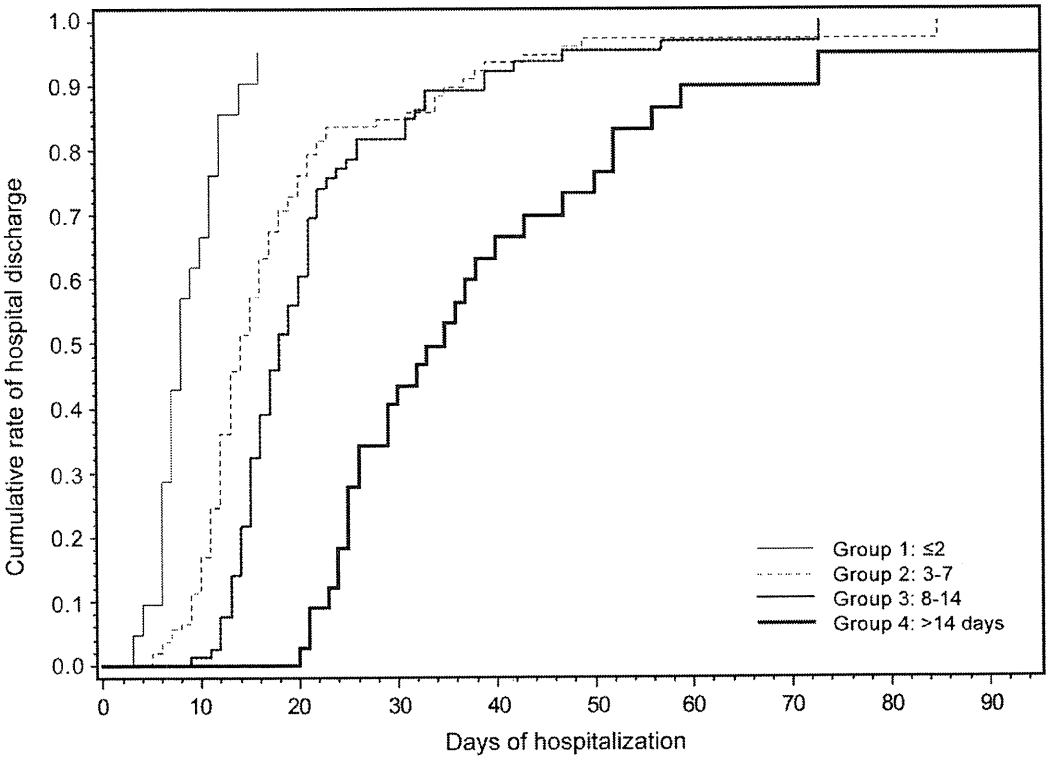

Figure 2. Cumulative rate of hospital discharge as a function of the time of oseltamivir administration. The cumulative rate of hospital discharge in each group using Kaplan-Meier's method was calculated using data on death as censored data. The groups of patients with earlier oseltamivir administration were discharged from the hospital significantly earlier ($p<0.001$, Tarone's test). Grouping of patients was based on days from symptom onset to oseltamivir administration: Group 1, ≤2 ; Group 2, 3–7; Group 3, 8–14; Group 4, >14days.
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obstruction, sore throat and conjunctivitis (Table 3). These findings suggest that the viral infection began in the upper respiratory tract and descended to the lower respiratory tract, and then the virus proliferated in the alveolar lung tissues in most pneumonia.

In this study, severity of respiratory features ranged from upper respiratory tract involvement without pneumonia to severe pneumonia. The proportions of patients with severe pneumonia and mild to moderate pneumonia increased from Groups 1 to 4. (Table 4). By contrast, the proportions of patients with upper respiratory tract involvement without pneumonia decreased from Groups 1 to 4. The association between severity of respiratory features and time to oseltamivir administration was found to be highly significant even after adjusting for socioeconomic levels, gender, hypertension, obesity, asthma and smoking (Table 5). Analysis of the probabilities of developing pneumonia indicated that the occurrence of any severity of pneumonia as well as that of severe pneumonia was associated with a longer interval from symptom onset to oseltamivir administration (Figure 1). The probability of occurrence of any severity of pneumonia was 50% at 3.4 days. The probability of severe pneumonia increased gradually and was approximately 10% at 3 days after symptom onset. These results indicate that early initiation of oseltamivir administration after the symptom onset is the significant factor for the reduction of severity of pneumonia. The probability of occurrence of severe pneumonia and any severity of pneumonia at 48 hours were $<10\%$ and $<50\%$, respectively, and increased gradually in this study. The estimations suggest that oseltamivir administration, even >2 days following symptom onset, still had considerable potential for reducing the occurrence of pneumonia of any severity. This study also found that the shorter the delay in starting oseltamivir, the shorter the length of hospitalization (Figure 2). This finding is compatible with previous studies [14,15].

Oseltamivir is a neuraminidase inhibitor that prevents cleavage of sialic acid on the surfaces of host cells, thus preventing new viral particles from being released by infected cells [10]. Viral neuraminidase is also known to play a role in the initial stages of airway epithelial cell infection [16] and to assist in hemagglutinin fusion [17]. Therefore, oseltamivir reduces viral cell entry as well as release. Seasonal influenza has been shown to replicate in humans for approximately 7 days post infection [18]. In pandemic H1N1 2009, it is likely that either the virus had an evasive phenotype [19] or the patient was predisposed to severe disease. This may lead to the assumption that patients who respond to oseltamivir at a later time after symptom onset still harbor actively replicating influenza virus [20]. This study might include patients who had difficulty in controlling influenza virus replication once it had taken hold within patients' bodies. The study also might constitute the population who has various host responses to the novel H1N1 influenza virus.

An important issue revealed in this study is the late access to medical care in Mexico. One of the main reasons for this may have been the cost consciousness of the patients; another may have been a lack of education. Such issues may have strongly influenced the severity of illness and need to be further investigated.

The present study has several limitations. First, the study was retrospective and there were no clear criteria for oseltamivir

administration when patients presented. Second, there were also patients who were not administered oseltamivir and were excluded from this study. Since we only included patients administered oseltamivir, there is a potential bias. Most patients with influenza recovered without antiviral treatment. The study patients, who visited the INER, were likely to be representative of those patients with more severe disease. Third, some patients may have had secondary bacterial infection in addition to primary viral infection [3]. This study was also unable to evaluate bacterial infection or antibiotic treatments because of insufficient data.

Regardless, the findings of this study will be valuable across many fields of medicine, science, and public health. Clinically, the present results support the initiation of treatment as soon as a patient presents, regardless of whether 48 hours have passed since disease onset. In addition, the effect of oseltamivir on the occurrence and severity of pneumonia shows that inhibition of infection of new cells is linked to better clinical outcomes. Moreover, these findings will help planning for future pandemics and may result in an increase in the availability of oseltamivir treatment to individuals in the community who have not recovered significantly after 2 days when afflicted with influenza-like illness.

In conclusion, the present findings indicate that earlier initiation of oseltamivir administration after symptom onset significantly reduced the occurrence and severity of pneumonia and shortened the length of hospitalization in patients with pandemic H1N1 2009. In addition, even when administered >48 hours after symptom onset, oseltamivir showed considerable potential to reduce the occurrence and severity of pneumonia. The results from this retrospective study which indicated the effectiveness of earlier administration of antiviral agents at any time after symptom onset for reducing the occurrence of pneumonia should benefit patients affected by the next influenza pandemic. However, continued investigation and further prospective studies to more fully define the effectiveness of early antiviral treatment are required.

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Author Contributions

Conceived and designed the experiments: ALHI KK. Performed the experiments: ALHI KK TM AECB ACB LAR RGG MEMZ JT SI EB JRPP. Analyzed the data: ALHI KK TM. Wrote the paper: KK TM.

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<Original Article>

Clinical Predictors of Pneumonia in Pediatric Influenza Virus Infection in H1N1pdm Pandemic Period

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Key words: H1N1pdm infection; Pneumonia; Preceding cough; Screening; Children

ABSTRACT

Objective: To identify clinical predictive factors for pediatric pandemic influenza virus (H1N1pdm)-associated pneumonia.

Methods: The medical records of 150 children epidemically presumed with H1N1pdm infection who visited our hospital between September and December 2009 were retrospectively analyzed for subsequent pneumonia.

Results: Thirteen patients were radiologically diagnosed with pneumonia and hospitalized (pneumonia group), and 112 children (control group) without pneumonia were treated as outpatients. The mean period from the onset of cough to the onset of fever up to 38.0℃ was significantly longer in the pneumonia group than in the control group (1.4 ± 1.5 days versus 0.7 ± 0.7 days, $P < 0.001$, Student's *t*-test). A complaint of dyspnea at the first visit and cough for over 12 h before the onset of pyrexia (preceding cough before fever) were potent predictive factors for pneumonia in the univariate and multivariate analyses, although their statistical independence could not be clarified directly because of the inadequate sample size. When either one or both predictors were required for predicting pneumonia, all of the pneumonia cases (sensitivity = 100%) and only 12 control cases (specificity = 89%) were recruited.

Conclusions: Preceding cough and a complaint of dyspnea at the first visit are appropriate clinical predictors of pediatric H1N1pdm-associated pneumonia and could be applied for triaging patients with this condition.

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INTRODUCTION

An outbreak of pandemic influenza virus (H1N1pdm) infection occurred in the United States [1] and Mexico [2,3] in April 2009, and spread globally between August and December 2009 [4]. An impressive clinical profile of some patients who presented with severe pneumonia and fulminant respiratory distress has been reported [5]. Recently, a report from Argentina warned that the pediatric death rate from H1N1pdm infection in 2009 was over 10 times that from seasonal influenza in 2007; in that study, 19% of the hospitalized pediatric patients were treated intensively, 17% required mechanical ventilation, and 5% died [6]. Moreover, in another study, the most common causes of death following H1N1pdm infection were pneumonia and acute respiratory distress syndrome [7]. Although some disorders such as asthma, diabetes, immunosuppression, and cardiovascular disease are suspected risk factors for H1N1pdm-associated pneumonia [1], to the best of our knowledge, no specific clinical signs that can predict the development of pneumonia subsequent to H1N1pdm infection have ever been identified. In Japan, over 99% of the influenza antigen A-positive samples from July to December 2009 were identified as H1N1pdm by polymerase chain reaction analysis of viral RNA [8]. Therefore in this study, we regarded patients who had influenza virus antigen A in H1N1pdm pandemic period as cases with H1N1pdm infection. And we retrospectively compared the clinical symptoms of children with H1N1pdm infection who developed pneumonia with those who recovered without pneumonia.

PATIENTS and METHODS

One hundred and fifty patients with type A influenza virus infection who visited the primary care clinic or the emergency unit in our hospital between September 1 and December 1, 2009, were enrolled. All cases of H1N1pdm infection were detected on the basis of influenza virus antigen A positivity by using nasopharyngeal samples in a commercial influenza rapid antigen test (ESPLINE Influenza A&B-N Kit; Fuji Revio Co., Tokyo, Japan). In this study, we regarded patients who had influenza virus antigen A in this period as cases with H1N1pdm infection.

As shown in **Figure 1**, we finally compared 13 cases in the admitted patients (pneumonia group) with 112 cases in the outpatients (control group). All the pneumonia patients were radiologically screened and chosen as patients in pneumonia group. All patients in the control group recovered without any remarkable complications, as indicated in their medical records at the second visit after over 2 days from when their fever subsided. In the case of the patients who had not made a second visit, telephone interviews with the parents were conducted nearly a month after the first visit to reconfirm that the patients had not developed pneumonia or other severe illnesses.

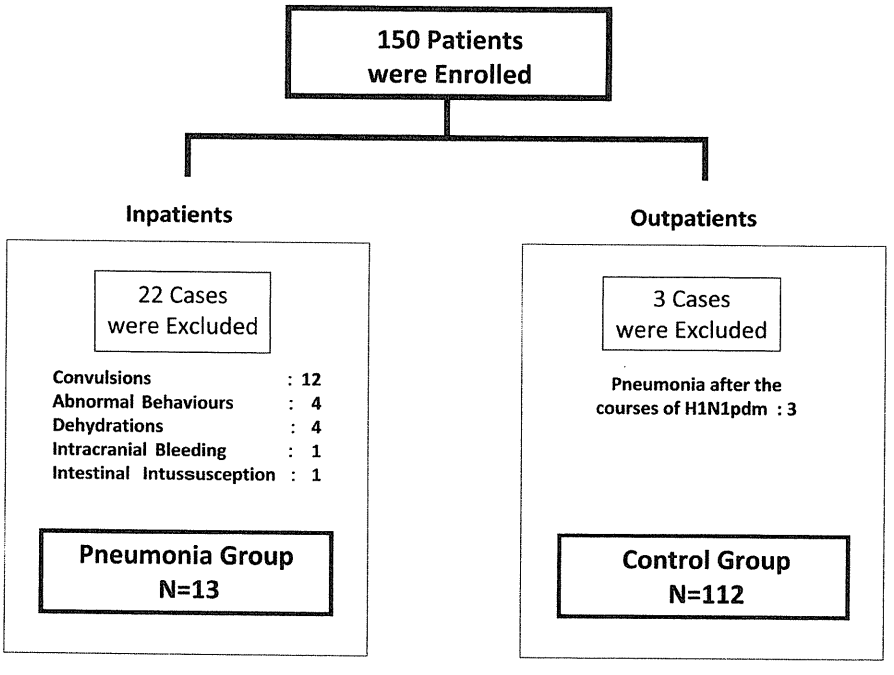

Figure 1 Patient flow in the study.

Predictive factors for pneumonia in the course of H1N1pdm infection were retrospectively sought by comparing the medical records of clinical information given by the patients themselves or their parents between the pneumonia group and the control group. Two time points, onset of fever and onset of cough, were considered. Onset of fever denotes the first time when the patient's body temperature elevated over 38.0℃, and onset of cough denotes the first time at which the patient presented with cough during the course of H1N1pdm infection. The Institutional Review Board at Osaka Medical College for the Protection of Human Subjects reviewed and approved this study.

STATISTICAL ANALYSIS

Comparisons of age and periods from the onset of cough to the onset of fever were performed by using Student's *t*-test without correspondence. The results of univariate analysis (pneumonia versus age, gender, history of asthma, administration of an anti-influenza virus medicine, dyspnea, and preceding cough) and those based on 2 × 2 classified tables were assessed with Fisher's exact probability test. Multivariate analysis (multiple logistic regression) was used to identify independent predictors of pneumonia. All analyses were performed by using JMP version 8.0 (SAS Institute, Cary, NC). All tests were two-sided, with a significance cutoff of $P = 0.05$.

RESULTS

Patient characteristics

Total one hundred and fifty patients identified with type A Influenza virus antigen who visited in our hospital were enrolled. The characteristics of the two groups are summarized in Table 1. Although the mean age in the pneumonia group was slightly lower than that in the control group, the difference was not significant (P = 0.13). Gender, past history of asthma, and administration of an anti-influenza virus medicine did not differ statistically between the groups.

Clinical characteristics of the pneumonia group

The clinical details of the pneumonia group are summarized in Table 2. The mean period from the onset of fever to hospitalization was only 1.2 ± 0.6 days. There were nine cases (69%) of a complaint of dyspnea at the first visit, and the mean percentile of percutaneous oxygen saturation (SpO_2) in room air was 90% ± 3.0%. All patients had one or more consolidations in their chest radiographs. The white blood cell (WBC) counts and serum C-reactive protein (CRP) levels were increased in almost all of the cases. Cultures of the nasopharyngeal samples revealed some pathogenic bacteria in seven cases (54%). Nine patients (69%) received oxygen support; among them, one required mechanical ventilation and one was assisted with a biphasic positive airway pressure (BiPAP) device. A drip of antibiotics (amoxicillin + sulbactam, ceftriaxone or meropenem) and an anti-influenza virus medicine (oral oseltamivir [Tamiflu; Chugai Pharmaceutics Co., Tokyo, Japan] or inhalation zanamivir [Relenza, GlaxoSmithKline Co., Tokyo, Japan]) was administrated in all cases. Ten (77%) patients were intravenously loaded with methylprednisolone. After hospital-based treatment for 9.0 ± 4.0 days, all of them were discharged without any adverse sequelae.

Table 1 Patient characteristics

	Pneumonia	Control	*P* value
N (cases)	13	112	
Age (years, mean±SD)	6.9±3.0	8.7±4.1	0.13
Gender (male, cases, %)	7 (54)	64 (57)	1.00
History of asthma (yes, cases, %)	5 (39)	30 (27)	0.51
Administration of anti-influenza virus medicine (yes, cases, %)	13 (100) **Oseltamivir: 13** **Zanamivir : 0**	104 (93) **Oseltamivir: 59** **Zanamivir : 45**	1.00

All data before the first visit were obtained from medical records based on patient self-reports.

Table 2 Clinical parameters of the pneumonia group

Parameters	Data
Fever to Admisson (days, mean±SD)	1.2±0.6
Age (years, mean±SD)	6.9±3.0 (2~14)
Gender (cases)	Male: 7, Female: 6
Past Medical Histories (cases)	Asthma: 5, KD: 2, None: 4
Body Temperature (℃, mean±SD)	38.7±1.0 (37.0~40.3)
Dyspnea at first visit (cases)	Yes: 9
SpO_2 (in room air, %, mean±SD)	90±3.0
Radiological Abnormalities (cases)	Yes: 13
PCR analysis of viral RNA	4 in 4 cases : H1N1pdm
WBC (/μL, mean±SD)	12169±3307
Neut. (/μL, mean±SD)	10678±3093
CRP (mg/dL, mean±SD)	5.2±3.6
Positive Bacterial Cultures (cases)	7 PSSP 2, MSSA 4, MC 3, GAS 1
Treatments (cases)	O_2 support: 9 MV 1, BiPAP 1 Steroids : 10, Antibiotics : 13, Anti-Influenza Drug : 13
Admission Periods (days,mean±SD)	9.0±4.0
Prognosis (recovered, no sequelae, cases)	Yes: 13

All data were obtained from medical records maintained at the first visit and during hospitalization.

Abbreviations: SpO_2, percutaneous oxygen saturation; PCR, polymerase chain reaction; WBC, white blood cell; Neut, neutrophils; CRP, C-reactive protein; KD, Kawasaki disease; PSSP, penicillin-sensitive *Streptococcus pneumoniae*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MC, *Moraxella catarrharis*; GAS, group A *Streptococcus pyogenes*; MV, mechanical ventilation; BiPAP, biphasic positive airway pressure.

Timing of the onset of cough between the groups

As shown in Figure 2, the time patterns from the onset of cough to the onset of fever obviously differed between the groups; the mean period was significantly longer in the pneumonia group than in the control group (1.4 ± 1.5 days versus 0.7 ± 0.7 days, $P < 0.001$).

Most of the patients with pneumonia had cough that started before their fever elevated (preceding cough); on the other hand, most of the control patients experienced cough simultaneously with or after the onset of pyrexia.

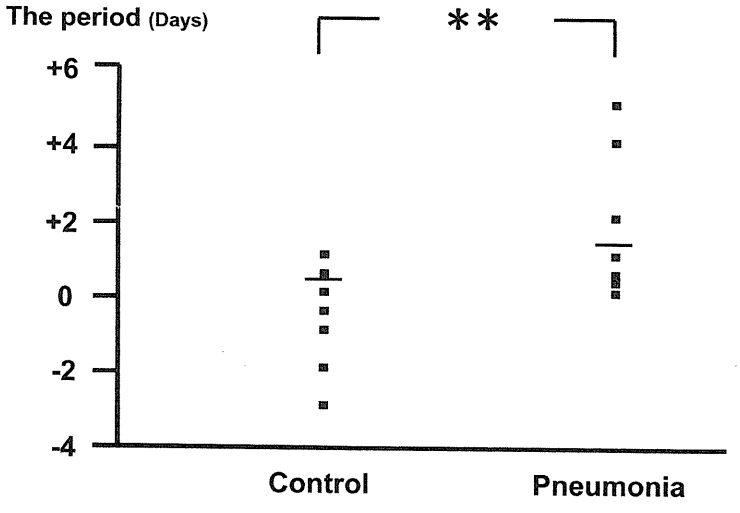

Figure 2 Comparison of the periods from the onset of cough to the onset of fever. The y-axis indicates the period (days). Point 0 indicates the first time at which the fever rose to 38.0℃. $^{**}P < 0.001$ by Student's *t*-test without correspondence.

Univariate analysis of predictors of pneumonia

In the univariate analysis (Table 3), a complaint of dyspnea at the first visit (OR = 123.8, $P < 0.001$) and preceding cough (OR = 34.0, $P < 0.001$) were significant predictive factors for pneumonia. However, age under 7 years, female gender, past history of asthma, and administration of an anti-influenza virus medicine were not predictive statistically.

Multivariate analysis of predictors of pneumonia

In the multivariate analysis of predictors of pneumonia, female gender and administration of an anti-influenza virus medicine were not approved because of weak statistical power. In the analysis including age under 7 years, past history of asthma, and preceding cough, age under 7 years (OR = 11.8, $P = 0.01$) and preceding cough (OR =104.5, $P < 0.0001$) were risk factors for pneumonia (Table 4A). Then, in the analysis of age, past history of asthma, and a complaint of dyspnea, only a complaint of dyspnea at the first visit (OR = 156.5, $P < 0.0001$) was associated with pneumonia (Table 4B). However, we could not prove the relationship between preceding cough and a complaint of dyspnea to be statistically independent because 89% (100/112) of the control group overlapped when neither factor was considered.

Analysis of predictors based on 2 × 2 classified tables

This analysis revealed that 77% (10/13) of the pneumonia group included patients with preceding cough (Table 5A) and 69% (9/13) had a complaint of dyspnea at the first visit. All of the patients in the pneumonia group fulfilled either one or both criteria whereas 100 patients in the control group did not (sensitivity = 100%, specificity = 89%; Table 5B).

Table 3 Univariate analysis of the risk factors for H1N1pdm-associated pneumonia

	OR	95%CI	*P* value
Gender (female)	1.1	0.4 - 3.5	1.00
History of asthma (yes)	1.7	0.5 - 5.4	0.51
Age (<7 years old)	2.7	0.9 - 8.2	0.12
Administration of anti-influenza medicine (yes)	0.0	0.0 - 4.1	1.00
Dyspnea at first visit (yes)	123.8	21.6 - 690.3	<.001**
Preceding cough for over 12 h before pyrexia (yes)	34.0	8.5 - 138.9	<.001**

The analysis was assessed with Fisher's exact probability test.

Table 4 Multivariate analysis of (A) preceding cough and (B) complaint of dyspnea as predictors of H1N1pdm-associated pneumonia

A	OR	95%CI	*P* value
History of asthma (yes)	1.0	0.2 - 5.5	0.99
Age (<7 years old)	11.8	1.2 - 111.4	0.01*
Preceding cough for over 12 h before pyrexia (yes)	104.5	11.6 - 946.2	<.0001**

B	OR	95%CI	*P* value
History of asthma (yes)	0.6	0.2 - 11.0	0.63
Age (<7 years old)	3.8	0.6 - 23.8	0.14
Dyspnea at first visit (yes)	156.5	20.3 - 1203.9	<.0001**

Table 5 Screening for pneumonia based on 2 × 2 classified tables

A			
Preceding cough before pyrexia	Over 12 h (cases)	Within 12 h (cases)	Total (cases)
Pneumonia (cases)	10	3	13
Control (cases)	10	102	112
Total (cases)	20	105	125

B			
Situations	Yes; A and/or B (cases)	No; A nor B (cases)	Total (cases)
Pneumonia (cases)	13	0	13
Control (cases)	12	100	112
Total (cases)	25	100	125

The analysis was assessed with Fisher's exact probability test.
(A) The power of screening for pneumonia by using preceding cough as a single predictor ($P < 0.001$, sensitivity = 0.77, specificity = 0.91, positive predictive value = 0.50, negative predictive value = 0.97).
(B) The efficacy of screening for pneumonia by using a combination of two queries (Query A: preceding cough and Query B: complaint of dyspnea at first visit; $P < 0.001$, sensitivity = 1.00, specificity = 0.89, positive predictive value = 0.52, negative predictive value = 1.00).

DISCUSSION

In general, the onset of seasonal type A influenza virus infection is abrupt, with fever, flushed face, chills, headache, myalgia, and malaise [9]. Moreover, respiratory symptoms including cough become prominent by 2–4 days from the onset [9]. We had the impression that the course in the control group was similar to that of seasonal influenza viruses reported in the previous years. However, we found that the mean time span from the onset of cough to the onset of fever in the pneumonia group was statistically longer than that in the control group. Moreover, we ascertained that 77% of the patients who developed pneumonia had experienced a unique cough for more than 12 h before fever. Therefore, we assumed that the inversion of timing between the onset of cough and the onset of fever, namely preceding cough, is one of the features of H1N1pdm-associated pneumonia. However, we cannot assert that preceding cough is a determinant of H1N1pdm-associated pneumonia because we did not compare the course in the pneumonia group with that followed in past seasonal influenza virus-associated pneumonia.

It is crucial to diagnose pneumonia in patients with H1N1pdm infection as soon as possible because some of them may shortly progress to acute respiratory distress syndrome [10]. In our data, the mean period from the onset fever to hospitalization in the pneumonia group was only one day or slightly longer (1.2 ± 0.6 days); however, only 69% of these patients had a complaint of dyspnea at the first visit. These discordant results suggest that H1N1pdm-associated pneumonia can quickly deteriorate, and 30% or more of the pneumonia cases are not identifiable by a physical complaint such as dyspnea at the first visit alone. Therefore, we used a combination of a complaint of dyspnea and preceding cough as the risk factors for pneumonia. The requirement of either a complaint of dyspnea or preceding cough led to successful identification of all the pneumonia cases. We consider that a complaint of dyspnea is suitable for determining cases of serious pneumonia and preceding cough is appropriate to identify patients with mild pneumonia whose conditions will probably worsen.

Our results can be easily applied to exclude patients without pneumonia at subsequent visits. In this study, the ratio of number of the patients in the pneumonia group to that in the control group was nearly 1:9 (Table 1), which means that 90% of the patients with H1N1pdm infection did not suffer from pneumonia that required intensive treatment. It is obviously unreasonable, from the point of view of both radiation safety and cost-effectiveness, to perform radiological tests on all patients with H1N1pdm infection only for reconfirming that pneumonia did not

develop subsequently. The condition of neither a complaint of dyspnea nor preceding cough led to the screening of 89% of the control group from the target of secondary examinations such as chest radiography or/and chest computed tomography. We consider that the combination of these two predictors is also suitable for excluding patients with low probability of developing pneumonia from further examinations in crowded outpatient clinics.

Cultures of the nasopharyngeal samples showed that 54% of the pneumonia cases had some pathogenic bacteria. Some bacteria, such as *Streptococcus pneumoniae* [11,12], *Haemophilus influenzae* [11], and *Staphylococcus aureus* [11,13,14], can cause pneumonia in patients infected with influenza virus. The high WBC count and serum CRP levels of the pneumonia group support the view that their pneumonia was associated with a bacterial infection. However, we cannot ascertain whether the detected bacteria primarily induced pneumonia in combination with H1N1pdm infection or were a secondary infection after H1N1pdm infection lead to pneumonia, because we did not perform more direct approaches to determine the cause of pneumonia, such as cultures of bronchoalveolar fluids or histological examination of lung specimens.

The pathophysiological background of preceding cough is unclear. In animals, H1N1pdm infection leads to virus-associated pneumonia in the early step of virus-to-host contact more frequently than in the case of seasonal influenza viruses because H1N1pdm has a robust affinity not only for nasopharyngeal epithelium but also for bronchiolar and alveolar epithelium [15,16]. We hypothesize that the pneumonia group experienced preceding cough because H1N1pdm-associated pneumonia had progressed to their peripheral bronchopulmonary system (lower respiratory tract) locally and occultly, whereas the control group did not have preceding cough because H1N1pdm had contacted only with their nasopharyngeal epithelium (upper respiratory tract) in the early stage of infection. However, the following question remains to be answered: why was the main lesion caused by the infection different between the groups? In mice, some alterations in host defense, such as CD4 T cells [17], B cells [18], CD8 T cells [19], or CD200 molecules on epithelial cells [20], have been shown to be associated with the severity of influenza virus infection. Further investigations are needed to validate our hypotheses.

This study has some limitations. First, our sample size was not sufficiently large to investigate the risk factors for pneumonia. However, it is worth mentioning that all of the enrolled patients were suspected to be infected with a common influenza virus strain, for over 99% of the influenza virus cases were genetically identified as being H1N1pdm in Japan [8] in nearly the same period. Second, the features such as onset of cough and onset of fever are possibly inaccurate because they were obtained from medical records based on subjective reports. Third, we did not examine the patients with negative results in the influenza rapid antigen test. The rapid test was selected in this study because it has been found to be able to detect influenza A viruses in pigs [21], and the performance of a rapid test for seasonal influenza A virus infection is generally high [22]. However, few patients with H1N1pdm infection may not have been detected because of false-negative results, considering that the sensitivity of rapid influenza tests has been found to be 45% [23] or 62% [24] in children with H1N1pdm infection. Finally, some patients in the control group may have had slight or mild pneumonia that was overcome spontaneously, because we reconfirmed only that they had never experienced pneumonia or required treatment for other illnesses. Some of the patients in this group may have shown mild pneumonia on detailed investigation such as high-resolution chest computed tomography [25].

In conclusion, despite the limitations, we believe that a complaint of dyspnea and preceding cough are useful keywords to triage patients with H1N1pdm-associated pneumonia. The combination of these two predictors can be used to divide such patients into high-risk and low-risk groups for pneumonia. We suggest that high-risk patients, meeting one or both predictors, should be checked radiologically and observed cautiously, whereas low-risk patients, without such predictors, can be treated as outpatients. As the next step, a prospective study including the recommendation for screening of H1N1pdm-associated pneumonia is warranted.

CONFLICT of INTEREST

No conflict of interest to declare.

ACKNOWLEDGMENTS

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Guidelines for Diagnosis and Treatment of Myocarditis (JCS 2009)

– Digest Version –

JCS Joint Working Group

Table of Contents

(*Circ J* 2011; **75:** 734–743)

Revision of the Guidelines

Myocarditis is an inflammatory condition mainly located in the myocardium. Its incidence and mortality in the Japanese population have not been determined, since definitive diagnosis of myocarditis is difficult. These "Guidelines for Diagnosis and Treatment of Myocarditis" have been compiled based on basic and clinical research on myocarditis which has been conducted using sound scientific methods in Japan, though the evidence obtained may not qualify as that of evidence-based medicine. In the guidelines, cardiac magnetic resonance (CMR) imaging is considered valuable as an effective means of diagnosis of myocarditis. In addition, information on cardiac sarcoidosis, autoimmune myocarditis, and drug-induced myocarditis is included.

I Classification, Diagnosis and Treatment of Acute Myocarditis

1. Etiology

Myocarditis is caused by a variety of bacterial and viral infections. Enteroviruses, especially coxsackievirus B, are often associated with acute myocarditis.[1] However, with the advent of genetic analysis, adenovirus and parvovirus B19 have also been found to be frequent causes of myocarditis.[2] Exposure to drug treatment, physical stimuli such as radiation and heat, metabolic disorders, immune disorders, and pregnancy are also causes of myocarditis. In the case of idiopathic myocarditis, the etiology is yet to be determined.

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This English language document is a revised digest version of Guidelines for Diagnosis and Treatment of Myocarditis reported at the Japanese Circulation Society Joint Working Groups performed in 2008 (website: http://www.j-circ.or.jp/guideline/pdf/JCS2009_izumi_d.pdf).

Joint Working Groups: The Japanese Circulation Society, The Japanese Association for Thoracic Surgery, The Japanese Society of Pediatric Cardiology and Cardiac Surgery, The Japanese Society for Cardiovascular Surgery, The Japanese College of Cardiology, The Japanese Heart Failure Society

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2. Classification

Myocarditis is classified by its etiology, cell type (lymphocytic type, giant cell type, eosinophilic type, granulomatous type), and clinical type (fulminant type, acute type, chronic type) as shown in **Table 1**.[3,4]

Table 1. Myocarditis Classification

Etiology	Cell type	Clinical type
Virus	Lymphocytic type	Acute
Bacteria	Giant cell type	Fulminant
Fungi	Eosinophilic type	Chronic
Rickettsia	Granulomatous type	(prolonged)
Spirochetes		(latent)
Protozoa, parasites		
Other causes of infection		
Drugs, chemical substances		
Allergy, autoimmune		
Collagen disease, Kawasaki disease		
Sarcoidosis		
Radiation, heat stroke		
Unknown cause, idiopathic		

3. Symptoms, Signs and Clinical Tests

1 Symptom

Myocarditis is preceded by flu-like symptoms (chills, fever, headache, muscle aches, general malaise) or gastrointestinal symptoms such as decreased appetite, nausea, vomiting, and diarrhea. Cardiac manifestations of myocarditis appear a few hours to a few days after the initial signs and symptoms.[5] Cardiac symptoms consist of (1) those of heart failure, (2) chest pain due to pericardial irritation, and (3) symptoms associated with heart block and arrhythmia. The possibility of myocarditis must be considered if a patient with such symptoms is febrile.

2 Sign

The clinical signs of myocarditis include fever, cardiac rhythm disturbance (tachycardia, bradycardia, and arrhythmia), hypotension, gallop rhythm, rales, jugular venous dilatation, and cardiac tamponade.

3 Blood Biochemistry

Myocarditis is confirmed by the findings of transient elevation of C-reactive protein (CRP), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), the MB form creatine kinase (CK-MB), and cardiac troponin T in blood.[6] Troponin T, which can be measured quickly and easily in whole blood by enzyme-linked immunosorbent assay (ELISA), is especially useful for immediate diagnosis. However, which type of troponin, T or I, in more useful for diagnosis has not been determined.[7]

4 Chest X-Ray

A chest X-ray is useful for visualizing cardiac enlargement and pulmonary congestion.

5 Electrocardiography (ECG)

The ECG is a sensitive and convenient means of diagnosis of myocarditis. It must be timely repeated, since minor abnormalities in the ECG detected initially may become clearer over time. Abnormal ST-T waves and conduction block are frequently observed in myocarditis. A gradual increase in the width of the QRS complex is a sign of exacerbation of myocarditis. Continuous ECG monitoring is crucial to detect potentially fatal arrhythmias.

6 Echocardiography

Myocarditis can be confirmed by transient wall thickening, reduced wall motion and reduced cardiac chamber size in addition to pericardial effusion on echocardiography.[8] Echocardiography is especially useful for pediatric patients.

7 Cardiac Magnetic Resonance (CMR)

In addition to the cinematic mode on magnetic resonance imaging (MRI), T1-weighted early signal enhancement and gadolinium-delayed imaging of the heart are useful to make a positive diagnosis of myocarditis.[9–11] T2-weighted images reveal the regions of the heart affected by inflammation. CMR imaging can differentiate acute myocarditis from acute myocardial infarction; acute myocarditis exhibits erosive or spotty areas in the epicardium, while lesions of acute myocardial infarction spread from the endocardium like a wave front.

8 Nuclear Medicine Techniques

In gallium-67 (^{67}Ga) myocardial imaging, ^{67}Ga uptake in the myocardium is highly specific for detection of myocarditis, though this method is not highly sensitive.[12] On the other hand, technetium-99m (^{99m}Tc) pyrophosphate myocardial scintigraphy has relatively high sensitivity but is not specific.[13]

9 Cardiac Catheterization Including Endomyocardial Biopsy

Cardiac catheterization may be performed in the acute phase of myocarditis if the patient's condition allows. After coronary lesion has been excluded, an endomyocardial biopsy should be performed to detect myocardial degeneration, myocyte necrosis, inflammatory infiltrates, and/or interstitial edema of the myocardium. Even if the results are negative, the presence of myocarditis cannot be excluded due to the possibility of sampling errors.[14] Biopsy sampling at three or more different sites is therefore strongly recommended.[15]

10 Diagnosis of Viral Infection

Viral infection is confirmed if the viral antibody titer is at least four times higher in an acute phase serum sample than in a sample obtained in remission phase collected at least two weeks apart. However, only approximately 10% of patients with viral infection exhibit a positive antibody titer. Polymerase chain reaction (PCR) is more useful for identifying the genomes of viruses causing myocarditis, but is not commonly performed.[16]

4. Methods of Diagnosis and Evaluation

Clinical diagnosis of myocarditis should be performed following the "Diagnostic guidelines for acute myocarditis"[17] (**Table 2**).

Table 2. Diagnostic Guidelines for Acute Myocarditis

1. In acute myocarditis, flu-like signs and symptoms[a], gastrointestinal signs and symptoms[b], skin rash, joint pain, or muscle pain may occur before cardiac signs and symptoms[c]. However, sudden death may occur without preceding clinical signs.
2. Cardiac findings such as tachycardia, bradycardia, arrhythmia, weakened heart sounds, gallop rhythm (III, IV), pericardial rub, and systolic murmur occur.
3. Generally, an abnormal ECG is observed during the course of myocarditis. ECG manifestations are diverse, and include atrioventricular block (I to III degree), intraventricular conduction delay (widened QRS complex), reduced R wave height, abnormal Q waves, ST-T segment changes, low voltage, frequent premature beats, supraventricular tachycardia, atrial fibrillation, sinus arrest, ventricular tachycardia, ventricular fibrillation, and asystole.
4. Localized or diffuse wall thickening, reduced wall motion, reduced cardiac chamber size, and pericardial effusion are found on echocardiography.
5. In myocarditis, myocardial constitutive proteins (cardiac troponin T and creatine kinase-MB) are detected in serum. C-reactive protein and white blood cell count are elevated. Early detection of troponin T using whole blood enables immediate diagnosis of myocarditis.
6. Since the conditions in items 2 and 5 above may progress within a few hours, changes over time in these conditions should be followed. If a patient has bradycardia, widened QRS complex, frequent premature beats, wall thickening, exacerbation of reduced wall motion, elevated troponin T, and continuous increase in troponin T level, the patient may have a cardiopulmonary emergency.
7. Definitive diagnosis of myocarditis requires that acute myocardial infarction be excluded.
8. The presence of abnormal histological findings on endomyocardial biopsy[d] makes the diagnosis of myocarditis definite. However, the absence of such findings does not exclude the possibility of myocarditis.
9. Elevation of viral titer in a sample collected in the acute phase to at least four times that in a sample obtained in remission is useful for identify viral infection as the cause. Polymerase chain reaction is often used to demonstrate the presence of viral infection and to detect the viral genome. Separation of virus or identification of virus by antibody titer in throat swabs, urine, feces, blood, and especially pericardial effusion or cardiac muscle tissue provides direct evidence of myocarditis.

[a] Flu-like symptoms: Fever, headache, cough, and throat pain.
[b] Gastrointestinal symptoms: Nausea, vomiting, stomach ache, and diarrhea.
[c] Cardiac symptoms: Chest pain, syncope, dyspnea, palpitations, shock, seizure, and cyanosis.
[d] See Table 3.
ECG, electrocardiography.
Adapted from the Ministry of Health and Welfare (MHW) Specific Disease Idiopathic Cardiomyopathy Study Group Report in 1986. 1987; 13–14.

If acute myocardial infarction is excluded but active lesions of myocarditis can be confirmed on endomyocardial biopsy[18] (Table 3), myocarditis is considered definitively diagnosed.

5. Treatment

The primary signs and symptoms and disease progression of myocarditis are relatively easy to grasp. The inflammatory phase lasts one to two weeks, and is followed by a recovery phase. Myocarditis causes myocardial necrosis and inflammation, which result in cardiac dysfunction and failure. Myocarditis is therefore treated in three ways: (1) intervention to eliminate the cause, (2) intervention to improve hemodynamic compromise, and (3) intervention in cardiac dysfunction (Figure 1).

Table 3. Diagnostic Criteria for Acute Myocarditis in Endomyocardial Biopsy

1. Infiltration of many large or small mononuclear cells* (occasionally, a few polymorphonuclear leukocytes and multinucleated giant cells appear)
2. Rupture, fusion and disappearance of cardiomyocytes
3. Interstitial edema (occasionally with fibril formation)

*Cell infiltrates are often observed adjacent to cardiomyocytes.
Factors involved in definitive diagnosis of myocarditis.
1. Endomyocardial biopsy may be performed after the occurrence of symptoms suggestive of viral infection.
2. Repeated biopsies over time are useful for determining the pathology and the effects of treatment.
3. Biopsy sampling from at least 3 sites is strongly recommended. The samples should be obtained from different angles.
4. Detailed findings can be obtained by electron microscopy and immunohistochemical methods.

Adapted from the MHW Specific Disease Idiopathic Cardiomyopathy Study Group Report in 1988. 1989; 181–182.

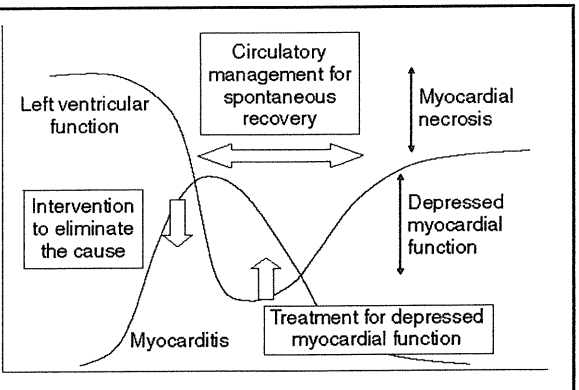

Figure 1. Course of cardiac dysfunction and timing of intervention in myocarditis.

1 Treatment of Asymptomatic or Mildly Symptomatic Myocarditis

Patients with asymptomatic or mildly symptomatic myocarditis with cardiac signs and symptoms should be admitted to the hospital, kept at bed rest, and monitored carefully. A regimen for cardiopulmonary emergency must be prepared beforehand, in the event of acute changes.

2 Treatment of Arrhythmia

Patients with arrhythmia caused by severe heart block should temporarily be treated with external pacing. However, use of drugs must be avoided in case of frequent premature beats and nonsustained in patients with ventricular tachycardia.

3 Management of Heart Failure

For patients with cardiac pump failure in the acute phase, use of catecholamines or carperitide is recommended. If the patient does not respond to treatment, a circulatory assist device should be used.

4 Additional Treatment for Refractory Myocarditis

In patients with persistent inflammation without signs of hemodynamic improvement, short-term treatment with large doses of corticosteroids may be attempted.[19] There are cases of

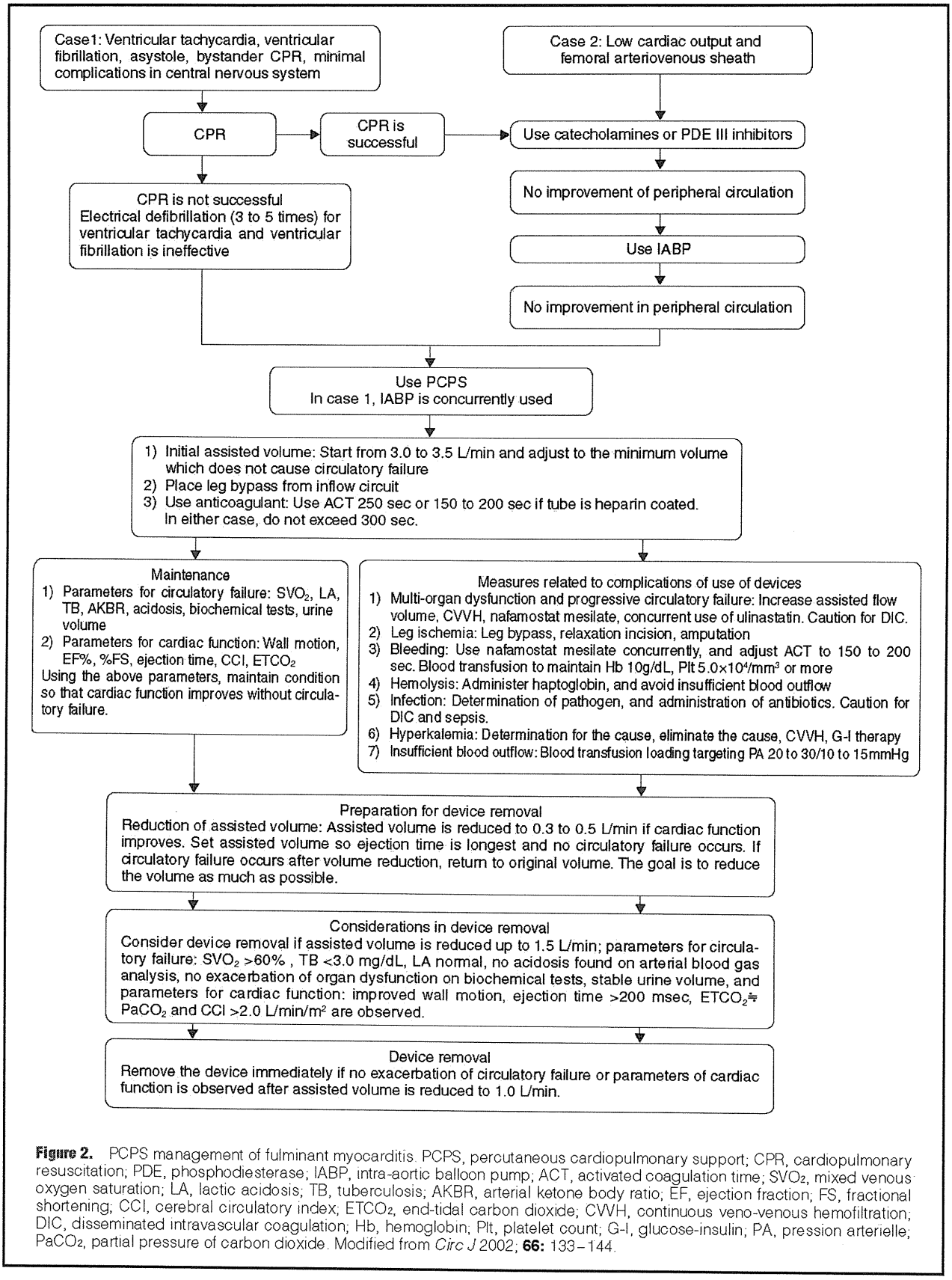

Figure 2. PCPS management of fulminant myocarditis. PCPS, percutaneous cardiopulmonary support; CPR, cardiopulmonary resuscitation; PDE, phosphodiesterase; IABP, intra-aortic balloon pump; ACT, activated coagulation time; SVO_2, mixed venous oxygen saturation; LA, lactic acidosis; TB, tuberculosis; AKBR, arterial ketone body ratio; EF, ejection fraction; FS, fractional shortening; CCI, cerebral circulatory index; $ETCO_2$, end-tidal carbon dioxide; CVVH, continuous veno-venous hemofiltration; DIC, disseminated intravascular coagulation; Hb, hemoglobin; Plt, platelet count; G-I, glucose-insulin; PA, pression arterielle; $PaCO_2$, partial pressure of carbon dioxide. Modified from *Circ J* 2002; **66:** 133–144.

remarkable recovery. Treatment with high dose immunoglobulin may also be considered.[20]

5 Management of Myocarditis in the Recovery Phase

Treatment with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers can be performed to protect the myocardium.

6. Prognosis and Natural History

In the acute phase, myocarditis management of cardiac pump failure and potentially fatal arrhythmias is the main clinical challenge. The prognosis of myocarditis varies depending on the pathogenesis and type of disease.[21]

II Diagnosis and Treatment of Specific Types of Myocarditis

1. Fulminant Myocarditis

1 Background

Fulminant myocarditis causes acute hemodynamic compromise which may prove fatal. External circulatory support is required to save the patient's life.

2 Diagnosis

The initial evidence of fulminant myocarditis is very similar to that of acute myocarditis, with cardiac shock and circulatory failure as the main crucial points to be handled. On blood chemistry test, blood cardiac troponin is of chief importance for diagnosis.[22] A continuous decrease in the cardiac troponin level suggests that the patient is stabilizing. Changes over time in the ECG are important, since widening of the QRS complex and frequent ventricular arrhythmia indicate that myocarditis is following a fulminant course.[23] Patients with fulminant myocarditis often have a reduced left ventricular ejection fraction. Monitoring of progressive concentric wall thickening and reduction of wall motion in echocardiography over time is important.[8] Fulminant myocarditis can not be identified by histology. Hemodynamics must be continuously evaluated always with echocardiography and guided often by Swan-Ganz catheterization in serious cases.

3 Treatment

Management of acute fulminant myocarditis should focus on prevention of hemodynamic which have been compromised and bridging the patient to natural recovery.[24] Intra-aortic balloon pump (IABP), percutaneous cardiopulmonary support (PCPS), and left ventricular assist device (LVAD) are available as circulatory assistance. Circulatory support should be performed for potentially fatal arrhythmias and low cardiac output. When such devices are used, the following are of great importance: (1) selection of device and timing of introduction, (2) assist volume setting, and (3) prevention of complications[4] (**Figure 2**). In patients refractory to such support, treatment with immunosuppressant may be acceptable. When cardiac dysfunction or heart block does not improve within 3 to 4 days after the initial signs and symptoms of fulminant myocarditis, brief treatment with high-dose corticosteroids or high-dose immunoglobulin may be considered.

2. Giant Cell Myocarditis

1 Background

The clinical presentation of giant cell myocarditis tends to be similar to that of fulminant myocarditis.[25] Allergy and/or autoimmune factors are thought to be involved in giant cell myocarditis.

Table 4. Diagnostic Guidelines for Eosinophilic Myocarditis

If the five minimally required conditions listed below are observed in a patient, eosinophilic myocarditis should be strongly suspected. However, acute myocardial infarction must be excluded by coronary angiography. The diagnosis of eosinophilic myocarditis must be confirmed by endomyocardial biopsy.

1. **Minimally required conditions**
   1) Increased eosinophil count in peripheral blood (≥500/mm^3)[a]
   2) Chest pain, dyspnea, and cardiac symptoms such as palpitations
   3) Elevated enzymes indicating myocardial injury, including creatine kinase-MB and the myocardial constitutive protein, including cardiac troponin T
   4) ECG changes[b]
   5) Transient left ventricular wall thickening[c] and abnormal wall motion on echocardiography
2. **Useful information**
   1) Approximately one-third of patients with eosinophilic myocarditis have allergic conditions (such as bronchial asthma, rhinitis and urticaria).
   2) Approximately two-thirds of patients with eosinophilic myocarditis have previous flu-like symptoms (such as fever, sore throat and cough).
3. **Endomyocardial biopsy**

   Histological findings in eosinophilic myocarditis include eosinophil infiltrates, degranulation of eosinophils, disappearance and fusion of cardiomyocytes, and interstitial edema and fibrosis. Occasionally, endocarditis is observed.

[a] Some patients have an increased eosinophil count in peripheral blood before cardiac symptoms appear, and some patients have cardiac symptoms with a normal eosinophil count, which gradually increases to above 500/mm^3. In the acute phase, the eosinophil count must be determined every 2 to 3 days. However, the eosinophil count increases in a different way in each patient.

[b] ST elevation is observed in approximately 50% and abnormal Q waves are observed in approximately one-third of patients with eosinophilic myocarditis. Atrioventricular block, which occurs in viral myocarditis and idiopathic myocarditis, only rarely occurs in eosinophilic myocarditis.

[c] Left ventricular wall thickening frequently occurs in eosinophilic myocarditis. Its severity varies among patients. Since wall thickening normalizes within 7 to 14 days, the patient must be monitored over time.

ECG, electrocardiography.

2 Diagnosis
Multinucleated giant cells can be recognized in inflammatory lesions in the myocardium. Differentiation from cardiac sarcoidosis is of crucial importance.[26]

3 Treatment
Although there are reports suggesting that corticosteroids and immunosuppressant may be useful for treatment of giant cell myocarditis, the prognosis of giant cell myocarditis is not favorable.[27]

3. Eosinophilic Myocarditis

1 Background
Eosinophilic myocarditis is caused by cytotoxic substances such as eosinophilic cationic protein contained in the granules of eosinophils, which infiltrate into the myocardium. Its etiology varies, and includes allergic conditions, drug hypersensitivity, and parasite infection, though it is usually idiopathic.[28]

2 Diagnosis (Table 4)
Eosinophilic myocarditis is diagnosed based on increased eosinophil counts in peripheral blood and significantly increased eosinophil infiltrates, as well as degranulation and degeneration of cardiomyocytes on biopsy. The timing of the onset of increased eosinophil counts in peripheral blood differs among patients.[29]

3 Treatment
Patients with mild eosinophilic myocarditis recover naturally. If the patient has heart failure or serious arrhythmia, corticosteroid treatment is necessary.[30] To prevent cardiac wall thrombi, anticoagulants are used. The prognosis is favorable.

4. Chronic Myocarditis

1 Background
The concept of chronic myocarditis has not been agreed upon between in Japan and outside of Japan.[3] There are reports suggesting the involvement of viral infection or autoimmunity in chronic myocarditis, though the cause of this condition has not been clearly determined.

2 Diagnosis
The diagnosis of chronic myocarditis is difficult. It begins in a latent fashion, but then becomes chronic.[3] Acute myocarditis rarely becomes chronic. The symptoms and signs of chronic myocarditis are non-specific and similar to those of dilated cardiomyopathy. Histological findings are characterized by mononuclear cell infiltrates, aggregated interstitial fibrosis, and fatty infiltration. ^{67}Ga or ^{99m}Tc pyrophosphate myocardial scintigraphy and CMR imaging may yield findings suggestive of chronic myocarditis. Blood cardiac troponin level has not been proven to be useful in diagnosis.

3 Treatment
Because the etiology of chronic myocarditis is unclear, palliative treatment such as general treatment for heart failure is performed. It has been reported that chronic myocarditis should be treated based on its pathogenesis, such as viral infection or autoimmunity.[31] However, the effectiveness of immunosuppressant has not been confirmed.

5. Pediatric Myocarditis

1 Background
Pediatric patients with myocarditis include 30 to 40% with the fulminant type and 40 to 50% with the acute type. Chronic myocarditis is rare in pediatric patients. Among pediatric patients, many have viral infections of types seen in daily life. However, adenovirus and enterovirus infections are common causes of pediatric myocarditis.[32] The prognosis of myocarditis in pediatric patients is similar to that in adult patients. The prognosis of fulminant myocarditis is particularly unfavorable in pediatric patients.[33]

2 Diagnosis
The typical manifestation of pediatric myocarditis is elevated blood cardiac troponin. Virus can be detected in feces, urine, blood, and sputum. The findings on ECG and echocardiography in pediatric myocarditis are similar to those in adult myocarditis. Echocardiography is the most useful diagnostic tool for pediatric patients.[34] It must be repeated over time, since the disease may progress rapidly over a few hours in pediatric patients. Nuclear medicine techniques with ^{67}Ga or ^{99m}Tc pyrophosphate and CMR may be helpful in diagnosis. An endomyocardial biopsy is relatively safe for older children.

3 Treatment
Once myocarditis is suspected, the patient must be transferred to a facility capable of performing pediatric emergency treatment. The primary goal of treatment is to maintain hemodynamics. Respiratory care and cardiopulmonary circulatory support must be concurrently administered. Treatment with antiviral agents or high dose immunoglobulin should be pathogen-specific.[35]

6. Neonatal Myocarditis

1 Background
Mothers of neonates with myocarditis often have signs of infection a few days prior to delivery, and affected neonates have signs of heart failure before birth.[36] The risk of horizontal vertical infection from the mother to the neonate is high. Two-thirds of neonates with myocarditis have fulminant-type disease, and the mortality rate is high, at 50% or more.[37] Coxsackie B virus infection, which causes fatal myocarditis, accounts for approximately 75% of cases of neonatal myocarditis.[38]

2 Diagnosis
Myocarditis occurs in neonates at birth. Initially, patients are presented with cardiopulmonary signs and symptoms without fever. The signs and symptoms may be non-specific, such as not doing well, feeding difficulty, vomiting, dyspnea, and seizures. Detection of elevated cardiac troponin level is useful for diagnosis. Viruses are isolated in approximately 50% of patients.

3 Treatment
Basically, systemic care and monitoring of the patient is important. Patients must be isolated to prevent spread of infection. Neonates with myocarditis must be immediately transferred to a facility with a neonatal intensive care unit (NICU) or pediatric ICU.

III Diseases Similar to Myocarditis

1. Cardiac Sarcoidosis

1 Background

Cardiac sarcoidosis is a systemic granulomatous disease of unknown etiology. The prognosis is closely related to the severity of cardiac manifestations. Attention has been given to *Propionibacterium acnes* as a cause, since this organism is isolated from tissue affected by sarcoidosis.

2 Diagnosis

According to the guidelines for cardiac sarcoidosis revised in 2006 (**Table 5**),[39] a myocardial abnormality of unknown cause is occasionally diagnosed as cardiac sarcoidosis after endomyocardial biopsy. If cardiac sarcoidosis is suspected, multidisciplinary collaboration is required for systemic screening for sarcoidosis.

3 Treatment[40]

Corticosteroid treatment is performed for patients with cardiac sarcoidosis, regardless of the severity of cardiac dysfunction. In general, treatment starts at 30 mg/day of prednisolone, and is continued at 5 to 10 mg/day. If arrhythmia or heart failure occurs, the patient should be given standard treatment. Use of a pacemaker, implantable cardioverter defibrillator, drug treatment for heart failure, and cardiac resynchronization therapy should also be considered.

Table 5. Diagnostic Guidelines for Cardiac Manifestations of Cardiac Sarcoidosis (2006)

(1) Patient group diagnosed based on histological findings

Histopathological findings include non-necrotizing epithelioid granuloma in the myocardium, and the patient is found to exhibit histopathological changes in organs other than the heart or by clinical signs.

(2) Patient group diagnosed based on clinical signs

Histopathological findings do not include non-necrotizing epithelioid granuloma in the myocardium. Patients are diagnosed with cardiac sarcoidosis when they have histopathological changes in organs other than the heart or by clinical signs, together with the following conditions and one or more of six primary diagnostic criteria.

1. Two or more major criteria
2. One major and two or more minor criteria
   1) Major criteria
      (a) Severe atrioventricular block
      (b) Ventricular septal thinning localized at the basal portion
      (c) Abnormal uptake of ^{67}Ga in the heart on ^{67}Ga scintigraphy
      (d) Left ventricular contraction failure (left ventricular ejection fraction less than 50%)
   2) Minor criteria
      (a) Abnormal ECG: Ventricular arrhythmia (ventricular tachycardia, multi-origin or frequent ventricular premature beats), right bundle branch block, axis deviation, or abnormal Q waves
      (b) Echocardiography: Localized abnormal left ventricular wall motion, or morphological abnormalities (ventricular aneurysm and/or ventricular wall thickening)
      (c) Nuclear medicine techniques: Abnormal blood flow on myocardial perfusion scintigraphy (thallium-201 chloride or technetium-99m methoxyisobutylisonitrile, technetium-99m tetrofosmin)
      (d) Abnormal imaging on delayed gadolinium-enhanced cardiac MRI
      (e) Endomyocardial biopsy: Moderate or more severe myocardial interstitial fibrosis and mononuclear cell infiltrates

Primary diagnostic criteria in tests:

1. Bilateral hilar lymphadenopathy
2. Elevated serum angiotensin converting enzyme
3. Negative tuberculin reaction
4. Abnormal uptake of ^{67}Ga in any organ on scintigraphy
5. An increased lymphocyte count and elevated CD4/CD8 ratio in bronchoalveolar lavage fluid
6. Elevated serum or urinary calcium level

Diagnostic exclusion: Giant cell myocarditis must be excluded.

Additional information:

1. Perform coronary angiography to differentiate from ischemic heart diseases.
2. Cardiac manifestations of sarcoidosis occasionally appear a few years after sarcoidosis in organs other than the heart, have been diagnosed. The patient must therefore be followed with ECG and echocardiography on a regular basis.
3. Abnormal uptake of fluorine-18 fluorodeoxyglucose PET in the heart is a useful diagnostic clue in cardiac sarcoidosis.
4. Some cases of cardiac sarcoidosis are manifested only by complete atrioventricular block without any other minor criteria as listed.
5. Cardiac sarcoidosis may initially manifest itself as pericarditis (as shown by ST segment elevation or pericardial effusion in the ECG).
6. Cases of non-necrotizing epithelioid granuloma are not observed frequently on the endomyocardial biopsy.

^{67}Ga, gallium-67; MRI, magnetic resonance imaging; ECG, electrocardiography; PET, positron emission tomography.
Adapted from *The Japanese Journal of Sarcoidosis and Other Granulomatous Disorders* 2007; **27**: 89–102.