Clinical features of 167 children with the novel influenza A (H1N1) virus infection in Xi'an, China

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Since its first recognition, the 2009 pandemic influenza A (H1N1) virus rapidly spread worldwide. We observed the clinical characteristics of 167 hospitalized patients who were confirmed by testing pharyngeal or nasopharyngeal swabs with the use of a real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay. The mean age of the 167 hospitalized patients was 4.1 years, and 58.7% were male. The most common symptoms and signs were fever (91.6%), cough (82.6%), pharyngeal congestion (95.2%), and swollen tonsils (34.1%). The major complications were bronchitis (19.2%), bronchial pneumonia (10.8%), neutropenia (49.7%), and leukopenia (38.9%). The duration of hospitalization, fever and the course of disease in the patients who were treated with oseltamivir were shorter than in those who were treated with ribavirin. All of the patients fully recuperated from the 2009 epidemic influenza A (H1N1) infection with one exception.

Key words: 2009 influenza A (H1N1), children, influenza, pandemic, treatment.

During the 20th century, historically, there have been five pandemics of influenza, causing numerous deaths in humans[1]. In early April 2009, the Centers for Disease Control and Prevention (CDC) in the United States identified the first two cases of human infection with the 2009 pandemic influenza A (H1N1) virus[2]. Subsequently, the 2009 H1N1 virus spread rapidly throughout the world[3]. On June 11, 2009, the World Health Organization (WHO) signaled the phase 6 alert level, the highest level[4]. As of October 11, 2009, 191 countries and territories had reported approximately 375,000 cases of 2009 pandemic (H1N1) with more than 4,500 deaths[5]. By October 26, 2009, there had been 35,664 cases with the novel influenza A virus infection in China since May 2009[6]. In this paper, we describe the clinical characteristics of children who were hospitalized for the treatment of the novel H1N1 influenza in Xi'an, China.

Material and Methods

From November 11, 2009 to March 3, 2010, a total of 1084 outpatients were confirmed as 2009 pandemic influenza A (H1N1) virus infection in Xi'an Children's Hospital, and 167 of them were hospitalized. We closely observed and recorded the clinical characteristics of the 167 inpatients. The criteria of diagnosis and treatment were in accordance with the third version guidelines recommended by the Chinese Ministry of Health[7]. A confirmed case was defined as having influenza-like symptoms and signs (fever, cough, rhinorrhea or sore throat, etc.), and by a positive result of an reverse-transcriptase polymerase chain reaction (RT-PCR) assay performed at a laboratory operated under the auspices of the CDC in Xi'an. The RT-PCR was performed according to the protocol recommended by the WHO[8]. The PCR products were sequenced with the use of the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). A severe case was defined as having one of the following manifestations in addition to the above criteria: 1. More than 3 consecutive days with hyperpyrexia (temperatures ≥39.1°C); 2. Severe cough, purulent sputa, bloody sputa or thoracalgia; 3. Tachypnea, dyspnea, cyanosis; 4. Consciousness disturbance; 5. Severe vomiting, diarrhea and dehydration; 6. Pneumonia signs

on chest radiographs; 7. Rapid elevation of creatine kinase (CK), CK-MB fraction; and 8. Progressive pre-existing medical condition. A critically ill case was defined as having one of the following conditions: respiratory failure; septic shock; multiple organ dysfunction syndrome; or other situations requiring patients to be admitted to the intensive care unit (ICU). A cured case was defined as the absence of influenza-like symptoms, and normal body temperature (36.0 to 37.5°C) taken on 3 consecutive days. All patients were randomly divided into two groups: Group 1 (86 cases) treated with oseltamivir and Group 2 (81 cases) treated with ribavirin (as the control group). Some patients who were suspected of bacterial coinfection were treated with antibiotics. The dosage and duration of oseltamivir were prescribed in accordance with the age and body weight and were the same as for seasonal influenza (Table I)[9,10]. The oral dosage of ribavirin was 10 mg/kg·D, three times daily, for 5 days. The duration of hospitalization, fever and the course of disease were compared between the two groups using a *t*-test. Continuous variables were expressed as the means ± standard deviation (SD). A value of $p<0.05$ was considered to indicate statistical significance. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) 16.0 software package. This study was approved by the Ethics Committee of Xi'an Children's Hospital.

Table I. Oseltamivir Dosing Recommendations

Age and weight	Treatment
>12 months	
Weight (kg)	
<15 kg	30 mg twice daily for 5 days
15-23 kg	45 mg twice daily for 5 days
24-40 kg	60 mg twice daily for 5 days
>40 kg	75 mg twice daily for 5 days
< 12 months	
<3 mos	12 mg twice daily for 5 days
3-5 mos	20 mg twice daily for 5 days
6-12 mos	25 mg twice daily for 5 days

Data from the Food and Drug Administration.[10]

Results

All 1084 outpatients were autochthonous, and 167 (15.4%) were admitted to the hospital.

Table II. Outcomes Data of the 167 Patients

Characteristics	Value	(%)
Sex		
Male	98	58.7
Female	69	41.3
Age		
Mean (y)	4.1	
Range (y)	0.25-14.5	
<5 y	109	65.3
A close contact*		
Yes	65	38.9
No	102	61.1
State of an illness		
Mild case	135	80.8
Severe case	31	18.6
Critically ill case	1	0.6
Past medical history		
Asthma	12	7.2
Congenital heart disease	2	1.2
Febrile convulsion	3	1.8
Henoch-Schönlein purpura	1	0.6
Acute glomerulonephritis	1	0.6
Myocarditis	2	1.2
Pneumonia	5	3.0
Repeated respiratory infection	2	1.2
Repeated abdominal pain	1	0.6
Hematuria and albuminuria	1	0.6
Hand-foot-mouth disease	2	1.2
Scarlet fever	1	0.6
Autism	1	0.6

*A close contact was defined as a person who lived with or was exposed to the respiratory secretions or other bodily fluids of someone with suspected or confirmed infection.

The remaining 917 (84.6%) cases without admission to hospital were quarantined and treated at home. (For any children whose symptoms worsened, hospital admission was required. During the 7 days' follow-up, none of them was hospitalized). Of the 167 inpatients enrolled in this study, 135 (80.8%), 31 (18.6%) and 1 (0.6%) were classified as mild, severe and critically ill cases, respectively. The mean age of infected individuals was 4.1 years (range: 3 months - 14.5 years) and 109 (65.3%) were under the age of 5.0 years. Among the inpatients, 34 (20.3%) cases had past history of illness, 12 of whom had a history of asthma (Table II).

The main symptoms on admission included fever, cough and rhinorrhea. Less common symptoms were wheezing, seizures and gastrointestinal symptoms consisting of vomiting and diarrhea. Of the 153 patients presented with fever, the majority manifested moderate to high fever. The median period of fever before admission was 1.9 days (range: 0.5-6.0), and the time course

Table III. Clinical Features of the 167 Patients

Presentations	No.	(%)
Symptoms		
Fever (≥37.5°C)	153	91.6
37.5~38°C	17	10.2
38.1~39°C	71	42.5
39.1~40.9°C	65	38.9
Cough	138	82.6
Rhinorrhea	42	25.1
Sore throat	31	18.6
Headache	17	10.2
Chills	10	6.0
Diarrhea	9	5.4
Vomiting	6	3.6
Wheezing	5	3.0
Convulsion	4	2.4
Muscular soreness	4	2.4
Hoarse voice	3	1.8
Skin rashes	2	1.2
Signs		
Pharynx congestion	159	95.2
Swollen tonsils	57	34.1
Wheezy sputa	34	20.4
Moist rale of lungs	15	9.0
Wheezing of lungs	11	6.7
Babinski sign positive	3	1.8
Hypomyotonia	3	1.8
Koplik's spots	1	0.6
Parotid enlargement	1	0.6
Complications/comorbidities		
Bronchitis	32	19.2
Bronchial pneumonia	18	10.8
Encephalitis	3	1.8
Rotavirus enteritis	2	1.2
Epidemic parotitis	1	0.6
Measles	1	0.6

of fever was 4.8±0.7 days (range: 0.5-9.0). The signs of pharyngeal congestion and/or swollen tonsils were frequent in the hospitalizations. Frequent complications were bronchitis and bronchial pneumonia (Table III).

The absolute leukocyte count and neutrophil count ranged from 910 to 18,520 and 190 to 10,230 cells/mm^3, respectively, and resolved within an average time of 4.6 days. C-reactive protein (CRP), liver function, myocardial enzyme abnormality, ECG change including first-degree atrioventricular block (I^o AVB), the change in T wave, prolonged R-T interval, and incomplete right bundle branch block (ICRBBB) returned to normal within approximately one week. Of the 167 patients who underwent chest radiography, 32 and 18 had findings of bronchitis and pneumonia, respectively (Table IV).

The median interval from onset of symptoms to definitive diagnosis and to initiation of antiviral therapy was 3.8 and 2.1 days, respectively. The duration of hospitalization and the course of disease were 5.6 days (range: 2.0-12.5) and 7.8 days (range: 4.5-19.5), respectively. The most common side effect of oseltamivir therapy was hypothermia (temperatures <36.0°C), which usually occurred on the second day after taking the medicine, and the incidence was 25 (29.1%). The symptoms of nausea and vomiting were so rare that only one child was compelled to terminate the treatment of oseltamivir due to vomiting. However, none of the above side effects was observed in Group 2. The statistical analysis showed that

Table IV. Laboratory and Radiograph Data of the 167 Patients

Results of examination	No.	(%)
Complete blood count		
Leukopenia×	65	38.9
Leukocytosis§	17	10.2
Neutropenia◊	83	49.7
Agranulocytosis*	14	8.4
Thrombocytopenia*	4	2.4
Urinalysis		
Proteinuria	3	1.8
Occult blood	2	1.2
Elevated CRPΔ	42	25.1
Myocardial enzymes elevation	18	10.8
Liver enzymes elevation	12	7.2
ECG change		
I^o AVB	5	3.0
Change of T wave	5	3.0
ICRBBB	4	2.4
Left ventricular hypertrophy	3	1.8
Prolonged R-T interval	2	1.2
Chest radiographs		
Normal	117	70.0
Bronchitis	32	19.2
Bronchial pneumonia	18	10.8

×Absolute leukocyte count < 4,000 cells/mm^3
§Absolute leukocyte count > 10,000 cells/mm^3
◊Absolute neutrophil count < 1,000 cells/mm^3
*Absolute neutrophil count < 500 cells/mm^3
*Absolute platelet count < 100,000 cells/mm^3
ΔC-reactive protein > 10 mg/L
AVB: Atrioventricular block. ICRBBB: Incomplete right bundle branch block.

taking oseltamivir can significantly reduce the duration of fever, hospitalization and the course of disease compared with results with ribavirin (Table V). Of all 167 inpatients, 18 (10.8%) received antibiotics therapy, and 166 were discharged; one died of acute respiratory failure. The exitus patient, who was confirmed as novel influenza A (H1N1) virus infection by means of RT-PCR assay, was a three-year-old boy. He was admitted to the Infectious Diseases Department with a three-day history of fever up to 39.4°C, cough, rhinorrhea, and neutropenia (neutrophil count was 940 cells/mm^3). Initial frontal chest radiograph showed multifocal, bilateral, asymmetrically distributed foci of ground-glass opacity. Because of consecutive hyperpyrexia and progressive dyspnea, he was transferred to the ICU and received mechanical ventilation on the second day after admission. The latest frontal chest radiograph showed extensive areas of consolidation in both lungs in association with areas of ground-glass opacity. The boy rapidly developed severe progressive respiratory failure and died on the third hospital day.

Discussion

Since it was first recognized in March 2009, the pandemic strain of influenza A (H1N1) virus has spread globally[3]. The first case of the novel virus infection in China was documented on May 10, 2009[11]. We report a cohort of 167 patients in Xi'an Children's Hospital between November 11, 2009 and March 3, 2010. In our study, we found that the clinical features of pediatric patients with 2009 H1N1 influenza were generally similar to those reported during the peak periods of seasonal influenza[12,13]. As is shown in Table III, the hospitalized patients typically present with classic influenza-like symptoms, including fever, cough, rhinorrhea, and sore throat. Meanwhile, it was assumed that the virulence level of the novel virus was so weak that the majority of patients manifested mild symptoms and convalesced within a few days, even without special medical treatment[14]. In our cohort, most of the inpatients (80.8%) experienced a mild clinical course. The laboratory findings including leukopenia, neutropenia and agranulocytosis were transient, which was consistent with the characteristics of virus infection. Of the 167 patients with available chest radiographs, 70.0% were normal; 19.2% showed peribronchial markings with hyperinflation and/or coarse linear markings radiating from the hila into the lungs, which is similar to other common lower respiratory viral infections.

The major complications were bronchitis (19.2%), followed by bronchial pneumonia (10.8%). However, the major complications in adults were infiltrating pneumonia instead of bronchitis and bronchial pneumonia[15]. Hypokalemia was documented in 25.4% of adult patients[16], while the serum electrolytes of our patients were normal. A recently published study in Argentina indicated that children with the novel H1N1 virus had coinfection with respiratory syncytial virus, parainfluenza virus, or adenovirus[17]. We found that children with influenza A (H1N1) virus infection had coexistent measles, epidemic parotitis or rotavirus enteritis, which probably implied that the immune functions were suppressed after influenza A (H1N1) virus infection. As compared with the high proportion of deaths in Argentina, the incidence of death in our cohort was very low. Possible explanations for this difference are the racial or regional disparities, delayed consultation or hospital admission, and the unrecognized presentation of 2009 H1N1 influenza. Asthma has been considered as a risk factor for the novel influenza requiring hospital admission[18]. Among the 167 patients in our study, 12 (7.2%) had a history of asthma. Of the 12 patients with preexisting asthma, five experienced severe clinical presentation.

To date, with few exceptions, the 2009 pandemic H1N1 virus remains susceptible to oseltamivir and zanamivir[19]. Recent guidelines from the CDC in America for the 2009 H1N1 and

Table V. Analysis of Oseltamivir Treatment and Ribavirin Treatment

Grp	No	Duration of fever (days)	Hospitalization (days)	Course of disease
1	86	4.2±0.6	5.1±0.7	6.7±0.8
2	81	5.4±0.7	6.1±0.8	8.9±0.9
t		11.98	8.61	16.74
P		<0.01	<0.01	<0.01

seasonal influenza recommend the use of either oseltamivir or zanamivir for all hospitalized patients with suspected or confirmed influenza and for outpatients who are at high risk for complications[20]. Treatment benefit is greatest if antiviral medications are initiated within 48 hours of symptom onset[21,22]. In addition, studies of oseltamivir therapy in hospitalized patients with influenza indicated reductions in mortality, duration of viral shedding and the incidence of complications, even when such medication was started more than 48 hours after illness onset[23,24]. The protective effect of oseltamivir was 80% in patients who were influenza-negative before beginning prophylaxis[25]. Data from our study suggest that the duration of fever, hospitalization and the disease course of the patients treated with oseltamivir were obviously shortened compared with results of the treatment with ribavirin (Table V). Consequently, it revealed that the oseltamivir medication was beneficial in hospitalized patients. However, multiple-center randomized controlled trials are needed to evaluate the efficacy of oseltamivir in the treatment of 2009 H1N1 virus infection. Meanwhile, the variant of the influenza A (H1N1) virus and strains resistant to oseltamivir were successively identified in America, Japan, Norway, and Hong Kong[26]. Thus, the benefits of oseltamivir should also be balanced against the risk of resistance, and the cost to and demand on the health care system.

Despite a lack of data on the safety and effectiveness of oseltamivir in patients under one year of age, it has been recently authorized by the Food and Drug Administration for emergency use in these patients[10]. In our cohort, 13 patients younger than one year were treated with oseltamivir, which provided a rapid resolution of symptoms and illness, and none of them had adverse effects. By clinical observation, 25 patients manifested hypothermia after oral administration of oseltamivir, which usually occurred on the second day without subjective symptoms. We presumed that the phenomenon probably resulted from the direct effect of oseltamivir on the thermoregulatory center and/or the inhibition of oseltamivir on the inflammatory factor.

In conclusion, our study suggested that most pediatric patients with the 2009 epidemic influenza A (H1N1) infection have classic influenza-like presentations and experience a mild clinical course. Oseltamivir therapy appears to have benefits, and no major adverse effects were noted. Nevertheless, more data from different regions are needed to illuminate the characteristics of children with this novel virus infection, and it is essential for medical workers to continue to investigate the clinical spectrum of the disease and share their experiences, which will allow for improvements in treatment guidance.

REFERENCES

1. Nicholson KG, Wood JM, Zambon M. Influenza. Lancet 2003; 362: 1733-1745.
2. Swine influenza A (H1N1) infection in two children – Southern California, March – April 2009. MMWR Morb Mortal Wkly Rep 2009; 58: 400-402.
3. Global Alert and Response (GAR) – Influenza-like illness in the United States and Mexico. World Health Organization Website. http://www.who.int/csr/don/2009_04_24/en/index.html. [Accessed on May 8, 2009].
4. Influenza A (H1N1) – update 14. Geneva: World Health Organization, 2009. Available from: http://www.who.int/csr/don/2009_05_04a/en/index.html. [Accessed on November 30, 2009].
5. World Health Organization (WHO). Pandemic (H1N1) 2009 – update 69. Available from http://www.who.int/csr/don/2009_10_09/en/index.html. [Accessed on October 11, 2009].
6. The information on influenza A (H1N1). Available from: http://www.moh.gov.cn/publicfiles/business/htmlfiles/H1N1/s10619/200910/45162.htm. [Accessed on November 10, 2009].
7. Guidelines for diagnosis and treatment of influenza A (H1N1) (the third version, 2009). Available from: http://www.moh.gov.cn/publicfiles/business/htmlfiles/H1N1/s10619/200910/45166.htm. [Accessed on November 1, 2009].
8. CDC protocol of realtime RTPCR for swine influenza A (H1N1). Geneva: World Health Organization, April 28, 2009. (Accessed November 30, 2009, at http://www.who.int/csr/resources/publications/swineflu/CDC realtime RTPCR protocol_20090428.pdf.)
9. Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children - diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009; 48: 1003-1032.
10. Food and Drug Administration. Emergency use authorization (EUA) review oseltamivir phosphate for swine influenza A. FDA Website. http://www.fda.gov/downloads/Drugs/DrugSafety/ImformationbyDrugClass/UCM153547.pdf. [Accessed on November 11, 2009].

11. Cao B, Li XW, Mao Y, et al. Clinical and epidemiologic characteristics of 3 early cases of influenza A pandemic (H1N1) virus 2009 infection, People's Republic of China, 2009. Emerg Infect Dis 2009; 15: 1418-1422.

12. Moore DL, Vaudry W, Scheifele DW, et al. Surveillance for influenza admissions among children hospitalized in Canadian immunization monitoring program active centers, 2003-2004. Pediatrics 2006; 118: e610-e619.

13. Komiya N, Gu Y, Kamiya H, et al. Clinical features of cases of influenza A (H1N1)v in Osaka prefecture, Japan, May 2009. Euro Surveill 2009; 14(29). pii: 19272. http://www.eurosurveillance.org/ViewArticle.aspx? ArticlId=19272. [Accessed on December 9, 2009].

14. Belgian Working Group on Influenza A(H1N1)v. Influenza A(H1N1)v virus infections in Belgium, May-June 2009. Euro Surveill 2009; 14(28). Pii: 19270. http://www.eurosurveillance.org/ViewArticle.aspx? ArticleId=19270. [Accessed on December 9, 2009].

15. Centers for Disease Control and Prevention (CDC). Update: novel influenza A (H1N1) virus infection – Mexico, March – May, 2009. MMWR Morb Mortal Wkly Rep 2009; 58: 585-589.

16. Cao B, Li XW, Mao Y, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. N Engl J Med 2009; 361: 2507-2517.

17. Libster R, Bugna J, Coviello S, et al. Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. N Engl J Med 2009; 362: 45-55.

18. 2009 pandemic influenza A (H1N1) virus infections – Chicago, Illinois, April – July 2009. MMWR Morb Mortal Wkly Rep 2009; 58: 913-918.

19. Itoh Y, Shinya K, Kiso M, et al. In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. Nature 2009; 460: 1021-1025.

20. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season. Atlanta: Centers for Disease Control and Prevention. http://www.cdc.gov/h1n1flu/ recommendations.htm. [Accessed on October 19, 2009].

21. McGeer A, Green KA, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clin Infect Dis 2007; 45: 1568-1575.

22. Domínguez-Cherit G, Lapinsky SE, Macias AE, et al. Critically ill patients with 2009 influenza A(H1N1) in Mexico. JAMA 2009; 302: 1880-1887.

23. Hanshaoworakul W, Simmerman JM, Narueponjirakul U, et al. Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. PLoS ONE 2009; 4: e6051.

24. Lee N, Chan PK, Hui DS, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis 2009; 200: 492-500.

25. Matheson NJ, Harnden AR, Perera R, et al. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev 2007; (1): CD002744.

26. World Health Organization. Pandemic (H1N1) 2009 – update 66. Available from: http://www.who.int/csr/don/2009_09_18/en/index.html. [Accessed on September 1, 2009].