



The First 100 Hospitalized Severe Complicated Influenza Cases Caused by 2009 Pandemic Influenza A (H1N1) in Taiwan

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Abstract

To understand the features of the severe complicated influenza patients caused by 2009 pandemic influenza A (H1N1), we retrospectively reviewed the medical records of the first 100 laboratory-confirmed cases (by date of onset), analyzed all clinical variables and described their clinical and epidemiologic characteristics.

The cases had onset dates from July 2 to August 29, 2009, half of them were adults and the other half was children. The median age was 16.5 years. Thirty-eight had preexisting medical conditions, 6 of the 50 adults were morbidly obese, 8 of the 50 children were obese, and 2 women were pregnant. The most common initial presentations were fever (99%)

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and cough (93%). Eighty-nine patients had viral pneumonia, 23 were complicated with respiratory failure requiring mechanical ventilation, and 9 were treated with concomitant support by extracorporeal membrane oxygenation. By September 18, 82 patients recovered and were discharged from the hospitals; 9 were still hospitalized; and the remaining 9 patients (including 2 obese patients and one pregnant woman) died. The median time between onset of symptoms and first doctor visit was 1 day, and the median hospital stay for those who had been discharged was 6 days. The average duration from onset of symptoms to the date of rapid testing, admission, or prescription of oseltamivir for patients with onset after August 15 was shorter than those with onset before August 15.

In conclusion, most of the severe complicated influenza patients caused by 2009 pandemic influenza A (H1N1) were children and young to middle-aged adults; overweight and pregnancy posed higher risk to these patients. The preventive and control measure conducted by the public health sector have effectively accelerated diagnosis and treatment. However, quality of medical care remains to be improved to further reduce the number of severe complicated influenza cases and mortality.

Keywords: 2009 pandemic influenza A (H1N1), severe complicated influenza infection, retrospective analysis

Introduction

The outbreak of novel influenza A (H1N1) virus began in April 2009 and became a pandemic in the subsequent months. From April 27, 2009 to June 19, 2009, in response to this emerging disease, Taiwan Centers for Disease Control (Taiwan CDC) classified infection with novel influenza A (H1N1) virus as a Category 1 notifiable infectious disease. By June 11,



2009, the World Health Organization (WHO) had received reports of 28,774 confirmed patients. Because most patients with infection experienced mild symptoms and made a rapid recovery, WHO described the pandemic as one with moderate severity. Therefore, Central Epidemic Command Center (CECC) removed the disease from the list of Category 1 notifiable diseases on June 19. However, patients infected by novel H1N1 virus with severe complications were managed and reported as other influenza infection with severe complications, a Category 4 notifiable infectious disease [1].

The number of deaths and critically ill patients in Taiwan gradually increased since early July. To understand their features, we retrospectively reviewed the medical records of the first 100 laboratory-confirmed cases, analyzed and described the epidemiologic and clinical characteristics.

Methods

From June 21 to August 29, a total of 100 hospitalizations associated with 2009 pandemic H1N1 virus infection were reported. Patients were enrolled in this study if they tested positive for novel H1N1 infection by RT-PCR and had at least one clinical relevant complication, including involvement of pulmonary, neurologic systems, myocarditis, pericarditis, or invasive bacterial infection. We retrospectively reviewed the medical records; baseline characteristics, underlying health conditions, clinical presentation, radiologic images, laboratory findings, hospital course, treatment and discharge status of the study population. Follow-up with respect to discharge status was updated until September 18, 2009.

Patients were defined as adults if they were aged ≥ 18 years,

otherwise were defined as children. Aboriginal was defined according to medical records or confirmed by self identification in telephone interviews. Smoking status and alcoholism were also defined according to charts. Ex-smokers, ex-drinkers or patients without available records were categorized as non-smokers and non-drinkers.

Body mass index (BMI) was used to assess adult body mass. BMI <18.5 kg/m², ≥ 18.5 but <24 , ≥ 24 but <27 , and ≥ 27 but <35 were defined as under-weight, normal, overweight, obese, respectively. BMI ≥ 35 was considered to be morbidly obese [2]. On the other hand, BMI adjusted by age and gender was used to classify elder children (≥ 2 years old) into one of the former four groups. For children aged <2 years, body weight was categorized according to the development curve. Body weight <15 th percentile, between 15th to 85th percentile, between 85th to 95th percentile, and above were defined as under-weight, normal, over-weight, and obesity, respectively [3-5].

Neurologic disorders (including dementia, mental retardation, cerebrovascular disease, and limb paralysis), asthma, chronic obstructive pulmonary disease (COPD), diabetes mellitus, cardiovascular disease (excluding hypertension), chronic anemia, liver function abnormality with or without cirrhosis, abnormal renal function with or without regular dialysis, cancer that is progressing or under treatment, autoimmune disease, use of steroid, chemotherapeutic agents, or other immune modulatory drugs were regarded as underlying conditions.

We applied the scoring method used in lung injury score to evaluate the severity of initial chest radiographs. Any quadrant with increased pulmonary infiltration was scored a point and the range of summation was



0 to 4 [6]. $\text{PaO}_2/\text{FiO}_2$ ratio (PaO_2 : partial pressure; FiO_2 : fraction of inspired O_2) at admission was used to evaluate the pulmonary oxygenation function if both data was available. If $\text{PaO}_2/\text{FiO}_2$ ratio was <200 at anytime during hospitalization, accompanied with acute and diffuse pulmonary infiltrates without evidence of left heart failure, the patient was defined to have acute respiratory distress syndrome (ARDS) [7].

Complications during hospital stay were recorded, without taking into account the time sequence. Diagnosis of viral pneumonia was recorded either by clinical diagnosis alone or by having compatible imaging studies. Use of ventilator and other modalities to improve ventilation or oxygenation were also documented. Complications of extra-corporal membranous oxygenation (ECMO) were defined by clinicians, and recorded accordingly. Use of vasopressors, including norepinephrine, dopamine, and epinephrine, were used as a proxy for the presence of shock [8]. Renal function deterioration was defined as the presence of serum creatinine >2 mg/dL or an acute increase of at least 0.5 mg/dL. Deterioration of liver function was defined as having >2 times the upper limit of aspartate aminotransferase (AST) or alanine aminotransferase (ALT). Patients with clinical presentations of heart failure and compatible findings on echocardiography were considered to have myocardial dysfunction. Identification of clinical significant bacteria in respiratory secretion or specimen from sterile site was recorded as secondary bacterial infection. We used a scoring system that combined clinical and laboratory criteria to categorize the presence of disseminated intravascular coagulation (DIC) [9].

To shorten the latency between onset of disease and medical service, CECC allocated antiviral agents to 300 clinics nationwide on August 1, so

that patients with positive influenza rapid test could receive antiviral agents earlier. The National Health Insurance began to cover the cost of antiviral agents on August 15. We therefore categorized all study population into three groups according to their onset date: on or before July 31, during August 1-14, and on or after August 15. By comparing the duration between onset of disease to rapid testing, and onset of disease to antiviral agents using univariate ANOVA test and post-hoc analysis with Tukey test, we could evaluate the impact of these interventions. We also use the Wilcoxon two-sample test to analyze the association between available variables and mortality.

Results

The number of patients increased considerably from early August (Fig. 1). By August 29, there were a total of 100 patients with severe complications reported.

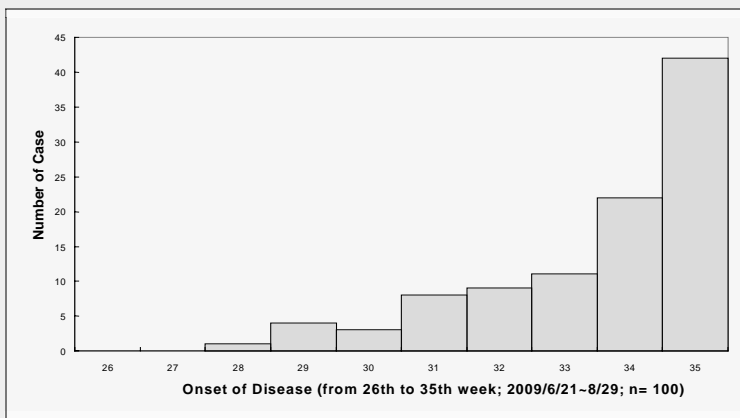


Figure 1. Severe complicated patients with laboratory-confirmed 2009 pandemic H1N1 infection, by week of onset - Taiwan, July 2 - August 29, 2009

Characteristics of the Study Population

The median age of the first 100 cases was 16 years. Half were adults and the other half were children. The ages of adults were 18 to 73 years (median 39) and the ages of children ranged from 9 months to 15 years (median 8 years). There were 64 male; 15 patients were current smokers; four patients had documented alcoholism; and two women were pregnant.

Figure 2 demonstrated the distribution of the number of study patients and rate to the general population in different age groups [10]. Even though the 2-5 year-old group did not have the highest number of cases, but this group had the highest rate of disease.

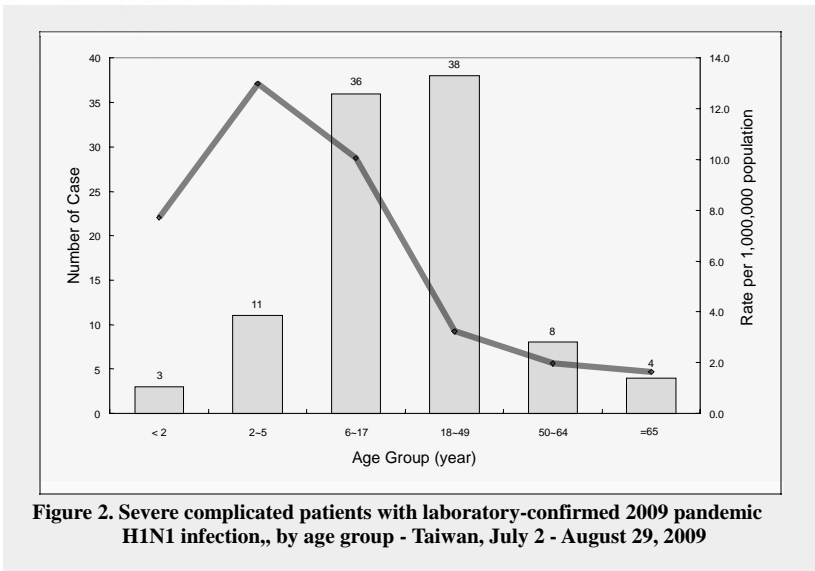


Figure 2. Severe complicated patients with laboratory-confirmed 2009 pandemic H1N1 infection., by age group - Taiwan, July 2 - August 29, 2009

The BMI of 42 adults with known height and weight ranged from 16.6 to 55.1 (median 25.7). Sixty-two percent of the 42 adults and 38% of the 50 children were either overweight or obese (Table 1).

Table 1. Body Weight Classification in Children and Adults

	Number of Children (%)	Number of Adults (%)
Under-weight	9 (18%)	2 (5%)
Normal	22 (44%)	14 (33%)
Overweight	11 (22%)	8 (19%)
Obese	8 (16%)	6 (14%)
Morbidly Obese	-	12 (29%)

Thirty-eight patients had preexisting medical conditions, including neurologic disorders in 12 patients, asthma or COPD in 12 patients, cardiovascular diseases (excluding hypertension) in 9 patients, diabetes mellitus in 9 patients, chronic anemia in 8 patients, liver diseases in 6 patients, cancer that is progressing or under treatment in 5 patients, chronic renal insufficiency in 5 patients, 4 bed-ridden patients and 4 patients with autoimmune diseases or use immune-modulatory medication.

Initial Presentation

Ninety-nine patients had fever, of which, 54 had fever ≥ 3 days. Ninety-three presented with cough, and 8 of them had hemoptysis. Other symptoms included fatigue (61), sore throat (49), rhinorrhea or nasal congestion (49), myalgia (42), dyspnea (42), nausea and vomiting (24), headache (19), diarrhea (17), chest pain (13), disturbance of consciousness (10), convulsions (5) and cyanosis (1).

Laboratory Findings and Chest Radiographs at Admission

At admission, the average leukocyte count of all 100 patients was $6630 \pm 3450/\text{mm}^3$ (range: 1260-19290). The average lymphocyte count in 97 patients was $986 \pm 763/\text{mm}^3$ (range: 54-5626), and the average platelet count in 96 patients was $178,000 \pm 62,000/\text{mm}^3$ (range: 7000-381000).



Serum creatinine kinase (CK) level was available in 31 patients, which ranged from 37 to 1029 U/L (median: 150). Only 7 patients had serum lactate dehydrogenase (LDH) level which ranged from 135 to 1249 U/L (median: 595.5).

Eighteen percent of all patients had leukocytosis ($>10,000/\text{mm}^3$) and 22% presented with leukopenia ($<4,000/\text{mm}^3$). Eight percent of 96 patients had thrombocytopenia (platelets $<10,000/\text{mm}^3$). Sixty percent of 87 cases presented with elevated C-reactive protein.

Ninety eight patients had chest radiographs at admission. Of which, eight only had subtle change and were scored 0. The remaining 90 radiographs, on average, showed infiltration in 1.8 ± 1.1 quadrants. Thirty five patients had pulmonary infiltration in one quadrant, 38 in two quadrants, nine in three quadrants, and eight patients had bilateral diffuse lesions.

Treatment

All patients had received oseltamivir. The dose for 45 adults (90%) was 75mg twice a day for a minimum of five days (range: 5-14 days). Three adults in ICU received 150 mg twice daily; they all recovered and were discharged from hospital without sequelae. Two adults with end-stage renal disease received 75mg once per day. The dose for children was adjusted according to age and body weight. It ranged from 1.8 to 7.8 mg/kg/day. Compared to the clinical treatment guideline published by Taiwan CDC, 6 children were under-dosed, receiving 50-75% of recommended dose, and 20 patients were prescribed 1.5-2 times the recommended dose [11].

Twenty-two patients, including 3 children, received steroid during hospitalization. Of these, eight received hydrocortisone $< 300\text{mg}/\text{day}$, 7 received methylprednisolone at a dose no more than 2 mg/kg/day. The

remaining 7 patients who received higher doses were all critically ill and died; one of them had proven secondary bacterial infection.

Two children and one adult with respiratory failure and at three additional organ dysfunction received intravenous immunoglobulin; the dose ranged from 32.5 to 120.3 mg per day for 2 to 6 days. All of them died.

Clinical Course and Complications during Hospital Stay

Complications occurred during hospitalization were listed in Table 2. Eighty-nine patients had viral pneumonia; of these, 46% were children and 39% had at least one preexisting medical condition. Fifty-two of 89 patients required supplementary oxygen; respiratory failure requiring mechanical ventilator developed in 23 patients. Nine of the 23 patients had used non-invasive positive pressure ventilator (NIPPV) initially, and 6 were later intubated because of progressive respiratory distress. Seventeen patients had ARDS; three of them required alternative support such as inhaled nitric oxide (NO) and 9 required ECMO support. The average duration for ECMO use was 17.7 ± 18.7 days. Five of the nine cases presented with fatal bleeding and/or blood stream infection. ECMO was successfully removed in two patients who made full recovery.

Thirteen patients had shock requiring use of vasopressors; this consisted of 31% of patients admitted to ICU. Seven of the 13 had renal function impairment and 6 had abnormal liver function test. Three patients had evidence of heart failure.

Fifteen of the 100 study patients developed deterioration of renal function, three of these had preexisting chronic kidney disease. Four patients required new renal replacement treatment: three used continuous

renal replacement therapy (CRRT) and one used intermittent hemodialysis.

Nineteen patients had deterioration of liver function during hospitalization. Of these, two had preexisting cirrhosis and one had documented abnormal liver function before admission.

Viral encephalitis was found in eight patients. Of these, there was only one adult. The average age of the 7 children was 9.1 ± 3.1 years. Four of the patients were diagnosed clinically and the other four had compatible MRI images.

Table 2. Complications during Hospitalization

Complications	Number of Patients (N=100)	Number of Deaths (N=9)
Viral pneumonia	89	9
ECMO	9	4
Shock requiring vasopressor	13	7
Heart failure	3	2
Deterioration of renal function	15	8
Liver function abnormality	19	6
Encephalitis	8	3
Secondary bacterial infection	12	2
Disseminated intravascular coagulation	4	3

Concerning the clinical course, 91 patients were discharged from hospital or died by September 18, 2009. The mean hospital stay for these 91 patients was 6 days (range: 1~34). Forty-two patients had been transferred to ICU and 5 of them were still there. The median ICU stay were 5 days (range: 1~33) in the 37 cases who had been transferred out and 26 days (range: 11~71) in the remaining 5 patients. One patient became infected while hospitalized for another medical illness. The median duration from onset of symptoms to the first doctor's visit, to rapid testing, and to antiviral agent use were 1 day (range: 0~14), 3 days (range: 0~14),

and 4 days (range: 0~21), respectively. Forty patients received oseltamivir within 24 hours.

The differences between the duration from symptom onset to rapid testing, from onset to admission and from onset to anti-viral treatment in different time periods were statistically significant (Table3).

Table 3. Impact of Intervention Measures

Date of Onset	(1) prior to Aug 1	(2) Aug 1~ Aug 14	(3) after Aug 15	p-value	Significant difference tested by Tukey test
(A) Days from onset of symptoms to rapid testing	6.4 days (n=11)	4.5 days (n=15)	2.8 days (n=64)	0.000	(3) and (1)
(B) Days from onset of symptoms to admission	5.0 days (n=14)	4.3 days (n=21)	2.5 days (n=65)	0.000	(3) and (1) (3) and (2)
(C) Days from onset of symptoms to treatment	7.2 days (n=14)	5.1 days (n=21)	3.1 days (n=65)	0.000	(3) and (1) (3) and (2)

Mortality

Nine of the 100 patients died, and the median duration from admission to death was 6 days (range: 2~27). Three of them had no pre-existing medical conditions; the others had more than one of the following conditions: morbid obesity, overweight, cerebral palsy, diabetes mellitus, COPD, or chronic renal insufficiency.

Comparing the baseline characteristics, past medical history, pre-existing conditions, laboratory findings at admission, and treatment received between those who survived and died, the duration from onset of disease to rapid testing and from onset of disease to treatment were significantly shorter in those who survived ($p < 0.01$).



Discussion

In this study of the first 100 severe pandemic H1N1 patients, 46% aged 18 to 65 years, and 38% had at least one pre-existing medical condition. These are similar to previous reports from Mexico and the United States [12]. More than half of adults were overweight; the phenomenon was less obvious in children. Although there were only 2 pregnant women, both were critically ill and one died. Treating infection among obese adults and pregnant women probably needs to be more vigilant.

Most patients presented with influenza-like illness initially, with fever, cough, and fatigue. About 40% had dyspnea but only 10% had altered consciousness, chest pain and other danger signs. These presentations are similar to those reported in other series [12, 13]. As for the laboratory finding at admission, leukocyte count, lymphocyte count, and platelet count are highly variable and of limited value. In patients whose LDH and CK level were checked at admission, the results were consistently elevated, but to a lesser extent compared with those of the first 18 cases reported by Mexico. In addition, more than half of our patients had elevated CRP, which went against the common belief that CRP was the indicator of bacterial infection.

All patients received oseltamivir as antiviral agent, but the dose in half of the children was either insufficient or beyond the recommended dose in treatment guidelines [11]. In severe complicated patients, use of steroid or IVIG is controversial and clinical practice varies significantly. As the number of patients with severe infection increases, evidence-based treatment guidelines should be published as soon as possible.

Viral pneumonia was the most common complication found during

hospitalization, but deterioration of renal, liver and other vital organ functions were also documented in 10-20% of the patients. If patients progressed to cardiopulmonary failure requiring ventilator or ECMO support, the mortality rate increased. Experts and clinicians should work together to elevate clinicians' critical care capability.

Most patients were discharged with no sequelae and the average hospital stay was around one week. However, if a patient required intensive care, the stay may increase up to a month. As the pandemic flu continues to spread, we may need to re-evaluate the surge capacity of hospitals and healthcare workers.

CECC allocated antiviral agents to 300 clinics nationwide on August 1, so that patients with positive influenza rapid test could receive antiviral agents earlier. The National Health Insurance began to cover the cost of antiviral agents on August 15. Because CECC efforts, high accessible medical care in Taiwan, and heightened awareness of our people, the average duration between onset of symptom and first doctor's visit was 1.7 days in this study, which is shorter than the 6 days found in Spain and Mexico. The impact of control measures is also reflected by the shortening of duration between onset of symptoms to rapid testing, onset to symptoms to treatment, and onset of symptoms to admission.

Comparing the baseline characteristics, past medical history, pre-existing conditions, laboratory findings at admission, and treatment between those who survived and died, only the duration from onset of disease to rapid testing and from onset of disease to treatment were significantly shorter in those who survived. Limited number of cases makes the interpretation of these results difficult.



There are limitations in this study. First, there was missing data and unclear documentation in the medical records. In addition, some patients with less severe symptoms were admitted because of patient or physician anxiety, diluting the number of severe complications. Because of these limitations, further studies are necessary to elucidate other potential risk factors and effective treatment.

In conclusion, H1N1 influenza affected mostly children and young adults. Morbid obesity and pregnancy are also risk factors for developing severe diseases. Even though the implementation of National Health Insurance coverage of antiviral drugs and rapid test has improved the quality of diagnosis and treatment, there are still more that we can do to decrease mortality.

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References

1. Centers for Disease Control, Department of Health, Taiwan. Reporting rules and diagnostic criteria for suspected severe complicated influenza patients, Appendix 3. 2008. Available at: <http://www.cdc.gov.tw/ct.asp?xItem=16138&ctNode=1816&mp=110>.
2. Executive Yuan, Taiwan. Definition of adult obesity, 2002. Available at: [http://www.doh.gov.tw/ufiile/doc/%e6%88%90%e4%ba%ba%e8%82%a5%e8%83%96%e5%ae%9a%e7%be%a9%e6%b5%b7%e5%a0%b1\[1\].ppt](http://www.doh.gov.tw/ufiile/doc/%e6%88%90%e4%ba%ba%e8%82%a5%e8%83%96%e5%ae%9a%e7%be%a9%e6%b5%b7%e5%a0%b1[1].ppt).

3. Bureau of Health Promotion, Department of Health, Taiwan. Development curve for children, 2009. Available at: http://www.bhp.doh.gov.tw/BHPnet/Portal/Them_Show.aspx?Subject=200712250006&Class=0&No=200905050001.
4. Department of Health, Executive Yuan. To cure obesity, start since childhood, 2007. Available at: <http://www.doh.gov.tw/ufile/doc/960404-%E8%82%A5%E8%83%96%E9%98%B2%E6%B2%BB%E8%A6%81%E5%BE%9E%E5%B0%8F%E7%B4%AE%E6%A0%B9.doc>
5. Bureau of Health Promotion, Department of Health, Taiwan. Manuals for Children's Health, 2008.
6. Murray JF, Luce JM. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 720-3.
7. Bernard GR, Brigham KL. The American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 818-24.
8. RP D. Cardiovascular management of septic shock. *Crit Care Med* 2003;946-55.
9. Taylor FB TC, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation (DIC). *Thromb Haemost* 2001; 1327-30.
10. Centers for Disease Control, Department of Health, Taiwan. Database of household registration. The number of general population in June, 2009. Available at: http://intranet.cdc.gov.tw/app/98_6.xls.
11. Centers for Disease Control, Department of Health, Taiwan. Treatment guideline for novel H1N1 2009. Available at: <http://flu.cdc.gov.tw/ct.asp?xItem=10531&ctNode=856&mp=150>.
12. Rogelio PP, Samuel PL. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med* 2009; 680-9.
13. Rello J. Intensive care of adult patients with severe respiratory failure caused by influenza A (H1N1) in Spain. *Critical Care* 2009; 148.