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Clinical characteristics of critical patients with pandemic influenza A (H1N1) virus infection in Chengdu, China

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Abstract: Objective: The critical illness of pandemic influenza A (H1N1) virus infection may be associated with relatively poor outcomes. The objective of this study is to describe clinical features and factors associated with the deaths of critical patients. Methods: Medical records of 26 critical patients with H1N1 infection admitted from Sept. 1 to Dec. 31, 2009, were retrospectively reviewed. Diagnosis was established by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay. Results: The mean age of the patients was (40.4±18.4) years and 73.1% of them were male. Clinical manifestations included fever, cough, and sputum production. The laboratory findings included leukocytosis, lymphopenia, C-reaction protein, and lactic dehydrogenase elevation. In this series, 17 subjects survived and 9 died. The parameters between the deaths and survivors were compared, which included acute physiology and chronic health evaluation II (APACHE II) scores (23.8±10.1 vs. 14.3±6.6, P<0.05), sequential organ failure assessment (SOFA) scores (13.3±3.0 vs. 6.6±3.3, P<0.05), and multiple organ dysfunction syndrome (MODS) scores (7.4±2.5 vs. 3.3±1.7, P<0.05). The cases of deaths had higher incidences of cardiovascular failure (100% vs. 41.2%, P<0.05), renal failure (55.6% vs. 11.7%, P<0.05), encephalopathy (44.4% vs. 5.9%, P<0.05), hepatic failure (33.3% vs. 5.9%, P<0.05), and septic shock (33.3% vs. 17.6%, P<0.05). Conclusions: The critical patients with H1N1 infection have high APACHE II, SOFA, and MODS scores, which may be associated with an increased risk of death and complex clinical courses.

Key words: Critical illness, H1N1, Infection, Influenza A virus, Mortality
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1 Introduction

During the spring of 2009, a novel pandemic influenza A (H1N1) virus emerged in North America (Centers for Disease Control and Prevention, 2009a; 2009c; 2009d). The virus then spread rapidly to other regions of the world (Centers for Disease Control and Prevention, 2009b; Naffakh and van der Werf, 2009), resulting in the first influenza pandemic since 1968. On May 7, 2009, a Chinese national network was organized to monitor the prevalence of H1N1 virus infection. On May 10, 2009 the first case of imported infection was identified in Chengdu, China. Since then, those who had a suspected viral infection, or a history of contact with those with suspected infection, were tested.

Although the surveillance showed that the majority of cases had mild symptoms at the initial stage (Cao *et al*., 2009a; Mu *et al*., 2010), those with H1N1 influenza usually had poor outcomes (Xi *et al*., 2010). On Dec. 7, 2009, a study showed that 4328 cases had severe symptoms in mainland China and

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326 of them died (Zheng *et al*., 2011). As of March 2010, more than 17700 deaths among laboratory-confirmed cases had been reported to the World Health Organization (WHO). To identify the high-risk patients at the early stage may be of help for improving the prognosis of the disease.

In this retrospective study, we studied the clinical characteristics and factors associated with mortality.

2 Materials and methods

2.1 Study design

From Sept. 1 to Dec. 31, 2009, 26 critically ill patients with a confirmative diagnosis of H1N1 virus infection were admitted to the West China Hospital of Sichuan University and the Chengdu Infectious Disease Hospital. Subjects' medical records were retrospectively reviewed. Data were collected by using a standard data collection instrument, which included demographic characteristics, coexisting medical conditions, clinical symptoms and signs, laboratory tests, and treatment course.

A confirmed case was defined by a positive result of virologic testing of samples from pharyngeal or nasopharyngeal swabs with the use of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay (World Health Organization, 2009a).

After admission, serial pharyngeal or nasopharyngeal swabs were collected and analyzed daily for real-time RT-PCR testing. The tests were performed by the Center for Disease Control and Prevention of Sichuan Province, China. Severity of the illness was assessed within 24 h after admission using the acute physiology and chronic health evaluation II (APACHE II) scores (Knaus *et al*., 1985), sequential organ failure assessment (SOFA) scores (Vincent *et al*., 1996), and multiple organ dysfunction syndrome (MODS) scores (Marshall *et al*., 1995). We reported the associated parameters with the worst values as appropriate. The diagnostic criteria for organ failure were adopted (Bone *et al*., 1992). The criteria for discharge were two readings of normal body temperature taken on two consecutive days and negative results on testing of the samples from two consecutive pharyngeal or nasopharyngeal swabs.

The demographic characteristics (age, sex distribution), symptoms and signs, underlying illness, severity index, laboratory findings, and treatment courses were summarized. The clinical data of the survivors and the deaths were compared.

2.2 Ethics

As the study was retrospective, no informed consent was attained. This study was carried out in accordance with the Helsinki Declaration. Patient confidentiality was maintained by recording only date of birth and sex on the data-collection form.

2.3 Statistical analysis

Data are expressed as mean±standard deviation (SD), median, percentage, or frequency. Continuous variables in normal and non-normal distributions were compared using unpaired Student's *t*-test and rank-sum test, respectively; categorical variables were compared using chi-square test or Fisher's exact test, as appropriate; the remaining were summarized with informal descriptive analysis. A two-sided P value less than 0.05 was considered to indicate statistical significance. All analyses were carried out with SPSS software for Windows (release 16.0).

3 Results

3.1 Clinical characteristics of patients

The mean age of the subjects was (40.4±18.4) years (range 5–70 years) and 73.1% of them were male (Table 1). All subjects developed fever with a mean temperature of (38.6±0.7) °C (range 37.4–40.2 °C). Other most common symptoms were cough (92.3%), sputum production (88.5%), and dyspnea (46.2%). The less common symptoms included fatigue, sore throat, bloody sputum, diarrhea, conscious disturbance, rhinorrhea, headache, myalgia or arthralgia, and nasal congestion. Physical examination at admission found that 73.1% and 65.4% of the subjects had the signs of congestion of throat and swelling of tonsils, respectively.

In this series, 15 subjects (57.7%) had at least one documented coexisting medical condition, six (23.1%) had two, and four (15.4%) had three. Chronic obstructive pulmonary disease (COPD) and diabetes occurred in 26.9% and 23.1% of the subjects, respectively. Other conditions included hypertension, asthma,

Table 1 Demographics, clinical symptoms, and signs of the critical patients with influenza A (H1N1) virus

Variable	Value
Age (year)	40.4±18.4 (5–70)[a]
Age group	
≤14 years	1 (3.8%)[b]
15–30 years	6 (23.1%)
31–50 years	9 (34.6%)
51–65 years	8 (30.8%)
>65 years	2 (7.7%)
Sex distribution	
Male	19 (73.1%)
Female	7 (26.9%)
Symptom	
Fever	26 (100%)
Temperature (°C)	38.6±0.7 (37.4–40.2)
Cough	24 (92.3%)
Sputum production	23 (88.5%)
Dyspnea	12 (46.2%)[*]
Fatigue	12 (46.2%)
Sore throat	8 (30.8%)
Bloody sputum	7 (26.9%)
Diarrhea	6 (23.1%)
Conscious disturbance	5 (19.2%)[#]
Rhinorrhea	5 (19.2%)
Headache	5 (19.2%)
Myalgia, arthralgia	6 (23.1%)
Nasal congestion	4 (15.4%)
Sign	
Congestion of throat	19 (73.1%)
Swelling of tonsils	17 (65.4%)

Data are expressed as mean±SD (range)[a] or *n* (%)[b]. [*] Eight patients died and four survived; [#] Four patients died and one survived

Table 2 Underlying illness and outcomes of the critical patients with influenza A (H1N1) virus

Variable	Value
Documented coexisting medical conditions	
Chronic obstructive pulmonary disease	7 (26.9%)[a]
Diabetes	6 (23.1%)
Hypertension	2 (7.7%)
Asthma	2 (7.7%)
Chronic hepatitis B	2 (7.7%)
Others[*]	6 (23.1%)
Outcomes (d)	
Duration of fever	7 (2–16)[b]
Interval of negative conversion of viral nucleic acid	6 (3–15)
Disease course	12 (6–20)
Length of hospital stay	7 (1–16)
Mortality	9 (34.6%)

Data are expressed as *n* (%)[a] or mean (range)[b]. [*] Other underlying illnesses included pregnancy, bronchiectasis, human immunodeficiency virus infection, chronic kidney disease, rheumatic heart disease, and systemic lupus erythematosus

pregnancy, bronchiectasis, chronic hepatitis B complicated by liver cirrhosis, human immunodificiency virus (HIV) infection, chronic kidney disease, rheumatic heart disease, and systemic lupus erythematosus (SLE) (details shown in Table 2).

Detailed laboratory values collected within 24 h after admission are demonstrated in Table 3. Leukocytosis and mild lymphopenia occurred in 42.3% and 50.0% of the subjects, respectively. The levels of creatine kinase (CK), creatine kinase MB fraction (CK-MB), lactate dehydrogenase (LDH), C-reactive protein (CRP), and CD4 T-lymphocyte were recorded. Abnormal alanine aminotransferase (ALT) ((62.9±49.0) U/L, range 5.0–195.0 U/L) and total bilirubin ((32.9±100.1) μmol/L, range 3.7–511.0 μmol/L) levels occurred in 42.3% (11/26) and 30.8% (8/26) of the subjects, respectively.

3.2 Outcomes

In this series, 17 (65.4%) subjects survived and 9 (34.6%) subjects died within 5 to 16 d after onset of the symptoms (Table 2). The median duration for viral nucleic acid from the onset to obtaining a negative test result of real-time RT-PCR was 6 d (range 3–15 d). The median durations of fever, total disease course, and hospital stay were 7 d (range 2–16 d), 12 d (range 6–20 d), and 7 d (range 1–16 d), respectively.

Table 3 Laboratory findings at admission

Variable	Value
Leukocyte count ($\times10^9$ L^{-1})	11.5±8.8 (4.4–39.6)[a]
>10.0×10^9 L^{-1}	11 (42.3%)[b]
Lymphocyte count ($\times10^9$ L^{-1})	2.6±0.4 (0.4–3.1)
<1.5×10^9 L^{-1} in adults	13 (50%)
CD4 T-lymphocyte count ($\times10^9$ L^{-1})	349.8±363.3 (4.0–1278.0)
Creatine kinase (U/L)	423.4±518.8 (26.0–2232.0)
>200 U/L	12 (46.2%)
Creatine kinase MB fraction (U/L)	43.7±67.8 (8.0–347.0)
>25 U/L	15 (57.7%)
Lactate dehydrogenase (U/L)	567.7±441.9 (182.0–2342.0)
Alanine aminotransferase (U/L)	62.9±49.0 (5.0–195.0)
Total bilirubin (μmol/L)	32.9±100.1 (3.7–511.0)
C-reactive protein (mg/L)	119.2±86.9 (6.0–325.2)
>10 mg/L	23 (88.5%)

Data are expressed as mean±SD (range)[a] or *n* (%)[b]

3.3 Clinical characteristics of the deaths

There were no significant differences between the deaths and the survivors regarding gender distribution, age, documented coexisting medical conditions, and laboratory findings (Table 4). After admission, 12 (46.2%) subjects developed dyspnea. Among them, eight (66.7%) subjects died and four (33.3%) survived with a significant difference. Four of five (80%) subjects with consciousness disturbance died (Table 1).

We also compared the measurements between the deaths and survivors. We found that the former was higher than the latter regarding APACHE II scores (23.8±10.1 vs. 14.3±6.6, $P<0.05$), MODS scores (7.4±2.5 vs. 3.3±1.7, $P<0.05$), SOFA scores (13.3±3.0 vs. 6.6±3.3, $P<0.05$) (Table 4), with statistical significance. The former was also higher than the latter regarding incidence of respiratory failure (100% vs. 88.2%, $P>0.05$), gastrointestinal dysfunction (22.2% vs. 17.6%, $P>0.05$), and coagulopathy (11.1% vs. 5.9%, $P>0.05$), with no statistical significance. The former was higher than the latter regarding incidence of cardiovascular failure (100% vs. 41.2%, $P<0.05$), renal failure (55.6% vs. 11.7%, $P<0.05$), encephalopathy (44.4% vs. 5.9%, $P<0.05$), and hepatic failure (33.3% vs. 5.9%, $P<0.05$), with statistical significance. The use of invasive mechanic ventilation was significantly higher in the deaths than in the survivors (77.8% vs. 35.3%, $P<0.05$). The differences between the deaths and the survivors in use of corticosteroids (100% vs. 70.6%, $P<0.05$), their dosage (135.6±70.6 vs. 53.3±26.7, $P<0.05$), and duration of application (6.0 vs. 4.0, $P<0.05$) were statistically significant. Comparisons of other clinical features between the survivors and the deaths are summarized in Table 4.

Table 4 Comparison of clinical features between survivors and deaths

Variable	Value		*P*
	Survivor (*n*=17)	Death (*n*=9)	
Age (year)	40.5±17.1[a]	40.3±21.2	NS
Male	14 (82.4%)[b]	5 (55.6%)	NS
No. of underlying diseases	1.0±1.2	1.4±1.2	NS
APACHE II score	14.3±6.6	23.8±10.1	<0.05
MODS score	3.3±1.7	7.4±2.5	<0.05
SOFA score	6.6±3.3	13.3±3.0	<0.05
No. of organ failure	2.3±1.4	3.9±1.4	<0.05
Organ failure			
Pulmonary failure	15 (88.2%)	9 (100%)	NS
Cardiovascular failure	7 (41.2%)	9 (100%)	<0.05
Renal failure	2 (11.7%)	5 (55.6%)	<0.05
Encephalopathy	1 (5.9%)	4 (44.4%)	<0.05
Hepatic failure	1 (5.9%)	3 (33.3%)	<0.05
Coagulopathy	1 (5.9%)	1 (11.1%)	NS
Gastrointestinal failure	3 (17.6%)	2 (22.2%)	NS
Secondary infection	12 (70.6%)	5 (55.6%)	NS
Septic shock	3 (17.6%)	3 (33.3%)	<0.05
Invasive ventilation	6 (35.3%)	7 (77.8%)	<0.05
Corticosteroids			
Usage	12 (70.6%)	9 (100%)	<0.05
Dosage (mg/d)	53.3±26.7	135.6±70.6	<0.05
Course (d)	4.0 (0–6)[c]	6.0 (1–10)	<0.05

Data are expressed as mean±SD[a], *n* (%)[b], or median (range)[c]
NS: no significance

4 Discussion

Since the spring of 2009, a novel influenza A (H1N1) virus emerged globally. On June 11, 2009, the WHO raised the pandemic alert level to phase VI, the highest level (Cao *et al*., 2009b; World Health Organization, 2009c). At least 3205 of 277607 documented patients died in the world (Dawood *et al*., 2009; World Health Organization, 2009b). It is necessary for clinicians to identify the high-risk patients at the early stage. In this case series, we report demographic features, and reveal the risk factors for critical illness.

In the previous studies, many hospitalized patients during the peak periods of the seasonal influenza were usually younger than 2 years of age or older than 65 years of age and associated with certain coexisting medical conditions (Thompson *et al*., 2004; Fiore *et al*., 2008). The epidemiological characteristics show that the mean age of our series is 40.4 years. Only one subject was 5 years of age and two were older than 65 years of age. The reported underlying medical conditions associated with the seasonal influenza included diabetes, cardiovascular, neurologic, and pulmonary diseases such as asthma (Schrag *et al*., 2006; Harper *et al*., 2009). In this study, 57.7% of the subjects had at least one or more documented coexisting medical conditions. The incidence of the conditions is higher than those reported previously

(Tomizuka *et al*., 2010). The most common coexisting medical conditions were COPD, diabetes, hypertension, and asthma.

A wide clinical spectrum of symptoms in patients with H1N1 was indicated. Fever occurs in all patients and the temperature is usually at or above 38.6 °C. Cough (92.3%), sputum production (88.5%), and dyspnea (46.2%) were the most common symptoms. Additionally, some patients experienced fatigue, sore throat, bloody sputum, diarrhea, conscious disturbance, rhinorrhea, headache, myalgia or arthralgia, and nasal congestion. On admission, the patients were characterized by leukocytosis, mild lymphopenia (Centers for Disease Control and Prevention, 2009e), and elevated levels of CK, CK-MB, LDH, CRP, ALT, and total bilirubin (Mu *et al*., 2010; Xi *et al*., 2010). The median interval of a negative test result of real-time RT-PCR was 6 d, which is consistent with the data reported by Cao *et al*. (2009a).

The mortality of this series (34.6%) is lower than that of Mexico (41.4%) (Domínguez-Cherit *et al*., 2009), but higher than that of California (11.0%) (Louie *et al*., 2009). Thompson *et al*. (2003) reported that influenza-related deaths occur in the old patients, but the deaths in our subjects had a median age of 40 years. The median time from symptom onset to death was 13 d, indicating that the disease progresses rapidly. In the previous study, 13.9% of the deaths were healthy, and high prevalence of co-morbidities was also not found in this study. There was no statistical significance in the gender distribution or in the laboratory findings. We found that eight of twelve patients with dyspnea died and four of five patients with consciousness disturbance also died. We believe that dyspnea and consciousness disturbance indicate a critical status and are associated with death. In the deaths, the severity index (APACHE II, SOFA, and MODS scores) and incidence rate of organ (the heart, kidney, encephalopathy, and liver) failure were significantly higher, associated with a severe episode of the disease. The more severe degree of disease in the cases of death resulted in a more complex treatment course. The use rate, dosage, and duration of corticosteroids are significantly higher in the deaths than in the survivors. As application of corticosteroids is associated with a trend of higher hospital mortality, routinely systemic application is not encouraged in our study unless the application was indicated for the respiratory failure (World Health Organization, 2010; Xi *et al*., 2010). Tamiflu (oseltamivir phosphate, Roche) was given to all patients as soon as possible in this study. Although there are no adequate data from a randomized trial, controlled trials have been performed for comparison among the antiviral medicines against the influenza. Application of oseltamivir is strongly recommended by the WHO, as the drug is especially important for the patients with underlying risk factors and severe or progressive infection of pandemic H1N1 2009 (Bautista *et al*., 2010; Smith *et al*., 2010).

Pregnant women are at risk of both influenza and its complications, which can particularly increase the mortality (Rasmussen *et al*., 2008; Jamieson *et al*., 2009). In this study, there was a 24-year-old pregnant woman with the underlying disease of rheumatic heart disease. She developed MODS, severe pneumonia, and septic shock. She died 9 d after onset of the symptoms. Descriptions of California and the United States have showed a substantial mortality rate of 8% among the pregnant women with severe 2009 H1N1 infection (Louie *et al*., 2010). The maternal mortality rate was 11% in the intensive care units in Australia and New Zealand, which was higher than those of patients with any other obstetric conditions (The ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System, 2010).

In this series, a subject with HIV was H1N1 infected. The subject's clinical course was complex due to having associated respiratory failure and pneumonia, severe leukopenia, and thrombocytopenia. These complications were relived after application of Tamiflu (150 mg twice daily), glucocorticoid (80 mg/d for 2 d), and non-invasive respirator. The similar case was previously reported by Iwata *et al.* (2010).

This study has potential limitations. First, as a retrospective study, collection of accurate data regarding the symptoms, signs, and patient's history at follow-up was not readily available. Second, when a negative result of real-time RT-PCR testing was indicated, the patient could be transferred to the community hospital or discharged home. Thus, the patient could have had a short hospital stay. Third, the study included all patients hospitalized with critical illness, minimizing the effect of selective triaging of critically ill patients and minimizing the potential for overrepresentation of patients with certain characteristics or

severity of illness. Larger samples of multicenter studies should be studied in the future.

Despite these limitations, data in this study could represent the typical features of the disease in this region, and could provide clinical experience in the treatment of H1N1 infection, as the majority of the confirmed cases with H1N1 infection in Chengdu were treated in the two hospitals. The strengths of this study include confirmation by standardized real-time RT-PCR criteria and relatively little missing data.

References

Bautista, E., Chotpitayasunondh, T., Gao, Z., Harper, S.A., Shaw, M., Uyeki, T.M., Zaki, S.R., Hayden, F.G., Hui, D.S., Kettner, J.D., *et al*., 2010. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N. Engl. J. Med.*, **362**(21):1708-1719.

Bone, R.C., Balk, R.A., Cerra, F.B., Dellinger, R.P., Fein, A.M., Knaus, W.A., Schein, R.M., Sibbald, W.J., 1992. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*, **101**(6):1644-1655. [doi:10.1378/chest.101.6.1644]

Cao, B., Li, X.W., Mao, Y., Wang, J., Lu, H.Z., Chen, Y.S., Liang, Z.A., Liang, L., Zhang, S.J., Zhang, B., *et al*., 2009a. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. *N. Engl. J. Med.*, **361**(26):2507-2517. [doi:10.1056/NEJMoa0906612]

Cao, B., Li, X.W., Shu, Y.L., Jiang, N.J., Chen, S.J., Xu, X.Y., Chen, W., National Influenza A Pandemic (H1N1) 2009 Clinical Investigation Group, 2009b. 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.*, **15**(9):1418-1422. [doi:10.3201/eid1509.090794]

Centers for Disease Control and Prevention, 2009a. Swine influenza A (H1N1) infection in two children—Southern California, March-April 2009. *MMWR Morb. Mortal. Wkly. Rep.*, **58**(15):400-402.

Centers for Disease Control and Prevention, 2009b. Update: infections with a swine-origin influenza A (H1N1) virus—United States and other countries, April 28, 2009. *MMWR Morb. Mortal. Wkly. Rep.*, **58**(16):431-433.

Centers for Disease Control and Prevention, 2009c. Outbreak of swine-origin influenza A (H1N1) virus infection—Mexico, March-April 2009. *MMWR Morb. Mortal. Wkly. Rep.*, **58**(17):467-470.

Centers for Disease Control and Prevention, 2009d. Swine-origin influenza A (H1N1) virus infections in a school—New York City, April 2009. *MMWR Morb. Mortal. Wkly. Rep.*, **58** (17):470-472.

Centers for Disease Control and Prevention, 2009e. Hospitalized patients with novel influenza A (H1N1) virus infection—California, April-May, 2009. *MMWR Morb. Mortal. Wkly. Rep.*, **58**(19):536-541.

Dawood, F.S., Jain, S., Finelli, L., Shaw, M.W., Lindstrom, S., Garten, R.J., Gubareva, L.V., Xu, X., Bridges, C.B., Uyeki, T.M., Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, 2009. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N. Engl. J. Med.*, **360** (25):2605-2615. [doi:10.1056/NEJMoa0903810]

Domínguez-Cherit, G., Lapinsky, S.E., Macias, A.E., Pinto, R., Espinosa-Perez, L., de la Torre, A., Poblano-Morales, M., Baltazar-Torres, J.A., Bautista, E., Martinez, A., *et al*., 2009. Critically ill patients with 2009 influenza A (H1N1) in Mexico. *JAMA*, **302**(17):1880-1887. [doi:10.1001/jama.2009.1536]

Fiore, A.E., Shay, D.K., Broder, K., Iskander, J.K., Uyeki, T.M., Mootrey, G., Bresee, J.S., Cox, N.S., Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP), 2008. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR Recomm. Rep.*, **57**(RR-7):1-60.

Harper, S.A., Bradley, J.S., Englund, J.A., File, T.M., Gravenstein, S., Hayden, F.G., McGeer, A.J., Neuzil, K.M., Pavia, A.T., Tapper, M.L., *et al*., 2009. 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.*, **48**(8):1003-1032. [doi:10.1086/598513]

Iwata, K., Shinya, K., Makino, A., Yoshida, H., Kinoshita, S., Ohji, G., Kato, K., 2010. A case of pandemic 2009 influenza A (H1N1) in a patient with HIV infection. *J. Infect. Chemother.*, **16**(4):298-300. [doi:10.1007/s10156-010-0054-8]

Jamieson, D.J., Honein, M.A., Rasmussen, S.A., Williams, J.L., Swerdlow, D.L., Biggerstaff, M.S., Lindstrom, S., Louie, J.K., Christ, C.M., Bohm, S.R., *et al*., 2009. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet*, **374**(9688):451-458. [doi:10.1016/S0140-6736(09)61304-0]

Knaus, W.A., Draper, E.A., Wagner, D.P., Zimmerman, J.E., 1985. APACHE II: a severity of disease classification system. *Crit. Care Med.*, **13**(10):818-829. [doi:10.1097/00003246-198510000-00009]

Louie, J.K., Acosta, M., Winter, K., Jean, C., Gavali, S., Schechter, R., Vugia, D., Harriman, K., Matyas, B., Glaser, C.A., *et al*., 2009. Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California. *JAMA*, **302**(17):1896-1902. [doi:10.1001/jama.2009.1583]

Louie, J.K., Acosta, M., Jamieson, D.J., Honein, M.A., for the California Pandemic (H1N1) Working Group, 2010. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N. Engl. J. Med.*, **362**(1):27-35. [doi:10.1056/NEJMoa0910444]

Marshall, J.C., Cook, D.J., Christou, N.V., Bernard, G.R., Sprung, C.L., Sibbald, W.J., 1995. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit. Care Med.*, **23**(10):1638-1652. [doi:10.1097/00003246-199510000-00007]

Mu, Y.P., Zhang, Z.Y., Chen, X.R., Xi, X.H., Lu, Y.F., Tang, Y.W., Lu, H.Z., 2010. Clinical features, treatments and prognosis of the initial cases of pandemic influenza H1N1 2009 virus infection in Shanghai China. *QJM*, **103**(5):311-317. [doi:10.1093/qjmed/hcq012]

Naffakh, N., van der Werf, S., 2009. April 2009: an outbreak of swine-origin influenza A (H1N1) virus with evidence for human-to-human transmission. *Microbes Infect.*, **11**(8-9):725-728. [doi:10.1016/j.micinf.2009.05.002]

Rasmussen, S., Jamieson, D., Bresee, J., 2008. Pandemic influenza and pregnant women. *Emerg. Infect. Dis.*, **14**(1):95-100. [doi:10.3201/eid1401.070667]

Schrag, S.J., Shay, D.K., Gershman, K., Thomas, A., Craig, A.S., Schaffner, W., Harrison, L.H., Vugia, D., Clogher, P., Lynfield, R., *et al*., 2006. Multistate surveillance for laboratory confirmed, influenza-associated hospitalizations in children: 2003–2004. *Pediatr. Infect. Dis. J.*, **25**(5):395-400. [doi:10.1097/01.inf.0000214988.81379.71]

Smith, J.R., Ariano, R.E., Toovey, S., 2010. The use of antiviral agents for the management of severe influenza. *Crit. Care Med.*, **38**(s4):e43-e51. [doi:10.1097/CCM.0b013e3181c85229]

The ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System, 2010. Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study. *BMJ*, **340**(mar18 3):c1279. [doi:10.1136/bmj.c1279]

Thompson, W.W., Shay, D.K., Weintraub, E., Brammer, L., Cox, N., Anderson, L.J., Fukuda, K., 2003. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA*, **289**(2):179-186. [doi:10.1001/jama.289.2.179]

Thompson, W.W., Shay, D.K., Weintraub, E., Brammer, L., Bridges, C.B., Cox, N.J., Fukuda, K., 2004. Influenza-associated hospitalizations in the United States. *JAMA*, **292**(11):1333-1340. [doi:10.1001/jama.292.11.1333]

Tomizuka, T., Takayama, Y., Shobayashi, T., Fukushima, Y., Suzuki, Y., 2010. Underlying medical conditions and hospitalization for pandemic (H1N1) 2009, Japan. *Emerg. Infect. Dis.*, **16**(10):1646-1647. [doi:10.3201/eid1610.091755]

Vincent, J.L., Moreno, R., Takala, J., Willatts, S., de Mendonça, A., Bruining, H., Reinhart, C.K., Suter, P.M., Thijs, L.G., 1996. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med.*, **22**(7):707-710. [doi:10.1007/BF01709751]

World Health Organization, 2009a. CDC Protocol of Realtime RTPCR for Swine Influenza A (H1N1). World Health Organization, Geneva. Available from http://www.who.int/csr/resources/publications/swineflu/CDCrealtimeRTPCRprotocol_20090428.pdf [Accessed on Oct. 26, 2010]

World Health Organization, 2009b. Global Alert and Response (GAR)—Pandemic (H1N1) 2009 Guidance Documents. World Health Organization, Geneva. Available from http://www.who.int/csr/resources/publications/swineflu/en/ [Accessed on Oct. 26, 2010]

World Health Organization, 2009c. Influenza A (H1N1)—Update 14. World Health Organization, Geneva. Available from http://www.who.int/csr/don/2009_05_04a/en/index.html [Accessed on Oct. 26, 2010]

World Health Organization, 2010. WHO Guidelines for Pharmacological Management of Pandemic Influenza A (H1N1) 2009 and Other Influenza Viruses. World Health Organization, Geneva. Available from http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html [Accessed on Oct. 26, 2010]

Xi, X., Xu, Y., Jiang, L., Li, A., Duan, J., Du, B., Chinese Critical Care Clinical Trial Group, 2010. Hospitalized adult patients with 2009 influenza A (H1N1) in Beijing, China: risk factors for hospital mortality. *BMC Infect. Dis.*, **10**:256. [doi:10.1186/1471-2334-10-256]

Zheng, Y., He, Y., Deng, J., Lu, Z., Wei, J., Yang, W., Tang, Z., Li, B., Zhang, J., Wang, L., *et al*., 2011. Hospitalized children with 2009 influenza a (H1N1) infection in Shenzhen, China, November-December 2009. *Pediatr. Pulmonol.*, **46**(3):246-252. [doi:10.1002/ppul.21359]