

2009 pandemic Influenza A (H1N1): clinical and laboratory characteristics in pediatric and adult patients and in patients with pulmonary involvement

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Accepted 30 April 2012. Published online 31 July 2012.

Background To better understand clinical and laboratory characteristics in children, adults, and patients with lung involvement suffering 2009 pandemic influenza A (H1N1).

Methods A total of 442 patients with 2009 pandemic influenza A (H1N1) were retrospectively analyzed.

Results Comparing to their adult counterpart ($n = 55$), pediatric patients ($n = 387$) had significantly higher frequencies of fever, rhinorrhea, cough, sore throat, nausea/vomiting, and longer length of fever; lower frequencies of chest pain and dyspnea; higher incidence of lymphopenia; and lower incidence of elevated serum C-reactive protein. Among the 227 patients with radiographs available, lung involvement was found in 19 (8.4%) (52.6% consolidation and 47.4% interstitial infiltrations), including 18 children and one adult. One child with lung consolidation died of multiorgan failure. Significant findings in patients with lung involvement included predominant young age

(≤ 10 years), prolonged fever, and delayed oseltamivir therapy (≥ 48 hours after onset of illness); higher frequencies of dyspnea, nausea/vomiting, and altered consciousness; and higher incidences of leukopenia, elevated serum creatine kinase, and lactic dehydrogenase.

Conclusions Among patients with 2009 pandemic influenza A (H1N1), we found significant difference in clinical manifestations between children and adults, and significant differences in clinical and laboratory manifestations between patients with lung involvement and those without. On the basis of data from this study and the existing literature, early treatment with oseltamivir is recommended for patients with 2009 pandemic influenza A (H1N1), regardless of age.

Keywords adults, children, consolidation, interstitial infiltrates, lung involvement, oseltamivir, pandemic influenza A (H1N1).

Please cite this paper as: Lee and Liu *et al.* (2012) 2009 pandemic Influenza A (H1N1): clinical and laboratory characteristics in pediatric and adult patients and in patients with pulmonary involvement. *Influenza and Other Respiratory Viruses* 6(601), e152–e161.

Introduction

Pandemic influenza A (H1N1) caused by a triple-reassortant virus containing genes from human, swine, and avian influenza viruses originated from Mexico and the United States in April, 2009 once rapidly spread worldwide.^{1–4} The clinical manifestations of 2009 pandemic influenza A (H1N1) greatly varied. While the mild-form 2009 pandemic influenza A (H1N1) with nonspecific symptoms/signs such as fever, sore throat, and myalgia are usually found, severe cases with fatal outcome have not been uncommonly encountered.^{5–10} The first case of pandemic influenza A (H1N1) was identified in Taiwan on May 20, 2009.¹¹ An epidemic of influenza A (H1N1) viral

infection once rapidly disseminated on this island, and until July 20, 2009, a case of clinically severe form of 2009 pandemic influenza A (H1N1) was first reported in Taiwan.¹² The information concerning global influenza issued by World Health Organization (WHO) in late-March 2011 indicated that while influenzas in the Americas were declining, 2009 pandemic influenza A (H1N1) has increased proportionately and accounted for 38% of all virus detections.¹³ The latest surveillance data disclosed that the 2009 pandemic influenza A (H1N1) and seasonal influenza A viruses cocirculated in the United States between October 2, 2011 and February 11, 2012, and 2009 pandemic influenza A (H1N1) began to increase in early February 2012.¹⁴ Early recognition and appropriate treatment of

2009 pandemic influenza A (H1N1) remains important.¹⁵ The 2009 pandemic H1N1 virus affected children and adults alike. To better understand the differences in clinical and laboratory manifestations in pediatric and adult patients, and in patients with lung involvement, we analyzed the demographic, clinical, radiographic, and laboratory data of patients with 2009 pandemic influenza A (H1N1) at Kaohsiung Chang Gung Memorial Hospital (KSCGMH), a 2600-bed primary care and referral medical center in southern Taiwan.

Methods

Patients and definitions

As part of the preparedness for the possible nationwide epidemic of 2009 influenza A (H1N1) in Taiwan, in July 2009 KSCGMH launched a screening program for 2009 influenza A (H1N1) for patients with flu-like illness and those with fever lacking obvious localizing signs to suggest an alternative diagnosis.¹⁶ Influenza-like illness was defined according to the WHO guidelines as fever ($\geq 38.0^{\circ}\text{C}$), cough, and/or sore throat.¹⁷ The diagnosis of 2009 pandemic influenza A (H1N1) was made when H1N1 influenza A virus-specific RNA in the respiratory specimen (nasopharyngeal swab and/or pharyngeal swab) of a patient was positive in a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test based on the recommended instructions using the QiAamp Viral RNA Mini Kit (TAIGEN Bioscience Corporation, Taiwan).^{18,19} The primers and probes used for the detection of 2009 influenza A (H1N1) were as follows: SW H1 forward primer GTG CTA TAA ACA CCA GCC TYC CA, SW H1 reverse primer CGG GAT ATT CCT TAA TCC TGT RGC, and SW H1 probe CA GAA TAT ACA "T"CC RGT CAC AAT TGG ARA A.¹⁹ All patients with the diagnosis of pandemic influenza A (H1N1) made between July and mid-August 2009 at KSCGMH were included for retrospective analyses. The medical charts of the included patients were reviewed for retrieval of their demographic, clinical, radiographic, and laboratory information for analyses. This study was conducted with a waiver of patient consent approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taiwan (CGMH-IRB 98-1570B).

An adult patient referred to one aged ≥ 18 years. Fever was defined as an ear temperature $\geq 38^{\circ}\text{C}$. Lymphopenia was defined as a peripheral lymphocyte count <1500 cells/ml in adults and <3000 cells/ml in children.²⁰ An elevated C-reactive protein (CRP) referred to a serum CRP >5 mg/l in the tested patient, regardless of age. Manifestations of lung involvement were radiographically classified as lung consolidation or interstitial infiltrates, with or without accompanying pleural effusion.²¹ Characteristic lung consolidation and infiltrates in chest radiographies are

illustrated in Figure 1. The use of oseltamivir was at the discretion of each patient's physician based on his or her personal experience and clinical judgment. For adults with normal renal function, the dosing of the prescribed oseltamivir was 75 mg twice per day; otherwise it was adjusted for body weight of each patient.¹⁷ Delayed oseltamivir therapy was defined as starting therapy with the antiviral agent ≥ 48 hours after onset of symptoms because of 2009 pandemic influenza A (H1N1). Fatality referred to death within 2 weeks after the patient was hospitalized because of 2009 pandemic H1N1 virus infection.

Statistical analyses

We compared clinical, laboratory, and radiographic manifestations between (i) pediatric and adult patients, and (ii) patients with lung involvement and those without. Student's *t*-test or Mann-Whitney *U*-test was used for comparison between continuous variables, while the chi-square test or Fisher's exact test was used for comparison between dichotomous variables, where applicable. A two-tailed *P* value <0.05 was considered statistically significant.

Results

Description of the overall included patients

A total of 442 patients (387 [87.5%] children and 55 [12.5%] adults; mean age, 12.7 ± 9.9 years) with 2009 pandemic influenza A (H1N1) were included for analyses. Of the overall included patients, half aged between 1 and 10 years, none was found to be overweight (body mass index <30)²² or pregnant woman, 6.3% had at least one underlying disease/condition and 2.7% had the most common underlying disease – bronchial asthma. Among the overall included patients, fever (98.2%) was most frequently found, followed by rhinorrhea (65.2%) and cough (64.9%); the mean interval from symptom onset to hospital presentation was 1.5 days. Of the 308 patients who received oseltamivir therapy, 235 (76.3%) began taking the antiviral agent <48 hours after the emergence of symptoms suggestive of 2009 pandemic influenza A (H1N1). Among the 252 patients with information available, regardless of age, the mean length of fever was 3 days. Elevated CRP (66.8%) and lactic dehydrogenase (39.5%) were found to be the two leading laboratory abnormalities. Among the 227 included patients (75.8% children and 16.2% adults) with chest radiograph available, lung radiographic abnormalities were found in 19 (8.4%), including 18 children and one adult. These patients' chest radiographs were taken at different time points, and the median time from the onset of symptoms to the finding of chest radiographic abnormalities was 4 days (range, 2–9 days). Among the overall 442 included patients, 63 (14.2%) lost to follow-up, 378 (85.5%) recovered, and one (0.3%) died. The demographic,

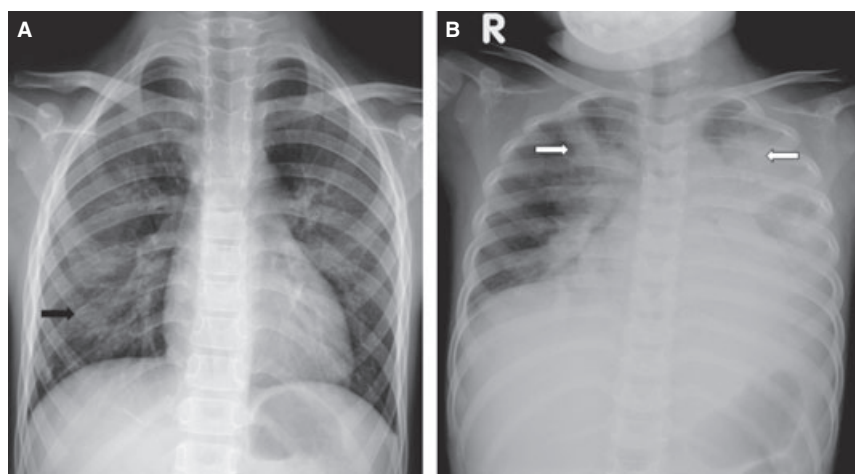


Figure 1. Chest radiographs showing infiltrates in the right lower lung field (black arrow) of a 8-year-old boy (A) and consolidations in both lungs (white arrows) with left pleural effusion of a 5-year-old girl (B).

clinical, laboratory and chest radiographic information of the included patients is summarized in Tables 1 and 2.

Of the 387 included children (mean age, 9.6 ± 3.9 years), 57.1% aged ≤ 10 years, 4.7% had at least one underlying disease/condition, and 2.6% had the most common underlying disease – bronchial asthma. The three leading symptoms found in the children were fever (98.7%), rhinorrhea (67.4%), and cough (67.4%). Among the 262 children who received antiviral treatment, 205 (78.2%) started therapy with oseltamivir <48 hours after onset of illness.

Of the 55 adults (mean age, 34.3 ± 12.2 years), 54 (98.2%) aged between 18 and 60 years; 18.2% had at least one underlying disease, and diabetes mellitus and hypertension (each 5.5%) were the two most prevalent ones. The three most common symptoms found in the adult patients were fever (67.3%), myalgia (50.9%), and rhinorrhea (49.1%). Among the 46 adult patients who received antiviral treatment, 30 (65.2%) received oseltamivir therapy <48 hours after onset of illness.

Comparisons between the pediatric and adult patients

When compared to their adult counterpart, pediatric patients were found to have significantly higher frequencies of fever, rhinorrhea, cough, sore throat, nausea/vomiting, and longer length of fever; lower frequencies of chest pain and dyspnea (Table 1); higher incidence of lymphopenia; and lower incidence of elevated CRP (Table 2).

Description of patients with pulmonary involvement

A total of 19 patients (18 [94.7%] children and one [5.3%] adult) suffered 2009 pandemic influenza A (H1N1) were found to have pulmonary involvement (detailed in Table 3). Among these 19 patients, radiographic lung consolidation was found in 10 (patients 2, 3, 5, 9, 11–13, 15,

17, and 18), while interstitial infiltrates in the rest nine (patients 1, 4, 6–8, 10, 14, 16, and 19). Of them, 11 (patients 1, 3, 5, 6, 8, and 12–17) were admitted to ordinary ward and three (patients 2, 4, and 11) to intensive care unit, whereas the rest five (patients 7, 9, 10, 18, and 19) were stayed and treated at the emergency department. Of these 19 patients, 17 received oseltamivir therapy, and two (patients 1 and 19) with radiographic lung interstitial infiltrates did not take antiviral agents and recovered uneventfully. Of the 17 patients who received oseltamivir therapy (10- and 14-day oseltamivir therapy each for one patient, and 5-day oseltamivir therapy for the rest 15), 12 (70.6%) (patients 2–5, 7, 10–13, and 15–17) started taking the antiviral agent ≥ 48 hours after the onset of illness (Table 4).

Blood specimens were sampled from nine patients (patients 2–5, 11, 12, and 15–17) for culture and all were negative for bacterial growth. *Mycoplasma pneumoniae* IgM was assayed for seven patients (patients 2, 3, 5, 11, 16, 17, and 19), which turned out to be positive in two (patients 17 and 19). Urine specimens were sampled from two patients (patients 2 and 12) for assay of the antigen of *Streptococcus pneumoniae* and all were negative. Throat swab test of group A streptococcus antigen was performed in one patient (patient 14), which turned out to be positive. Negative bacterial and fungal cultures of bronchoalveolar lavage were found in the two (patients 2 and 11) who underwent bronchoscopic investigation. Negative bacterial culture of pleural effusion was found in the two (patients 11 and 15) who received pleurocentesis. PCR detection of microbes in respiratory and/or blood specimens was not performed for these patients. Elevated CRP was found in 11 (64.7%) of the 17 patients with data available. Of the three (3/19 [15.8%]) patients (patients 8, 17, and 19) with bacterial coinfection, all had an elevated CRP level ranging from 7.3 to 49.8 mg/dl (median, 42.8 mg/dl). Among

Table 1. Demographic and clinical information of 442 patients with 2009 pandemic influenza A (H1N1)

Variable	Overall patients (n = 442)	Pediatric patients (n = 387)	Adult patients (n = 55)	P value*
Age, year				–
Mean (\pm SD)	12.7 (\pm 9.9)	9.6 (\pm 3.9)	34.3 (\pm 12.2)	
Median (range)	10 (0.3–63)	10 (0.3–17)	31 (18–63)	
Age group				
<1 year	1 (0.2)	1 (0.3)	–	–
1–10 years	221 (50)	221 (57.1)	–	–
11–17 years	165 (37.3)	165 (42.6)	–	–
18–60 years	54 (12.4)	–	54 (98.2)	–
\geq 61 years	1 (0.2)	–	1 (1.8)	–
Male gender	271 (61.3)	247 (63.8)	24 (43.6)	0.005
Underlying disease/condition**				
Bronchial asthma	12 (2.7)	10 (2.6)	2 (3.6)	–
Diabetes mellitus	3 (0.7)	0	3 (5.5)	–
Hypertension	3 (0.7)	0	3 (5.5)	–
Miscellaneous***	12 (2.7)	6 (1.6)	7 (12.7)	–
Symptom/Sign†				
Fever	434 (98.2)	382 (98.7)	33 (67.3)	<0.001
Rhinorrhea	288 (65.2)	261 (67.4)	27 (49.1)	0.010
Cough	287 (64.9)	261 (67.4)	26 (47.3)	0.004
Sore throat	229 (51.8)	208 (53.7)	21 (38.2)	0.043
Myalgia	183 (41.4)	155 (40)	28 (50.9)	0.144
Headache	138 (31.2)	117 (30.2)	21 (38.2)	0.276
Vomiting/nausea	91 (20.6)	88 (22.7)	3 (5.5)	0.002
Diarrhea	47 (10.6)	45 (11.6)	2 (3.6)	0.098
Abdominal pain	38 (8.6)	35 (9.1)	3 (5.5)	0.605
Chest pain	22 (5.0)	15 (3.9)	7 (12.7)	0.012
Dyspnea	15 (3.4)	10 (2.6)	5 (9.1)	0.028
Altered consciousness	4 (0.9)	3 (0.8)	1 (1.8)	0.413
Mean interval from onset of symptoms to hospital presentation, day (\pm SD)	1.5 (\pm 0.9)	1.5 (\pm 0.9)	1.9 (\pm 1.1)	<0.001
Mean length of fever, day (\pm SD), (n = no. of patients with data available)	3 (\pm 1.44) (n = 252)	3 (\pm 1.4) (n = 227)	2.5 (\pm 1.7) (n = 25)	<0.001
Hospitalization	82 (18.5)	74 (19.1)	8 (14.5)	0.848
Antibiotic(s) used	41 (9.3)	34 (8.8)	7 (12.7)	0.325
Use oseltamivir <48 hours, no./total no. (%)	235/308 (76.2)	205/262 (78.2)	30/46 (65.2)	0.062
Outcomes				>0.99
Survived	378 (99.5)	335 (86.6)	43 (78.2)	
Fatal	1 (0.3)	1 (0.3)	0	
Loss to follow-up	63 (14.3)	51 (13.2)	12 (21.8)	0.095

Data are presented as number of patients (%) unless stated otherwise.

*Comparison between pediatric and adult patients.

**An individual patient might have more than one underlying disease/condition. As the prevalence of an individual underlying disease is often age dependent, comparisons of underlying disease between pediatric and adult patient were not performed.

***Including hepatitis C carrier and liver cirrhosis, hepatitis B carrier, liver cirrhosis, hepatocellular carcinoma, pancreatic tumor, acute lymphocytic leukemia, end stage renal disease, post-liver transplant, ventricular septal defect, atrial septal defect, mitral valve prolapsed, schizophrenia, and thalassemia each was found in one.

†An individual patient might have more than one symptom/sign.

Table 2. Laboratory and chest radiographic findings of 442 patients with 2009 pandemic influenza A (H1N1)

Variable	Overall patients (n = 442)	Pediatric patients (n = 387)	Adult patients (n = 55)	P value*
Leukocyte count				
Leukocytosis (White cell count $>10 \times 10^9$ cells/l, no./total no. (%))	20/216 (9.3)	18/184 (9.8)	2/32 (6.3)	0.745
Leukopenia (White cell count $<3 \times 10^9$ cells/l, no./total no. (%))	9/216 (4.2)	7/184 (3.8)	2/32 (6.3)	0.625
Lymphocyte count				0.010
$<3.0 \times 10^9$ cells/l in children, no./total no. of children (%)	–	170/182 (93.4)	–	
$<1.5 \times 10^9$ cells/l in adults, no./total no. of children (%)	–	–	24/31 (77.4)	
Platelet count				
Thrombocytosis ($>450 \times 10^9$ cells/l, no./total no. (%))	1/215 (0.5)	1/183 (0.5)	0/32 (0)	>0.99
Thrombocytopenia ($<149 \times 10^9$ cells/l, no./total no. (%))	38/215 (17.7)	27/183 (14.5)	9/32 (24.4)	0.074
C-reactive protein >5 mg/l (reference value <5 mg/l, no./total no. (%))	139/208 (66.8)	116/183 (63.4)	23/25 (92)	0.003
Creatine kinase >130 U/l (reference value 15–130 U/l, no./total no. (%))	31/144 (21.5)	28/130 (21.5)	3/14 (21.4)	>0.99
Lactic dehydrogenase >225 U/l (reference value 135–225 U/l, no./total no. (%))	55/139 (39.5)	50/126 (39.6)	5/13 (23.1)	>0.99
Aspartate aminotransferase >40 U/l (reference value >40 U/l, no./total no. (%))	26/181 (14.4)	24/168 (14.3)	2/13 (15.4)	>0.99
Alanine aminotransferase >40 U/l (reference value >40 U/l, no./total no. (%))	18/182 (9.9)	14/164 (8.5)	4/18 (22.2)	0.084
Abnormalities on chest radiograph, no./total no. (%)	19/227 (8.4)	18/190 (9.5)	1/37 (2.7)	0.326
Features of abnormalities appeared on chest radiography, no./total no. with abnormalities (%)				
Lung infiltration	9/19 (47.4)	9/18 (50)	–	–
Lung consolidation	7/19 (36.8)	7/18 (38.9)	–	–
Lung consolidation with pleural effusion	3/19 (15.8)	2/18 (11.1)	1/1 (100)	–

*Comparison between pediatric and adult patients.

patients with pulmonary involvement, elevated CRP between patients with and those without bacterial coinfection did not statistically differ ($P = 0.166$).

Eleven patients (58%) (patients 2–5, 11–15, 17, and 19) received an additional antibiotic therapy. The prescribed antibiotics included amoxicillin/clavulanate (patients 12–15, 17, and 19), azithromycin (patients 2, 3, 5, 11, 17, and 19), vancomycin/teicoplanin (patients 2 and 11), cefepime (patients 2 and 11), ceftriaxone (patient 2), meropenem

(patient 11), and amikacin (patient 11). Of note, radiographic lung consolidation developed prior to starting antibiotic was found in 80% of the overall 11 patients who received antibiotic therapy.

Among the five patients (median age, 9 years [range, 7–12]) who were treated at the emergency department, radiographic lung infiltrates were found in 3, whereas consolidation in the other 2. Four (patients 7, 9, 10, and 18) received oseltamivir therapy, and of them, two with

Table 3. Detailed information of 19 patients experienced 2009 pandemic influenza A (H1N1) with pulmonary involvement

Patient no.	Age (years)/sex	Underlying disease/condition	Days from symptom onset to admission	Location of treatment	Chest radiographic finding(s)	Osetamivir therapy*	Timing of starting osetamivir therapy after onset of symptoms	Complication(s)	Blood culture	Other diagnostic test(s) for bacterial coinfection
1	11/M	None	4	Medical ward	Interstitial infiltrates	No	–	None	ND	ND
2**	6/F	Thalassemia	7	ICU	Consolidation and pleural effusion	Yes	≥2 days	Respiratory failure; renal failure; myocarditis; intracranial hemorrhage; ARDS	Negative	Negative for <i>Mycoplasma</i> IgM and urine <i>Streptococcus pneumoniae</i> antigen; negative bacterial and fungal culture for bronchoalveolar lavage
3	2/M	None	5	Medical ward	Consolidation	Yes	≥2 days	None	Negative	Negative for <i>Mycoplasma</i> IgM
4	14/M	None	5	ICU	Interstitial infiltrates	Yes	≥2 days	Seizure***	Negative	ND
5	4/M	None	1	Medical ward	Consolidation	Yes	≥2 days	None	Negative	Negative for <i>Mycoplasma</i> IgM
6	4/M	None	1	Medical ward	Interstitial infiltrates	Yes	<2 days	None	ND	ND
7	8/M	None	3	ED	Interstitial infiltrates	Yes	≥2 days	None	ND	ND
8	10/F	None	2	Medical ward	Interstitial infiltrates	Yes	<2 days	None	ND	ND
9	7/F	None	1	ED	Consolidation	Yes	<2 days	None	ND	ND
10	12/M	Glycogenosis, status post-liver transplant	3	ED	Interstitial infiltrates	Yes	≥2 days	None	ND	ND
11	4/F	None	6	ICU	Consolidation and pleural effusion	Yes	≥2 days	ARDS	Negative	Negative for <i>Mycoplasma</i> IgM; negative bacterial culture and fungal for bronchoalveolar lavage and pleural effusion
12	11/F	None	5	Medical ward	Consolidation	Yes	≥2 days	None	Negative	Negative for urine <i>Streptococcus pneumoniae</i> antigen
13	1/F	None	6	Medical ward	Consolidation	Yes	≥2 days	None	ND	ND
14	8/M	None	2	Medical ward	Interstitial infiltrates	Yes	<2 days	None	ND	Positive throat swab for Group A <i>Streptococcus</i> antigen
15	50/M	Liver cirrhosis	3	Medical ward	Consolidation and pleural effusion	Yes	≥2 days	None	Negative	Negative bacterial culture for pleural effusion
16	3/M	None	3	Medical ward	Interstitial infiltrates	Yes	≥2 days	None	Negative	Negative for <i>Mycoplasma</i> IgM
17	9/M	Asthma	2	Medical ward	Consolidation	Yes	≥2 days	None	Negative	Positive for <i>Mycoplasma</i> IgM†
18	9/M	None	1	ED	Consolidation	Yes	<2 days	None	ND	ND
19	10/M	None	2	ED	Interstitial infiltrates	No	–	None	ND	Positive for <i>Mycoplasma</i> IgM†

M, male; F, female; ICU, intensive care unit; ED, emergency department; ARDS, acute respiratory distress syndrome; ND, not done.

*Patients no. 11 and 12 received 14- and 10-day osetamivir therapy; the rest 15 patients each received a standard course of 5-day osetamivir therapy.

**The only case turned out to be fatal.

***The patient received treatment acyclovir because of herpes encephalitis was clinically suspected.

†The patients received treatment with azithromycin.

Table 4. Demographic, clinical, and laboratory information of patients experienced 2009 pandemic influenza A (H1N1) with and without lung involvement detected by chest radiography

Variable	Lung involvement (<i>n</i> = 19)	Non-lung involvement (<i>n</i> = 208)	<i>P</i> value*
Demographic, clinical features and outcome			
Age, years			0.007
Mean age (\pm SD)	9.6 (\pm 0.5)	14.1 (\pm 11.6)	
Median (range)	8 (1–50)	11 (1–63)	
Age group			
≤10 years	14** (73.7)	93 (44.7)	0.017
11–17 years	4*** (21.1)	79 (37.9)	0.213
≥18 years	1† (5.3)	36 (17.3)	0.326
Male gender	13 (68.4)	125 (60.1)	0.625
Underlying disease/condition††			
Bronchial asthma	1 (5.3)	6 (2.9)	0.462
Diabetes mellitus	0	3 (1.4)	>0.99
Hypertension	0	3 (1.4)	>0.99
Thalassemia	1 (5.3)	0	0.084
Post-liver transplant	1 (5.3)	0	0.084
Liver cirrhosis	1 (5.3)	1 (0.5)	0.161
Mean from onset of symptoms to hospital, day (\pm SD)	3.3 (\pm 1.9)	1.6 (\pm 1.0)	<0.001
Mean duration of fever, day (\pm SD), (<i>n</i> = no. of patients with data available)	4.8 (\pm 2.5) (<i>n</i> = 17)	3.1 (\pm 1.3) (<i>n</i> = 133)	0.001
Patient receipt oseltamivir therapy	17 (89.5)	147 (70.7)	0.108
≥48 hours from symptom onset to oseltamivir therapy, no./total no. receipt oseltamivir therapy (%)	12/17 (70.6)	37/147 (25.2)	<0.001
Antibiotic(s) used	11 (57.9)	19 (9.1)	<0.001
Bacterial coinfection	3 (15.7)	0	–
Overall fatality	1 (5.3)	0	0.084
Symptom/sign†††			
Rhinorrhea	15 (78.9)	141 (67.8)	0.440
Sore throat	6 (31.6)	103 (49.5)	0.155
Cough	11 (57.9)	125 (60.1)	>0.99
Chest pain	2 (10.5)	18 (8.7)	0.677
Dyspnea	5 (26.3)	10 (4.8)	0.004
Fever	18 (94.7)	203 (97.6)	0.412
Diarrhea	1 (5.3)	25 (12)	0.705
Nausea/vomiting	9 (47.4)	46 (22.1)	0.023
Headache	5 (26.3)	65 (31.3)	0.798
Altered consciousness	3 (15.8)	1 (0.5)	0.002
Myalgia	3 (15.8)	79 (38)	0.079
Abdominal pain	3 (15.8)	19 (9.1)	0.398
Laboratory characteristics			
Leukocytosis (White cell count $>10 \times 10^9$ cells/l), no./total no. (%)	2/17 (11.8)	14/156 (8.9)	0.660
Leukopenia (White cell count $<3 \times 10^9$ cells/l), no./total no. (%)	4/17 (23.5)	4/156 (2.6)	0.004
Lymphopenia, no./total no. (%)	13/17 (76.4)	181/196 (92.3)	0.051
Thrombocytosis ($>450 \times 10^9$ cells/l), no./total no. (%)	1/17 (5.9)	0/155 (0)	0.099
Thrombocytopenia ($<149 \times 10^9$ cells/l), no./total no. (%)	4/17 (23.5)	27/155 (17.4)	0.366
C-reactive protein >5 mg/l (reference value <5 mg/l), no./total no. (%)	11/17 (64.7)	105/150 (70)	0.782
Creatine kinase >130 U/l (reference value 15–130 U/l), no./total no. (%)	6/9 (66.7)	23/115 (20)	0.005
Lactic dehydrogenase >225 U/l (reference value 135–225 U/l), no./total no. (%)	7/9 (77.8)	41/113 (36.3)	0.028

Data are presented as number of patients (%) unless stated otherwise.

*Comparison between patients with and without lung involvement.

**Of the 14 pediatric patients aged ≤10 years, eight with lung consolidation and six with lung infiltrates.

***Of the four pediatric patients aged 11–17 years, one with lung consolidation and three with lung infiltrates.

†A 50-year-old man with liver cirrhosis developed lung consolidation.

††An individual patient might have more than one underlying disease/condition.

†††An individual patient might have more than one symptom/sign.

radiographic lung consolidation started taking oseltamivir <48 hours after onset of symptoms.

Thirteen (patients 2–5, 9, 11–13, and 15–19) (68.4%) of these 19 patients with pulmonary involvement needed oxygen supplements. Among these 13 patients, two (patients 2 and 11) developed acute respiratory distress syndrome. One child (patient 2) was additionally treated with extracorporeal membrane oxygenation for refractory hypoxemia; she subsequently developed shock, disseminated intravascular coagulation and intracranial hemorrhage, and eventually died of multiorgan dysfunction.

Comparison between patients with pulmonary involvement (18 children and one adult) and without pulmonary involvement (172 children and 36 adults)

Significant findings (see Table 4 for details) in patients with pulmonary involvement were age ≤ 10 years, late hospital presentation, prolonged fever, higher proportions of receiving additional antibiotic therapy, and delayed oseltamivir therapy; higher frequencies of dyspnea, nausea/vomiting, and altered consciousness; higher incidences of leukopenia and elevated serum creatinine kinase and lactic dehydrogenase levels.

Discussion

Our data showed that among patients with 2009 pandemic influenza A (H1N1) with similar timing of starting oseltamivir, fever, rhinorrhea, cough, and sore throat were more commonly found in children, while chest pain and dyspnea were more often encountered in adults (Table 1). Vomiting/nausea and diarrhea were reported to be more prevalent in 2009 influenza A (H1N1) epidemic than in seasonal influenza ones.^{9,23} In an animal experimental model, the pandemic 2009 influenza A (H1N1) virus was recovered from the gastrointestinal tract of the intranasally inoculated ferrets.²⁴ Isolation of the 2009 influenza A (H1N1) viruses from the human gastrointestinal tissue²⁵ and prolonged viral shedding from respiratory tract in younger children were previously reported.²⁶ The incidences of vomiting/nausea (20.6%) and diarrhea (10.6%) in the overall patients in our series were lower than those (vomiting/nausea and diarrhea each 25%) reported in patients (60% aged ≤ 18 years) in the United States,³ but higher than those (vomiting/nausea, 1.9% and diarrhea, 2.8%) reported in patients (27% aged <15 years) in China.²⁷ Remarkably, the incidences of vomiting/nausea and diarrhea in our series were significantly higher in pediatric patients as compared to their adult counterpart (Table 1). It is unknown whether or not the higher incidences of vomiting/nausea and diarrhea in pediatric patients resulted from the higher burden of the 2009 pan-

demic influenza A (H1N1) virus in the affected children,²⁶ higher chances of exposure to the crowding environments at school,^{28,29} and/or poorer compliance to the widely advised hand hygiene in the 2009 influenza A (H1N1) epidemic.^{30,31}

When it comes to leading underlying diseases in our patients, bronchial asthma (2.6%) was found in children, while diabetes mellitus and hypertension (each 5.5%) were encountered in adults. The prevalence of an individual underlying disease is often age dependent; in Taiwan, the reported prevalence of bronchial asthma in a nationwide children cohort was 4.4%³², and the prevalences of diabetes mellitus and hypertension in nationwide adult cohort was 12.8% and 13%, respectively.^{33,34} Our data suggest that children with bronchial asthma and adults with diabetes mellitus or hypertension are not at risk of the 2009 influenza A (H1N1) virus infection.

The time lapse between onset of symptoms and chest radiographic abnormalities identified in our patients ranged from 2 to 9 days (median, 4 days), which was similar to those reported previously.^{8,35} Lung consolidation and infiltrates with or without pleural effusion were the two plain film patterns found in chest radiographies in our patients. The possibility of an under-diagnosis of pulmonary embolism and pneumo-mediastinum that had previously been observed in patients with pandemic influenza A (H1N1) could not be excluded,³⁶ as our patients were evaluated by plain chest radiographs which were less sensitive in the detection of such abnormalities than a computed tomography.³⁷

Bacterial coinfection rates ranging from 20% to 33% were reported in patients with severe influenza.^{35,38,39} Bacterial coinfections were found to be 15.8% in the 19 patients with lung involvement in this series; chances of under-diagnosis of bacterial coinfection in these patients were high, as aggressive diagnostic work-up for bacterial infections was carried out in only some of them (Table 3). Nonetheless, more than half of our patients with lung involvement received an additional antibiotic therapy.

The overall fatality rate in patients with pandemic influenza A (H1N1) was reported to be less than 0.5%.³⁵ Unfortunately, one pediatric patient with chest radiographic consolidation in our series developed multiorgan failure and turned out to be fatal. Of note, delayed oseltamivir therapy was significantly found in patients with lung involvement. In consistent with previous reports,^{35,40,41} our data recommended an early treatment with oseltamivir for patients whenever 2009 pandemic influenza A (H1N1) is diagnosed or epidemiologically suspected, regardless of age, and this may be particularly important for those with pulmonary involvement.

Of note, significant clinical and laboratory findings in patients with lung involvement in this series included prolonged fever (>4 days), nausea/vomiting, dyspnea, altered

consciousness, leukopenia, and elevated serum creatinine kinase and lactic dehydrogenase. Myositis with rhabdomyolysis were observed in patients with severe 2009 pandemic influenza A (H1N1),⁴² and increased serum lactic dehydrogenase was reported to be associated with poor prognosis in this infectious entity.^{3,35} Our data suggested that clinicians should pay attention to the possible emergency of any of the aforementioned symptoms/signs and/or laboratory features, as each of them may potentially be an early warning sign for disease progression in patients with 2009 pandemic influenza A (H1N1).

The limitations of this study should be addressed. First, being a retrospective study, missing data for some included patients were inevitable. Second, obese patients and pregnant women who were previously reported to subject to higher risk of severe complications were not found in this series.^{43,44} Third, the decision to perform a test for confirming or excluding a patient with 2009 pandemic influenza A (H1N1) was based on the individual physicians' judgment of the existence of an alternative diagnosis or not for the febrile patients; as a result, patients included in this series might be biased by individual clinicians' personal experience and judgment. Fourth, the small number of lung involvement cases made the statistical power quite small, and only one fatal case involving a patient with delayed oseltamivir therapy was found in this series. Fifth, the study was conducted in a single tertiary hospital, thus generalizability of the findings may be limited.

In conclusion, our data show that among patients with 2009 pandemic influenza A (H1N1), cough, sore throat, and nausea/vomiting were more frequently encountered in children, while chest pain and dyspnea were more commonly found in adults. Delayed oseltamivir therapy, dyspnea, nausea/vomiting, and altered consciousness were significantly found in patients with radiographic lung abnormalities. Early treatment with oseltamivir is recommended for patients whenever 2009 pandemic influenza A (H1N1) is diagnosed or epidemiologically suspected, regardless of age.

Acknowledgements

We thank the staff members of Emergency Department of Kaohsiung Chang Gung Memorial Hospital for their assistance in collection of throat swabs for RT-PCR and virus cultures.

Authors' contribution

I.K. Lee and J.W. Liu designed the study protocol and drafted the manuscript; I.K. Lee, J.W. Liu, L. Wang, C.C. Li, H.L. Eng, and K.D. Yang were involved in the analysis and interpretation of the data. J.W. Liu critically reviewed

and edited the manuscript. All authors read and approved the final manuscript. I.K. Lee and J.W. Liu are guarantors of the paper.

Financial disclosure

This work was supported by a grant (CMRPG880991) from Kaohsiung Chang Gung Memorial Hospital, Taiwan.

Competing interests

The authors declare no competing interests.

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