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ORIGINAL ARTICLE

# Characteristic findings of pediatric inpatients with pandemic (H1N1) 2009 virus infection among severe and nonsevere illnesses

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**Abstract** We analyzed the clinical features of inpatients at a Japanese pediatric department who were infected with pandemic (H1N1) 2009 virus. Study participants included 46 children hospitalized from July 2009 to January 2010. Infection with the virus was confirmed using real-time reverse transcriptase polymerase chain reaction (RT-PCR). The epidemic month was October 2009; 34 patients were boys, and median age was 7 years. Pandemic influenza-associated respiratory diseases included pneumonia ($n = 42$), bronchitis ($n = 3$), and pharyngitis ($n = 1$). The median time from onset to admission was 3 days. Children were divided into those with severe ($n = 32$) versus nonsevere illnesses ($n = 14$) according to Japanese guidelines. Significant features in the severe group were younger age, previous asthmatic attack, exacerbation of asthma, decreased oxygen saturation, elevated white blood cell/neutrophil counts and serum lactate dehydrogenase, and longer times from admission to being afebrile and discharged. Both groups showed lymphopenia at admission. Additional infection with *Streptococcus pneumoniae* was frequent in the severe group. Whereas 44 patients received antiviral therapy (median times from onset to initiation 2 days), 32 received antibiotics (median duration 7 days). All children recovered, with a median hospital stay of 8 days. Our observations suggest that history of asthma and preschool age might be risk factors for severe illness. Prompt initiation of antiviral and antibiotic treatments should be considered to prevent development of severe illness.

**Keywords** Pandemic (H1N1) 2009 virus · Pediatric inpatients · Clinical aspects · Disease severity · Laboratory findings · Treatment

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## Introduction

In spring 2009, outbreaks of febrile respiratory infections caused by a novel influenza A (H1N1) virus were reported in Mexico, the USA, and Canada [1]. Patient samples were sent for real-time polymerase chain reaction (PCR) testing to the Centers for Disease Control and Prevention (CDC), which, between 15 April and 5 May 2009, confirmed 642 infections with the virus, now called pandemic (H1N1) 2009 virus (pdmV). Of the 642 patients, 59.8% were younger than 19 years, suggesting that children may be particularly susceptible [1]. The CDC also reported surveillance data concerning pediatric deaths ($n = 36$) associated with pdmV infection between April and August 2009 [2]. On 13 November 2009, the Japan Pediatric Society issued surveillance data concerning pediatric deaths ($n = 60$) associated with pdmV infection [3]. Main

causes of death were rapidly progressive severe pneumonia and sudden death. Additionally, we encountered Japanese children infected with pdmV who developed spontaneous pneumomediastinum [4] or plastic bronchitis [5].

Among 98 patients hospitalized in Mexico due to acute respiratory disease from 24 March to 24 April 2009, 18 had pdmV-infection-associated pneumonia, including five who were younger than 16 years [6]. All patients had fever, cough, dyspnea, increased serum lactate dehydrogenase (LDH), and patchy bilateral pulmonary shadows on roentgenograms. Other common observations were increased creatine kinase and lymphopenia. Mechanical respiratory support was necessary for 12 patients, and seven patients died. Mauad and colleagues [7] observed three distinct patterns of lung histopathology associated with fatal pdmV infection: diffuse alveolar damage, necrotizing bronchiolitis, and intense alveolar hemorrhage.

As clinical risk factors predisposing to severe illness in pdmV infection remain unclear among the Japanese pediatric population, we retrospectively compared differences in clinical features of pediatric inpatients with pdmV infection ($n = 46$) between severely and nonseverely ill children. The patients were hospitalized at a single institution from July 2009 to January 2010. Our aim was to identify predictors of severe disease in Japanese children with pdmV infection so that intensive care could be initiated immediately for children likely to develop severe illness.

## Patients and methods

### Ascertainment of infected inpatients at a pediatrics department, collection of respiratory samples, and clinical information gathering

Active procurement of respiratory specimens from pediatric inpatients with pdmV infection was conducted by the Department of Pediatrics at the National Hospital Organization Tokyo Medical Center. Clinical data and specimens were collected at the department from 1 July 2009 to 31 January 2010. Our research was exempt from institutional review, as previously described [6]. Pneumonia associated with pdmV infection was defined by the presence of both of the following items: (1) influenza-like illnesses having opacities on chest radiographs, and (2) laboratory-confirmation of pdmV [6]. Pharyngitis or bronchitis associated with pdmV infection was diagnosed according to guidelines adopted in 2007 for managing children with respiratory infectious diseases in Japan [8], together with confirmation of pdmV. Indication of hospitalization was the requirement of continuous parenteral infusion for dehydration due to the infection. Patients were classified as having either severe or nonsevere illnesses based on criteria in the same guidelines [9]. Severe illness was defined by the presence of any of the following items: tachypnea; labored breathing, including inspiratory retraction; or percutaneously measured oxygen saturation ($SpO_2$) while breathing under room air at or below 93%. Standardized items of information regarding clinical features and laboratory findings on admission, such as white blood cell (WBC), neutrophil, and lymphocyte count, serum C-reactive protein (CRP) concentration, and serum lactate dehydrogenase (LDH) concentration were obtained from the medical charts of all patients enrolled. Findings in chest roentgenograms on admission were classified by extent of pulmonary infiltrates (localized vs. diffuse) and their distribution (bilateral vs. unilateral; upper, middle, or lower lung field), as judged by expert pediatricians in the department [9]. Judgment as to patients' discharge was performed when they showed improved dehydration and had no need of the parenteral infusion.

### Microbiologic identification

After informed consent was obtained from a patient's family member, nasopharyngeal swab specimens ($n = 46$) were collected from the children before interventions such as antiviral and antibiotic therapy. First, a rapid immunoassay (Quick Chaser Flu A, B; Mizuho Medy, Japan) for detecting pdmV [10] was performed by the pediatricians using the swab samples. In addition, separate samples from nasopharyngeal swabs were sent to the Laboratory of Molecular Epidemiology for Infectious Agents at the Graduate School of Infection Control Sciences of Kitasato University for microbiologic identification. Presence of pdmV in the specimens was confirmed using real-time reverse transcriptase (RT)-PCR, as previously described [4, 5]. Moreover, comprehensive real-time RT-PCR was carried out to identify respiratory coinfections with respiratory syncytial virus (RSV) subgroups A and B, seasonal influenza (SI) viruses A and B, parainfluenza viruses 1–3, rhinovirus, enterovirus, human metapneumovirus, human bocavirus, and adenovirus [11]. Multiplex real-time PCR also was performed to detect *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydophila pneumoniae*, and *S. pyogenes* [12]. Bacterial culture also was carried out, and serotypes of all *S. pneumoniae* strains were determined by the capsular swelling reaction using antiserum purchased from the Statens Serum Institute (Copenhagen, Denmark). Genotypes determining antibiotic resistance were identified for strains of *S. pneumoniae* [13] and *H. influenzae* [14] as previously described. Genetically determined resistance classes for these organisms were specified by attaching the letter ''g'' to indicate this method of identification.

### Statistical analyses

Microsoft Excel (version 2003) was used for data analysis. Patient characteristics, symptoms, physical findings, treatments, and clinical courses were compared between patients with severe and nonsevere illness. We used the chi-square test for analysis of categorical variables and applied the Mann–Whitney *U* test for analysis of continuous variables. WBC, neutrophil and lymphocyte counts, serum CRP, and serum LDH were analyzed using box-and-whisker plots. A $P$ value <0.05 was considered to indicate significance.

## Results

### Ascertainment of infected inpatients in a pediatric department

Forty-six inpatients at the pediatric department were enrolled into this study during a 7-month period (1 July 2009 to 31 January 2010). According to the Japanese guidelines for management of children with respiratory infectious diseases, all children had pdmV-infection-associated respiratory illnesses, including pneumonia ($n = 42$; 91.3%), bronchitis ($n = 3$; 6.5%), and pharyngitis ($n = 1$; 2.2%). Rapid immunoassay to detect SI antigens was carried out for 45 patients—all but one—and real-time RT-PCR assay to confirm pdmV was performed for all patients. Relationships between pdmV rapid antigen test results and RT-PCR results are shown in Table 1. Although the rapid test result was positive for 31 patients (68.9%), the remaining 14 children (31.1%) had negative results using this test. Among patients whose PCR data showed degrees of positivity graded as 1+ to 3+, false negative results with the rapid test were observed in six (13.3%), two (4.4%), and six (13.3%) patients, respectively.

**Table 1** Comparison of results between rapid immunoassay and real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay for pandemic (H1N1) 2009 virus ($n = 45$)

| Rapid antigen test[a] | Real-time RT-PCR[b] | | | Total |
|---|---|---|---|---|
| | 1+ | 2+ | 3+ | |
| Negative | 6 (13.3) | 2 (4.4) | 6 (13.3) | 14 (31.1) |
| Positive | 2 (4.4) | 5 (11.1) | 24 (53.3) | 31 (68.9) |
| Total | 8 (17.8) | 7 (15.6) | 30 (66.7) | 45 (100) |

Number (percent)

[a] The Quick Chaser Flu A, B immunoassay was used as the rapid antigen test

[b] PCR positivity is indicated as follows: 1+, 30 or more cycles; 2+, 26–29 cycles; 3+, 25 or fewer cycles

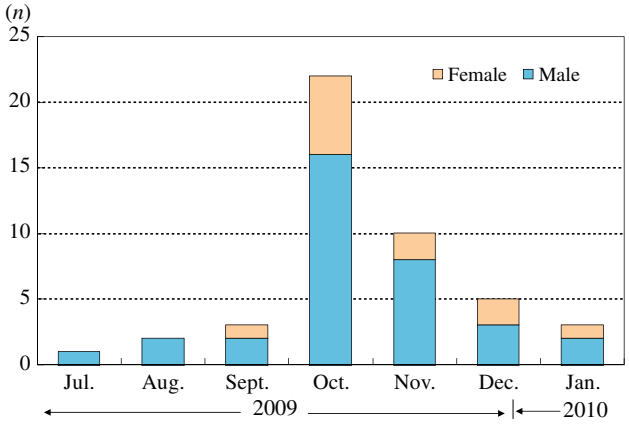


**Fig. 1** Number of inpatients with pandemic (H1N1) 2009 virus infection in a pediatric department from July 2009 to January 2010

Figure 1 shows numbers of infected inpatients by month. From July through September, 1–3 pdmV-infected children were hospitalized per month. The epidemic month ($n = 22$; 47.8%) was October.

### Patient characteristics and clinical presentations

Based on criteria elaborated in the Japanese guidelines, 46 infected inpatients were divided into those with severe ($n = 32$) and nonsevere illnesses ($n = 14$). Patient characteristics, underlying medical conditions, and clinical presentations are compared between severe and nonsevere groups in Table 2.

Overall, 34 children were male (73.9%); gender predominance did not differ between groups. Median patient age was 7 years. We observed a significant difference in median age between severe and nonsevere illnesses (6 vs. 10 years, respectively; $P < 0.05$). Twenty-two patients (47.8%) had an underlying disease, such as bronchial asthma ($n = 17$), atopic dermatitis ($n = 4$), or cerebral palsy ($n = 1$). A history of previous asthmatic attack was present significantly more often in the severe group than in the nonsevere group (15 vs. 2 patients, respectively; $P < 0.01$). Median time from onset to admission was 3 days. Twenty-eight children (60.9%) were hospitalized within 48 h after onset, with no difference evident between groups. We identify 15 instances of exacerbation of asthma (i.e., moderate or severe attacks) (32.6%) and five instances of encephalopathy (delirium and abnormal behavior) (10.9%) as pdmV-infection-associated complications. Exacerbation of asthma was significantly more widespread in the severe than in the nonsevere group (14 vs. 1 patient, respectively; $P < 0.01$). Clinical presentations included fever (>38.0°C), tachypnea, upper respiratory and gastrointestinal tract symptoms, and others. However, no differences in occurrence were evident between groups except

**Table 2** Patient characteristics, clinical presentations, and underlying diseases among children with severe and nonsevere pandemic (H1N1) 2009 virus

| Patient characteristics | Total[a] ($n = 46$) | Nonsevere[a] ($n = 14$) | Severe[a] ($n = 32$) | $P$ value |
|---|---|---|---|---|
| Gender | | | | |
| Male | 34 (73.9) | 10 (71.4) | 24 (75.0) | NS |
| Female | 12 (26.1) | 4 (28.6) | 8 (25.0) | NS |
| Age in years (range) | 7 (0.75–15)[b] | 10 (0.75–15)[b] | 6 (1–14)[b] | <0.05 |
| <1 | 1 (2.2) | 1 (7.1) | 0 (0.0) | NS |
| 1–5 | 15 (32.6) | 3 (21.4) | 12 (37.5) | NS |
| ≥6 | 30 (65.2) | 10 (71.4) | 20 (62.5) | NS |
| Underlying disease | 22 (47.8) | 2 (14.3) | 20 (62.5) | <0.01 |
| Asthmatic attack | 17 (37.0) | 2 (14.2) | 15 (46.9) | <0.05 |
| Hours from onset to admission | 3 (1–9)[b] | 2 (2–7)[b] | 2 (1–9)[b] | NS |
| <24 | 5 (10.9) | 0 (0.0) | 5 (15.6) | NS |
| 24 to <48 | 23 (50.0) | 8 (57.1) | 15 (46.9) | NS |
| ≥48 | 18 (39.1) | 6 (42.9) | 12 (37.5) | NS |
| Clinical presentation | | | | |
| Fever ≥ 38.0°C (%) | 45 (97.8) | 14 (100) | 31 (96.9) | NS |
| Tachypnea | 25 (54.3) | 0 (0.0) | 25 (78.1) | <0.01 |
| Cough, rhinorrhea, sore throat | 40 (87.0) | 10 (71.4) | 30 (93.8) | NS |
| Abdominal pain, diarrhea, vomiting | 6 (13.0) | 1 (7.1) | 5 (15.6) | NS |
| Headache | 4 (8.7) | 1 (7.1) | 3 (9.4) | NS |
| Convulsion | 2 (4.3) | 2 (14.3) | 0 (0.0) | NS |
| Arthralgia | 2 (4.3) | 1 (7.1) | 1 (3.1) | NS |
| $SpO_2$ of ≤93% | 24 (52.2) | 1 (7.1) | 23 (71.9) | <0.01 |

$SpO_2$ percutaneously measured oxygen saturation while breathing room air, *NS* not significant

[a] Data are expressed as patient numbers (followed by percentages except as indicated)

[b] Median (range)

for tachypnea and room-air $SpO_2$ of 93% or less (both $P < 0.01$). Unilateral infiltrates in right or left lower lung fields occurred in 21 patients (50%). We observed no differences in chest roentgenographic findings between the two groups.

## Results of clinical laboratory test

Figure 2 shows blood test results, including WBC, neutrophil, and lymphocyte counts as well as serum CRP and LDH concentrations on admission, according to patient age 5 years or younger versus 6 years or older, and also disease severity. In children 6 years or older, WBC, neutrophil, and LDH values were significantly higher in the severe than in the nonsevere group ($P < 0.01$), whereas we found no differences in lymphocyte count or CRP concentration between the two groups.

## Treatment, inpatient course, and disease outcome

Information regarding treatment and inpatient course is given in Table 3. Twenty-seven children with severe illness (84.4%) required oxygen supplementation (median duration 2 days), whereas no patient with nonsevere illness needed oxygen administration. Eight patients (17.4%), all with severe illness, received corticosteroids intravenously for an asthma attack. A bronchodilator was given by inhalation to two children (4.3%).

Median time from onset to initiation of antiviral therapy was 2 days, showing no differences between groups. Forty-four children (95.7%) received antiviral treatment with either oseltamivir ($n = 33$) or zanamivir ($n = 11$) for 5 days. Antibiotics were administered to 32 patients (69.6%; median duration 7 days). Antibiotics included sulbactam (SBT)/ampicillin (ABPC, $n = 18$), azithromycin (AZM) or clarithromycin ($n = 7$), cefotaxime or ceftriaxone (CTRX, $n = 3$), ABPC ($n = 1$), meropenem ($n = 1$), CTRX and AZM in combination ($n = 1$), and SBT/ABPC and AZM in combination ($n = 1$). No differences in antibiotic use or median treatment duration were noted between groups. Time from admission to being afebrile was significantly longer in the severe group than in the nonsevere group ($P < 0.01$). No deaths occurred, and all patients recovered. Hospital stay was longer in the severe group (median 8 days) than in the nonsevere group (6 days; $P < 0.01$).

## Detection of other microorganisms

Figure 3 compares groups concerning coinfection with other organisms, including respiratory viruses, *S. pneumoniae*, *H. influenzae*, *Staphylococcus aureus*, and other bacteria. Other respiratory viruses were detected in six

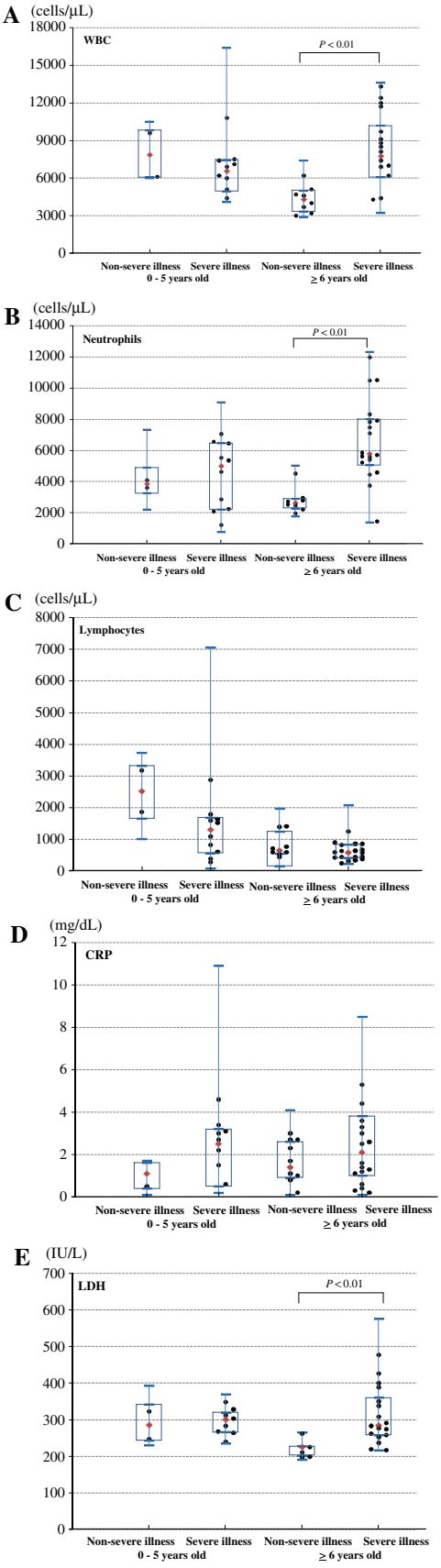


**Fig. 2** Laboratory data on admission, including white blood cell (*WBC*) count (**a**), neutrophil count (**b**), lymphocyte count (**c**), serum C-reactive protein (*CRP*) concentration (**d**), and serum lactate dehydrogenase (*LDH*) concentration (**e**). Normal range for WBC (cells/μl): <1 year, 7,000–15,000; 1–5 years, 7,000–11,000; 6 years or older, 6,500–10,000. Normal range for neutrophils (cells/μl): <1 year, 4,000–8,000; 1–5 years, 2,500–5,500; 6 years or older, 3,000–5,000. Normal range for lymphocytes (cells/μl): <1 year, 4,000–11,000; 1–5 years, 3,000–7,000; 6 years or older 2,500–4,500. Normal upper limits for LDH (IU/L) and CRP (mg/dl) are 400 and 0.4, respectively. The lower limit, median, and upper limit within each *box* correspond to the 25%, 50% (*red diamond*), and 75% percentiles, respectively; half of the cases are included in a *box*. A *vertical line* extending from each box is used to represent 1.5 times the quartile deviation

swab specimens (13.0%), including rhinovirus ($n = 2$), RSV subgroup B ($n = 2$), enterovirus ($n = 1$), and rhinovirus in combination with human bocavirus ($n = 1$). No difference in viral detection was evident between groups.

*S. pneumoniae* was isolated from 17 swab samples (37.0%); detection was significantly more frequent in the severe group than in the nonsevere group ($P < 0.05$). Coinfection with *S. pneumoniae* and *H. influenzae* was confirmed in 11 samples (23.9%). *H. influenzae* and *S. aureus* were isolated from 12 (26.1%) and 11 (23.9%) specimens, respectively, showing no difference in detection between these organisms. Serotypes and genotypes for antibiotic resistance in *S. pneumoniae* and *H. influenzae* isolates are shown in Table 4. Serotyping of *S. pneumoniae* strains indicated type 19 ($n = 5$), type 6 ($n = 2$), and others; genotyping showed penicillin-sensitive *S. pneumoniae* (gPSSP, $n = 4$), penicillin-insensitive *S. pneumoniae* (gPISP, $n = 8$), and penicillin-resistant *S. pneumoniae* (gPRSP, $n = 4$). *H. influenzae* isolates seemed mostly nontypeable, except for one type b isolate; genotyping for resistance demonstrated β-lactamase nonproducing, ampicillin-resistant (BLNAR) *H. influenzae* (gBLNAR, $n = 2$), β-lactamase producing, amoxicillin-clavulanic acid-resistant (BLPACR-I) *H. influenza* (gBLPACR-I, $n = 1$), and β-lactamase producing, amoxicillin-clavulanic acid-resistant (BLPACR-II) *H. influenza* (gBLPACR-II, $n = 2$).

## Discussion

The pdmV pandemic that first broke out in Mexico [1] is a matter of worldwide concern. According to an updated report from the World Health Organization (WHO) [15], approximately 17,000 people around the world had died of pdmV infection by the end of January 2010. In Japan, the epidemic period began in the summer of 2009 [16] and largely abated by the end of January 2010. Many Japanese children with pdmV-infection-associated encephalopathy

**Table 3** Treatment and inpatient course

| Treatments and inpatient course | Total[a] ($n = 46$) | Nonsevere[a] illnesses ($n = 14$) | Severe illnesses[a] ($n = 32$) | $P$ value |
|---|---|---|---|---|
| Oxygen supplementation | 27 (58.7) | 0 (0.0) | 27 (84.4) | <0.01 |
| Duration (days) | 3 (1–5)[b] | 0 | 2 (1–5)[b] | NS |
| Days from onset to initiation of antiviral treatment | 2 (1–7)[b] | 2 (1–7)[b] | 2 (1–7)[b] | NS |
| Antiviral treatment | 44 (95.7) | 14 (100) | 30 (93.8) | NS |
| Antibiotic treatment | 32 (69.6) | 10 (71.4) | 22 (68.8) | NS |
| Duration (days) | 7 (3–8)[b] | 6 (4–7)[b] | 7 (3–8)[b] | NS |
| Corticosteroid therapy | 8 (17.3) | 0 | 8 (25.0) | NS |
| Days from admission to be afebrile | 2 (1–6)[b] | 1 (1–3)[b] | 2 (1–6)[b] | <0.01 |
| Duration of fever in hospital (days) | 5 (3–12)[b] | 4 (3–8)[b] | 5 (3–12)[b] | NS |
| Duration of hospital stay (days) | 8 (5–11)[b] | 6 (5–9)[b] | 8 (5–11)[b] | <0.05 |

[a] Data are expressed as patient numbers (followed by percentages except as indicated)

[b] Median (range)

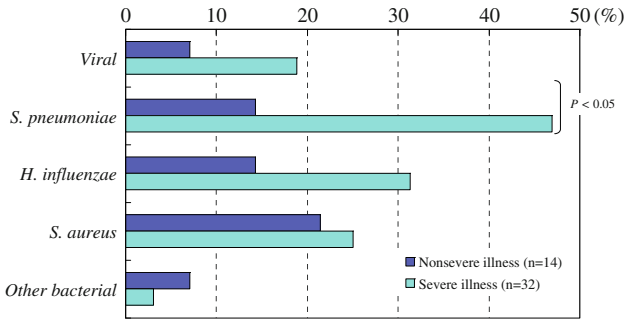


**Fig. 3** Differences in detection of other respiratory viruses and respiratory bacteria in pediatric inpatients with pandemic (H1N1) 2009 virus infection associated with severe and nonsevere illnesses

or rapidly progressive respiratory distress were observed in this epidemic period [17]. However, pdmV infection in Japan had caused only 198 deaths by the end of March 2010 [18], representing a relatively low mortality rate (deaths per 100,000 population) compared with the Western Hemisphere and Europe. Different disease outcomes might reflect differences in care delivery between countries, including health insurance systems. In addition, individual environments of medical resources, including antiviral and antibiotic reagents, might lead to distinction of disease outcomes, since prompt initiation of antiviral and antibiotic treatments would help prevent the development of severe illness. As detailed clinical descriptions of Japanese pdmV-infected patients have been limited so far, we set out to identify differences in patient backgrounds, clinical presentations, laboratory data, treatments, and inpatient courses between children with severe and nonsevere illnesses.

As stated in "Results", the epidemic month of pdmV infection was October 2009. After the number of pdmV-infected patients had decreased, children with RSV infection in the absence of SI were frequent in our Japanese community; interestingly, this epidemic season for RSV infection was delayed 2–3 months compared with most years (data not shown). The median age of pdmV inpatients was 7 years in our study, and the significant difference in median age between severe and nonsevere illnesses (6 vs. 10 years) was found. The Japan Pediatric Society [3] reported the pdmV epidemic among children aged 5 years or younger and the seven deaths in this population in November 2009. Therefore, pediatric patients predisposed to severe pdmV illness seem to be of preschool age.

Similarly to previously reported findings [19], about half of pdmV inpatients had underlying medical conditions (mainly asthma). The other half had no underlying diseases, suggesting that pdmV was pathogenic, even in isolation. Characteristic features of patients with severe illness were lower age, previous history of asthma, exacerbation of asthma, decreased oxygen saturation, elevated WBC/neutrophil counts and serum LDH concentrations, and longer times from admission to be afebrile and discharge from hospital. Further analysis of inflammatory biomarker and immunoglobulin E concentrations in blood is needed.

As described previously [1], pdmV infection is difficult to distinguish from SI based on clinical symptoms alone. One rather consistent laboratory feature among our patients was lymphopenia (fewer than 1,000 cells/μl), which has been reported to be a diagnostic biomarker in adults with either pdmV infection [6, 20] or SI [21]. When examining patients with lymphopenia on day 1–2 of illness, clinicians should be aware of both pdmV infection and SI as diagnostic possibilities.

The median time from onset to initiation of antiviral therapy was 2 days; 44 patients (95.7%) received antiviral treatment. This finding differed considerably from reported

**Table 4** Genetic resistance types and capsule types of *Streptococcus pneumoniae* and *Hemophilus influenzae* isolates

| Strain no. | Bacterial numbers[a] | Genotype | Serotype[c] | Percent |
|---|---|---|---|---|
| *Streptococcus pneumoniae* | | | | |
| 1 | +++ | gPSSP | 10A | 21.4 |
| 2 | +++ | gPSSP | 11A | |
| 3 | +++ | gPSSP | D[b] | |
| 4 | +++ | gPSSP | D[b] | |
| 5 | +++ | gPISP(*pbp2x*) | 3 | 57.1 |
| 6 | ++ | gPISP(*pbp2x*) | 19A | |
| 7 | +++ | gPISP(*pbp2x*) | 19A | |
| 8 | +++ | gPISP(*pbp2x*) | 6A | |
| 9 | +++ | gPISP(*pbp2x*) | 14 | |
| 10 | +++ | gPISP(*pbp1a* + *2x*) | NT | |
| 11 | ++ | gPISP(*pbp1a* + *2x*) | 19 | |
| 12 | +++ | gPISP(*pbp2x* + *2b*) | NT | |
| 13 | ++ | gPRSP | 19F | 21.4 |
| 14 | +++ | gPRSP | 19A | |
| 15 | +++ | gPRSP | 6B | |
| 16 | +++ | gPRSP | NT | |
| *Haemophilus influenzae* | | | | |
| 1 | +++ | gBLNAS | NT | 44.4 |
| 2 | +++ | gBLNAS | NT | |
| 3 | +++ | gBLNAS | NT | |
| 4 | +++ | gBLNAS | NT | |
| 5 | +++ | gBLNAR | b | 22.2 |
| 6 | ++ | gBLNAR | NT | |
| 7 | +++ | gBLPACR-II | NT | 22.2 |
| 8 | +++ | gBLPACR-II | NT | |
| 9 | +++ | gBLPACR-I | NT | 11.1 |

*NT* nontypeable

[a] Bacterial numbers are represented as follows: ++, $10^3$ to $<10^4$/sample; +++, $\geq 10^4$/sample

[b] Serotype D contains 3 capsule polysaccharide types (16, 36, and 37)

[c] Serotype b, capsule type b

observations in other countries. Perez-Padilla and colleagues [6] stated that no patients with pneumonia and respiratory distress in their Mexican study had received oseltamivir before admission. Jain et al. [22] reported that only 39% of hospitalized patients in the USA had received antiviral therapy within 2 days after onset, but ultimately, 75% of patients were given antiviral agents (median interval after onset, 3 days). Prompt initiation of antiviral treatment appears to be associated with less disease progression and favorable outcomes.

When postmortem lung specimens from 77 pdmV-infected patients were examined from 1 May to 20 August 2009 [23], bacterial coinfection (*S. pneumoniae*) was observed in samples from ten patients (13.0%). Similarly, *S. pneumoniae* was isolated from the 17 swab samples (37.0%) in our study. This detection rate was significantly higher for severe than for nonsevere illness, although whether the finding represented colonization or coinfection was not determined. Antibiotics were administered to 32 patients (69.6%) in our investigation. Our data suggest a role for empiric antibiotic therapy against secondary bacterial infection in Japanese pediatric inpatients with pdmV infection.

Infections with multiple pathogens have been reported in hospitalized children with acute respiratory infection [24]. Viral coinfection occurred predominantly in August and was more frequent in children between 3 and 6 years old. A significantly higher proportion of SI viruses A/B and parainfluenza virus 1 was detected in samples with two or more pathogens per sample than in samples with a single pathogen. We found no difference in viral coinfection with pdmV and other respiratory viruses between severe and nonsevere illnesses. In fact, whether viral coinfection is likely to result in severe illness remains unknown. The significance of such coinfection should be examined using a comprehensive real-time RT-PCR assay when the next pdmV infection occurs.

Several guidelines for managing pdmV infection have been developed in various countries [25–27]. We could add that our data suggest a history of asthma episode and preschool age of 6 years or younger might be risk factors for severe illness and that pediatricians should consider prompt initiation of antiviral and antibiotic treatments to prevent development of severe illness. A multi-institutional clinical study including a large number of patients will be needed in the future to confirm or refine our findings.

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