Risk factors of severe novel influenza A (H1N1) infections in hospitalized children

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Background/Purpose: Data on hospitalized novel influenza A (H1N1) infected children are limited and urgently in demand. We conducted a clinical study to identify clinical features and risk factors associated with severe novel H1N1 infections of children in Taiwan.

Methods: From July 24, 2009 to December 4, 2009, data from 61 hospitalized children infected with 2009 novel H1N1 were collected. Demographics, underlying medical conditions, clinical data, receipt of antiviral therapy, need for intensive care and outcome were analyzed to identify clinical features and risk factors of severe infections.

Results: Of the 61 inpatients, the male to female ratio was 41 to 20 and the most common age group was between 6 and 12 years (36%). Almost all (98%) patients had fever, 53 (87%) patients received oseltamivir treatment and 51% of them received oseltamivir within 48 hours. Fourteen (23%) needed intensive care and 3 died. Obesity (a Body Mass Index ≥ 25 kg/m² in children ≥ 2 years of age, or a body weight ≥ the 95th percentile in children <2 years of age), dyspnea, C-reactive protein (CRP) > 3 mg/dL, pleural effusion, and delayed antiviral therapy were significantly associated with the need for intensive care and/or death.

Conclusion: Obesity, dyspnea, CRP > 3 mg/dL, pleural effusion, and delayed antiviral therapy are significantly associated with severe novel H1N1 infections in children.
Introduction

Since April 15, 2009 and April 17, 2009, when the first two cases of novel influenza A (H1N1) infection were identified in two southern California counties, cases of H1N1 were documented throughout the world with most occurring in the United States and Mexico at that time. Since then, the virus has spread worldwide and there have been more than 213 countries and overseas territories or communities that reported laboratory-confirmed cases of pandemic influenza H1N1 2009. Given the evidence of sustained community-level outbreaks of novel H1N1 in more than one World Health Organization (WHO) region, the WHO declared a global pandemic of influenza A (H1N1) on June 11, 2009, designating the virus “pandemic influenza A (H1N1) 2009 virus.”

Children younger than 5 years or with certain chronic medical conditions are at increased risk for complications and death from seasonal influenza. Frequently reported complications due to seasonal influenza include pneumonia, seizure, and bronchitis in hospitalized children. However, data on hospitalized novel H1N1 virus infected children are limited and urgently in demand. Therefore, we conducted a clinical study to identify clinical features and risk factors associated with severe novel H1N1 infections of pediatric patients who were hospitalized for the treatment of novel H1N1 influenza in Taiwan.

Methods

Identification of novel H1N1 patients

At National Taiwan University Hospital in Taiwan, we included patients who were hospitalized for laboratory-confirmed novel H1N1 virus infections. Laboratory-confirmed novel H1N1 virus infection was defined as either positive influenza A virus isolation followed by positive novel H1N1 real-time reverse transcription-polymerase chain reaction (RT-PCR), or positive rapid influenza A test (QuickVue A þ B test, Quidel, San Diego, CA, USA) followed by a positive novel H1N1 real-time RT-PCR. Virus isolation was performed following standardized protocol in the virology laboratory of this tertiary medical center.

Data collection and study design

From July 24, 2009 to December 4, 2009, the patients were identified through daily review of hospitalized pediatric patients and their virological results at National Taiwan University Hospital. We collected basic information on demographics, underlying medical conditions, clinical signs and symptoms, laboratory data, influenza-associated complications such as invasive bacterial infections (defined as isolation of a bacterial pathogen from blood or cerebrospinal fluid), pneumonia (defined as lung infiltrate or consolidation on chest X-ray), need for intensive care unit (ICU) care, receipt of antiviral therapy and other treatment, and final outcome. Underlying medical conditions that increased an individual’s risk for complications from influenza were abstracted from the admission history and physical notes, and included the following: asthma, chronic cardiovascular disease, immunosuppressive condition or therapy, and neuromuscular or cognitive dysfunction (broadly defined to include developmental delay, spinal cord injuries or other forms of paralysis, cerebral palsy, and autism). Secondary bacterial infections were defined as positive bacterial blood culture, positive urine pneumococcal antigen test, or positive bacterial culture obtained from bronchoalveolar lavage.

For time calculations, the day of admission was considered to be hospital day 0. The Body Mass Index (BMI) was calculated by the formula: weight in kilograms divided by the square of the height in meters. Obesity was defined as a BMI $\geq 25$ kg/m² in children $\geq$ 2 years of age, or a body weight $\geq$ the 95th percentile of the normal range in children <2 years of age.

We divided the patients into two groups, one group consisted of patients who did not need intensive care and survived while the other group consisted of patients who needed intensive care and/or died. The second group was defined as the severe novel H1N1 infection group. We then compared these two groups to identify risk factors for severe novel H1N1 infection in children.

Statistics

Comparisons of selected parameters were performed using the chi-square test with Yates correction for categorical variables and by the Mann–Whitney U test for continuous variables. All statistical analyses were performed with SPSS version 16.0 (SPSS, Chicago, IL) for Windows. A p value <0.05 was considered statistically significant.

This study was approved by the ethics committee of National Taiwan University Hospital.

Results

Demographics and comorbidities

From July 24, 2009 to December 4, 2009, 61 children infected with the 2009 H1N1 virus were hospitalized in National Taiwan University Hospital. Table 1 shows patient demographics and comorbidities. The most common age group was 6 to 12 years (38%). Of the 61 patients, 25 (41%) had underlying medical conditions. Immunocompromised patients or those with immunosuppression status were the most common underlying medical condition seen in children (21%), cardiovascular disease was the second most common (8%), and neurocognitive, neuromuscular, or seizure disorders were seen in 7% of all patients.

Three children (5%) were obese. Two of the obese children passed away and one was admitted to the ICU; therefore, obesity in children was significantly associated with the need for ICU care and/or death ($p = 0.008$).

Clinical manifestations and laboratory findings

Symptoms at presentation are listed in Table 2. Shortness of breath was found in 26% of all patients, 17% in patients belonging to the group without ICU care, and 57% in those belonging to the group with ICU care and/or death. Of all the
symptoms, only shortness of breath was significantly associated with the need for ICU care and/or death ($p = 0.008$).

Table 3 shows the laboratory data and radiographic characteristics. We found that 50% of 12 patients with ICU care and/or death had a C-reactive protein (CRP) value $>3$ mg/dL, but only 11% of patients without ICU care had a CRP value $>3$ mg/dL ($p = 0.008$). Therefore, a higher CRP level was also a significant parameter for severe novel H1N1 infection. More secondary bacterial infections were found in the group with ICU care and/or death ($p = 0.03$).

Of the 56 patients who underwent chest radiography, 45 (80%) patients had findings that were consistent with pneumonia. Pleural effusion predicted severe novel H1N1 infection and occurred significantly more frequently in the group with ICU care and/or death ($p = 0.02$).

### Diagnosis, treatment and outcome

Of the 61 patients, 14 (21%) were admitted to the ICU and 3 died. Among these 14 patients with severe novel H1N1 infections, six required mechanical ventilation, two had acute respiratory distress syndrome (ARDS), and two had a clinical diagnosis of sepsis and shock.

Table 4 shows patient treatments: 53 (87%) received oseltamivir antiviral drug treatment. The median time from the onset of illness to the initiation of antiviral therapy was 2 days (range, 0–11 days); 51% of patients received antiviral therapy within 48 hours after the onset of symptoms. The group with ICU care and/or death received antiviral therapy significantly later than the group without ICU care ($p = 0.035$). Thirty-seven (61%) patients also received

### Table 1  Demographics and comorbidities.

<table>
<thead>
<tr>
<th>Variables(^a)</th>
<th>All ($n = 61$)</th>
<th>No need of intensive care and recovery ($n = 47$)</th>
<th>With intensive care and/or death ($n = 14$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female, no.</td>
<td>41/20</td>
<td>30/17</td>
<td>11/3</td>
<td>0.48</td>
</tr>
<tr>
<td>Age, y</td>
<td>Median (range)</td>
<td>7.3 (0.1–18.1)</td>
<td>7.1 (0.1–17.3)</td>
<td>8.1 (0.6–18.1)</td>
</tr>
<tr>
<td></td>
<td>&lt;1</td>
<td>8 (13)</td>
<td>6 (13)</td>
<td>2 (14)</td>
</tr>
<tr>
<td></td>
<td>1–2</td>
<td>8 (13)</td>
<td>5 (11)</td>
<td>3 (21)</td>
</tr>
<tr>
<td></td>
<td>3–5</td>
<td>8 (13)</td>
<td>7 (15)</td>
<td>1 (7)</td>
</tr>
<tr>
<td></td>
<td>6–11</td>
<td>22 (36)</td>
<td>18 (38)</td>
<td>4 (29)</td>
</tr>
<tr>
<td></td>
<td>12–18</td>
<td>15 (25)</td>
<td>11 (23)</td>
<td>4 (29)</td>
</tr>
<tr>
<td>BMI</td>
<td>17.7 (±3.6)</td>
<td>17.2 (±2.8)</td>
<td>19.3 (±5.5)</td>
<td>0.35</td>
</tr>
<tr>
<td>Obesity(^b)</td>
<td>3/50 (6)</td>
<td>0/39 (0)</td>
<td>3/11 (27)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Comorbidities

| Any | 25 (41) | 17 (36) | 8 (57) | 0.28 |
| Asthma | 2 (3) | 1 (2) | 1 (7) | 0.94 |
| Immunosuppression | 13 (21) | 10 (21) | 3 (21) | 0.72 |
| CV disease | 5 (8) | 3 (6) | 2 (14) | 0.70 |
| CNS anomaly | 4 (7) | 2 (4) | 2 (14) | 0.47 |

BMI = body mass index; CNS = central nervous system; CV = cardiovascular system; ICU = intensive care unit; SD = standard deviation.

\(^a\) Data were expressed as number (%) or mean (±SD).

\(^b\) Body weight ≥ 95th percentile in children <2 years of age or BMI ≥ 25 kg/m² in children ≥ 2 years of age.

### Table 2  Clinical symptoms and signs of the patients.

<table>
<thead>
<tr>
<th>Symptoms(^a)</th>
<th>All ($n = 61$)</th>
<th>No need of intensive care and recovery ($n = 47$)</th>
<th>With intensive care and/or death ($n = 14$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>60 (98)</td>
<td>47 (100)</td>
<td>13 (93)</td>
<td>0.52</td>
</tr>
<tr>
<td>Fever ≥ 3 d</td>
<td>33 (54)</td>
<td>23/47 (49)</td>
<td>10/14 (71)</td>
<td>0.24</td>
</tr>
<tr>
<td>Cough</td>
<td>58 (95)</td>
<td>45 (96)</td>
<td>13 (93)</td>
<td>0.79</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>34 (56)</td>
<td>30 (64)</td>
<td>4 (29)</td>
<td>0.59</td>
</tr>
<tr>
<td>Sore throat</td>
<td>18 (30%)</td>
<td>15 (32)</td>
<td>3 (21)</td>
<td>0.67</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (11%)</td>
<td>7 (15)</td>
<td>0 (0)</td>
<td>0.29</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (20%)</td>
<td>10 (21)</td>
<td>2 (14)</td>
<td>0.85</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (13%)</td>
<td>9 (15)</td>
<td>1 (7)</td>
<td>0.51</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8 (13%)</td>
<td>7 (15)</td>
<td>1 (7)</td>
<td>0.76</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>16 (26%)</td>
<td>8 (17)</td>
<td>8 (57)</td>
<td>0.008</td>
</tr>
<tr>
<td>Malaise</td>
<td>18 (30%)</td>
<td>15 (32)</td>
<td>3 (21)</td>
<td>0.67</td>
</tr>
<tr>
<td>Myalgia</td>
<td>10 (16%)</td>
<td>10 (21)</td>
<td>0 (0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Seizure</td>
<td>4 (7%)</td>
<td>2 (4)</td>
<td>2 (14)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

\(^a\) Data were expressed as number (%).
antibiotic treatment during hospitalization: 50% of patients without ICU care and 100% of patients with ICU care and/or death \((p = 0.002)\).

### Risk factors associated with severe novel H1N1 infections

In comparison with the group without ICU care, the group with severe novel H1N1 infections had a significantly higher percentage of obesity, shortness of breath, CRP levels \(>3 \text{ mg/dL}\), secondary bacterial infections, and radiographically confirmed pleural effusion. In addition, the time interval between the onset of symptoms and the start of antiviral therapy was significantly longer in the group with severe novel H1N1 infections. This group had a significantly lower percentage of influenza-like illness, which might reflect delayed suspicion or diagnosis of influenza, resulting in deferred antiviral therapy. This group was also more likely to receive antimicrobial agents.

### Table 3  Laboratory data and radiographic characteristics.

<table>
<thead>
<tr>
<th>Laboratory data (^a)</th>
<th>All ((n = 61))</th>
<th>No need of intensive care and recovery ((n = 47))</th>
<th>With intensive care and/or death ((n = 14))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC &lt; 5000 cells/(\mu)L</td>
<td>28/61 (46)</td>
<td>21/47 (45)</td>
<td>7/14 (50)</td>
<td>0.96</td>
</tr>
<tr>
<td>WBC &gt; 11000 cells/(\mu)L</td>
<td>9/61 (15)</td>
<td>5/47 (11)</td>
<td>4/14 (29)</td>
<td>0.22</td>
</tr>
<tr>
<td>Lymphocyte &lt; 1000 cells/(\mu)L</td>
<td>23/61 (38)</td>
<td>17/47 (36)</td>
<td>6/14 (43)</td>
<td>0.89</td>
</tr>
<tr>
<td>Monocyte &lt; 200 cells/(\mu)L</td>
<td>13/61 (21)</td>
<td>11/47 (23)</td>
<td>2/14 (14)</td>
<td>0.72</td>
</tr>
<tr>
<td>Anemia (^b)</td>
<td>5/61 (8)</td>
<td>3/47 (6)</td>
<td>2/14 (14)</td>
<td>0.70</td>
</tr>
<tr>
<td>Platelets &lt; 100,000 cells/(\mu)L</td>
<td>5/61 (8)</td>
<td>4/47 (9)</td>
<td>1/14 (7)</td>
<td>0.70</td>
</tr>
<tr>
<td>AST &gt; 100 U/L</td>
<td>3/51 (6)</td>
<td>2/41 (5)</td>
<td>1/10 (10)</td>
<td>0.90</td>
</tr>
<tr>
<td>ALT &gt; 100 U/L</td>
<td>1/38 (3)</td>
<td>1/28 (4)</td>
<td>0/10 (0)</td>
<td>0.59</td>
</tr>
<tr>
<td>CRP &gt; 3 mg/dL</td>
<td>11/58 (19)</td>
<td>5/46 (11)</td>
<td>6/12 (50)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**Novel H1N1 virus study**

- Positive, virus isolation 37/54 (69) 32/44 (73) 5/10 (50) 0.31
- Positive, rapid test 36/48 (75) 30/36 (83) 6/12 (50) 0.05
- Positive, both virus isolation and rapid test 24/42 (57) 21/34 (62) 3/8 (38) 0.40
- HAI titer \(>40\) 22/31 (71) 19/26 (73) 3/5 (60) 0.96

**Secondary bacterial infection** \(^c\)

- 6/61 (10) 2/47 (4) 4/14 (29) 0.03

**Chest X-ray**

- Clear 11/56 (20) 9/42 (21) 2/14 (14) 0.85
- Infiltration 39/56 (70) 33/42 (79) 6/14 (43) 0.03
- Patch 9/56 (16) 4/42 (10) 5/14 (36) 0.06
- ARDS 1/56 (2) 0/42 (0) 1/14 (7) 0.56
- Pleural effusion 3/56 (5) 0/42 (0) 3/14 (21) 0.02

ALT = alanine aminotransferase; ARDS = acute respiratory distress syndrome; AST = aspartate transaminase; CRP = C-reactive protein; CXR = chest X-ray; HAI = hemagglutination inhibition; Hb = hemoglobin; ICU = intensive care unit; Lab = laboratory; WBC = white blood cell.

\(^a\) Data were expressed as the number of positive results/number tested (%).

\(^b\) Anemia was defined as Hb < 10 mg/dL.

\(^c\) Secondary bacterial infection refers to the evidence of a positive bacterial culture from the sterile site or positive urine pneumococcus antigen: sputum from bronchoaveolar lavage — one with methicillin-resistant *Staphylococcus aureus*; one with *Acinetobacter baumannii*; one with *Moraxella catarrhalis*; three positive for urine pneumococcus antigen in two patients with pneumonia and one patient with acute sinusitis.

### Table 4  Treatment of patients.

<table>
<thead>
<tr>
<th>Type of treatment (^a)</th>
<th>All ((n = 61))</th>
<th>No need of intensive care and recovery ((n = 47))</th>
<th>With intensive care and/or death ((n = 14))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiviral treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>53/61 (87)</td>
<td>40/47 (85)</td>
<td>13/14 (93)</td>
<td>0.76</td>
</tr>
<tr>
<td>(\leq 2) days after onset</td>
<td>27/53 (51)</td>
<td>23/40 (58)</td>
<td>4/13 (31)</td>
<td>0.18</td>
</tr>
<tr>
<td>Days from onset</td>
<td>2 (0–11)</td>
<td>2 (0–8)</td>
<td>4 (1–11)</td>
<td>0.035</td>
</tr>
<tr>
<td><strong>Antibiotic treatment</strong></td>
<td>37/61 (61)</td>
<td>23/47 (49)</td>
<td>14/14 (100)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

\(^a\) Data were expressed as the number of patients/total number of patients (%) or as median (range).
which may reflect the disease severity and increased likelihood of secondary bacterial infections.

Discussion

We reported on hospitalized pediatric patients infected with the 2009 novel H1N1 influenza virus during the 2009 pandemic in Taiwan. The pandemic strain of the H1N1 virus caused severe illness in the pediatric group, which included pneumonia, ARDS, shock, and encephalitis, resulting in ICU admission of 21% of patients and death in 5% of patients. This finding is similar to another study conducted in Argentina in the pediatric group and a nationwide study conducted in the United States.7–11

In our study, we found that obesity was a risk factor associated with ICU admission and/or death in the pediatric group. In a nationwide study in the US, it was found that the prevalence of morbid obesity (26%) was higher in hospitalized adult H1N1 patients than in the estimated adult U.S. population (5%).7 Another study included 10 patients with novel influenza A (H1N1) virus infection and ARDS at a tertiary-care ICU in Michigan and reported that among these 10 patients, nine were obese (BMI > 30 kg/m²).12 In a mouse model, diet-induced obese mice had significantly higher mortality when they were infected with the seasonal influenza virus compared with their leaner counterparts.13 It is our unique and new finding that obese children may be particularly vulnerable to life-threatening H1N1 infections; clinicians should be aware of the potential of severe novel H1N1 infections in obese children as well as in obese adults. However, because there were only three cases of obese children in our study, we need to conduct more clinical studies or gather further evidence to prove that obesity in children is an important risk factor for severe novel H1N1 infection.

In this study, we found that shortness of breath is a poor indicator for outcome, which is consistent with Jain et al.7 We suggest that novel H1N1 infected patients with shortness of breath or dyspnea should be closely monitored. Regarding our laboratory findings, we found that a higher CRP level could be an indicator for a more severe novel H1N1 disease. The patients in the ICU/death group had significantly higher CRP levels. This phenomenon stands for a more severe inflammation condition in the selected group, which would face a worse outcome.

During the 1957–1958 influenza pandemic, Louria et al reported findings of diffuse bilateral infiltrates in patients with primary influenza viral pneumonia, whereas lobar infiltrates were seen in patients with secondary bacterial infections.14 We noticed that patients without ICU admission tended to present as infiltrates but patients who were admitted to the ICU or died tended to present with a pneumonia patch, ARDS pattern, or pleural effusion, and had more secondary bacterial infections with higher CRP levels.

According to Jain et al,7 the significant variable that was associated with a better outcome for novel H1N1 inpatients was the receipt of antiviral drugs within 2 days after the onset of illness. Louie et al10 also reported similar findings in California. The Centers for Disease Control and Prevention suggested that antiviral treatment is most effective when it is started in the first 48 hours of illness onset.15 In our study, we also found that patients without ICU care had a significantly shorter interval between symptoms onset and oseltamivir administration. Therefore, we suggest that the treatment should be started empirically, based on clinical judgment, as early as possible, even before definitive diagnostic test results become available, i.e., treatment should not wait for laboratory confirmation of influenza.

In conclusion, we found that 21% of hospitalized children infected with novel H1N1 needed ICU care and 5% of them died. Children with obesity, shortness of breath, CRP > 3 mg/dL, pleural effusion, and delayed antiviral therapy carry a higher risk for severe infection and poorer outcome. Cautious monitoring of these parameters and early treatment may improve the outcome.

Acknowledgments

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References


