MAJOR ARTICLE

Early Use of Glucocorticoids Was a Risk Factor for Critical Disease and Death From pH1N1 Infection

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Background. Glucocorticoids increase the risk of developing critical disease from viral infections. However, primary care practitioners in China use them as antipyretics, potentially exposing hundreds of millions to this risk.

Methods. We enrolled all patients with confirmed pandemic influenza A (pH1N1) virus infection aged ≥3 years with available medical records at 4 Shenyang City hospitals from 20 October to 30 November 2009. A critical patient was any confirmed, hospitalized pH1N1 patient who developed ≥1 of the following: death, respiratory failure, septic shock, failure or insufficiency of ≥2 nonpulmonary organs, mechanical ventilation, or ICU admission. In a retrospective cohort study, we evaluated the risk of developing critical illness in relation to early (≤72 hours of influenza-like illness [ILI] onset) glucocorticoids treatment.

Results. Of the 83 hospitalized case-patients, 46% developed critical illness, 17% died, and 37% recovered and were discharged. Critically ill and other patients did not differ by underlying conditions and severity, median temperature at first clinic visit, and other measured risk factors. Of 17 patients who received early glucocorticoid treatment, 71% subsequently developed critical disease compared with 39% of 66 patients who received late (>72 hours) or no glucocorticoid treatment ($RR_{M\text{-}H}$ = 1.8, 95% CI = 1.2–2.8, after adjusting for 2 summary variables; ie, presence of underlying diseases and presence of underlying risk factors). Proportional hazards modeling showed that use of glucocorticoids tripled the hazard of developing critical disease (hazard ratio [HR] = 2.9, 95% CI = 1.3–6.2, after adjusting for the same summary variables).

Conclusions. Early use of parenteral glucocorticoids therapy for fever reduction and pneumonia prevention increases the risk for critical disease or death from pH1N1 infection. We recommend that guidelines on glucocorticoid use be established and enforced.

The 2009 pandemic influenza A (pH1N1) virus caused tens of thousands of deaths globally [1], including 800 reported deaths in China [2]. Known risk factors associated with the development of severe pH1N1 influenza include diabetes; immunosuppression; cardiovascular, neurologic, and pulmonary diseases; obesity; pregnancy; and other underlying comorbidities. Typically >50% of the hospitalized patients and 70%–98% of the patients admitted to intensive care units (ICUs) in western countries had at least 1 of these underlying risk factors [3–9]. In China, however, these conditions appeared to be less prevalent in severely ill patients. Of the 4328 severely ill patients reported in China between 10 May and 7 December 2009, 32% had underlying diseases, 19% were obese, and 7.5% were pregnant; of the 326 patients who died, 47% had underlying diseases, 18% were obese, and 14% were pregnant [10].

Immunosuppression constituted an important portion of the underlying conditions for critically ill pH1N1 patients in the published literature. Studies conducted in the United States [6], Australia [11], and Canada [8]

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showed that 15%–20% of the patients with severe pH1N1 were immunosuppressed. However, in China, analysis of pH1N1 surveillance data showed that only 2.9% of the severe pH1N1 patients (as defined by the Ministry of Health of China [12]) reported between 10 May and 7 December were immunosuppressed.

Rural practitioners in China frequently used glucocorticoids parenterally to treat fever. During an outbreak of hand, foot, and mouth disease in 2008, the odds of developing critical and life-threatening human enterovirus 71 infection was nearly 5-fold (odds ratio [OR] = 4.8, 95% CI: 1.2–21) for children receiving glucocorticoid injections alone, and 21-fold (OR = 21, 95% CI: 1.8–305) for children receiving injections containing both glucocorticoids and pyrazolones (a class of nonsteroidal anti-inflammatory drugs that have been associated with agranulocytosis and other serious conditions, and hence have been banned in most developed countries for decades), compared with children receiving neither drugs [13]. Investigation of the first death due to pH1N1 infection in a remote area in China also showed that the 17-year-old previously healthy woman received parenteral glucocorticoid treatment for fever and other mild symptoms immediately prior to the worsening of her symptoms.

In October 2009, Shenyang City, in northeastern China's Liaoning Province, reported an outbreak of critical disease and death due to pH1N1 infection. We investigated the association between the use of glucocorticoids and development of critical disease and death from pH1N1 infection.

METHODS

During this outbreak, health care providers referred patients with influenza-like illness (ILI) or severe acute respiratory illness for laboratory testing of pH1N1 infection, based on the guidelines by the Chinese Ministry of Health [14]. A confirmed case of pH1N1 infection was defined as development of ILI and detection of pH1N1 virus by real-time reverse transcription–polymerase chain reaction (RT-PCR) from throat swabs. A critical patient was defined as a confirmed, hospitalized pH1N1 case-patient who developed ≥1 of the following: death, respiratory failure, septic shock, failure or insufficiency of ≥2 nonpulmonary organs, mechanical ventilation, or ICU admission.

We enrolled all confirmed case-patients ≥3 years of age with illness onset from 20 October to 30 November that were admitted to the 4 general hospitals designated for pH1N1 influenza treatment in Shenyang City. We conducted in-person or telephone interviews of patients and their family members to gather patients' demographic and epidemiologic information and treatment history. We also reviewed the medical records of all clinics and hospitals the patients visited after ILI onset to obtain information on the patients' underlying diseases or conditions, treatments, complications, and outcomes.

We used physiological variables from the Pandemic Medical Early Warning Score (PMEWS, developed to triage patients for hospital admission during influenza pandemics) [15] to assess the condition of all patients during the first 72 hours after onset and at the time of first glucocorticoid administration. These variables were: systolic blood pressure, pulse rate, respiratory rate, temperature, consciousness, and blood oxygen saturation. For every patient, we used the most extreme available value from all determinations during the first 72 hours. For comparisons after 72 hours, we used values at the time of first glucocorticoid administration or, if unavailable, during the 8 hours prior to the first glucocorticoid administration. For patients who did not receive glucocorticoids, we imputed a reference day as follows: We selected all patients with initiation of glucocorticoid treatment and determined the interval from ILI onset to initiation of glucocorticoid treatment. We imputed an interval between glucocorticoid use and critical illness onset for patients who did not use glucocorticoids by randomly assigning an interval based on the range of the intervals for patients who used glucocorticoids (ie, 0–23 days). For all patients, we calculated the reference day by adding the interval to the date of onset of ILI. We then determined the PMEWS for the respective patient on the reference day.

Of 268 pH1N1-confirmed case-patients with ILI onset from 20 October to 30 November 2009, 80% (214/268) were evaluated at the 4 hospitals. Of those, 48% (102/214) were hospitalized. We were able to retrieve and review 81% (83/102) of these records. We conducted a retrospective cohort study to assess critical pH1N1 infection in those 83 patients in relation to the use of glucocorticoids (dexamethasone and methylprednisolone). We analyzed the use of these drugs before the first intervention for critical disease (eg, ICU admission, tracheotomy) or for patients without critical disease, before hospital discharge. We divided glucocorticoid use into 2 time periods: the first 72 hours of ILI onset and from 72 hours until the end point. We also assessed the use of other drugs, including pyrazolones (aminopyrine or dipyrone) and antiviral drugs. We obtained the patients' medication history in 4 ways: checking the drug records in clinics or hospitals where the patients had visited, copying data from medication records onto the questionnaire, calling patients or their family members and letting them read the medication records in their medical charts, or asking the patients or their family members to recall the medications they were given. All inpatient drug use information was obtained from medical records. Of the outpatients' drug information, <30% was obtained through recall by the patients or their family members.

We examined the development of critical illness in 3 groups of patients according to glucocorticoids use after ILI onset: early (≤72 hours), late (>72 hours), and never users. The primary comparison was between the early users and all other patients

(including late and never users). In sensitivity analyses, we also compared outcomes of ever (early or late), early, and late users with never users.

To control for confounding, we created 2 summary variables: (1) presence of any underlying diseases (including pulmonary tuberculosis, chronic pulmonary diseases [ie, asthma, chronic bronchitis, or emphysema], heart diseases [ie, Tetralogy of Fallot, rheumatic heart disease, coronary artery disease, atrial fibrillation, and myocardial ischemia], chronic renal disease [ie, glomerulonephritis, uremia, renal insufficiency], chronic liver disease [ie, hepatitis B, fatty liver], nervous system diseases [ie, stroke, Parkinson's disease], diabetes, anemia, and granulocytopenia), and (2) presence of known risk factors, including ≥65 years of age, pregnancy, and obesity (defined as body mass index >28 for adults aged ≥18 years, excluding pregnant women [16], or based on deviance from the reference norm of body mass index for Chinese children and adolescents aged 7–18 years[17]). We used the Cochran–Mantel–Haenszel method to adjust the risk ratios for the 2 summary variables.

Using the proportional hazards model, we estimated the probability of developing critical disease (failure probability) and hazard ratio between different treatment groups, controlling for the summary variables ''presence of underlying diseases'' and ''presence of risk factors.''

This investigation was part of the response to a public health emergency and accordingly was exempt from the requirement for institutional review.

RESULTS

Patients

From 20 October to 30 November 2009, 83 confirmed pH1N1 case-patients had onset of ILI and were admitted to the 4 designated hospitals in Shenyang City. Of these case-patients, 46% (38/83) developed critical illness, including the 14 who died. During this period, in Shenyang, the cumulative incidence rate of confirmed pH1N1 infection was 4/100 000 and the confirmed pH1N1-specific mortality rate was 14/10 000 000.

Case-patients who received glucocorticoids early (≤72 hours after ILI onset; $n = 17$) did not differ significantly from other patients by age; sex; underlying diseases; pregnancy; obesity; PMEWS; median temperature at first clinic visit; proportions with cough, productive cough, or sore throat during the first 72 hours of ILI; or other factors; nor did case-patients who received late glucocorticoids (>72 hours after ILI onset) and case-patients who received glucocorticoids before first intervention for critical disease (Table 1). None of the patients were being treated for these conditions with glucocorticoids.

One noncritically ill case-patient had a diagnosis of acute respiratory distress syndrome (ARDS) but did not require mechanical ventilation and did not have other organ function insufficiencies. Critically ill case-patients were not more likely to have an underlying condition than less severely ill patients (Table 2). The median interval from hospital admission to major intervention (tracheotomy, mechanical ventilation, or ICU admission) for critical illness was 2 days (range, 0–11 days), and from ILI onset to major intervention was 8 days (range, 2–15 days). None of the patients had received pH1N1 or seasonal influenza vaccines.

Early Glucocorticoid Exposure

For the 17 case-patients who received glucocorticoids (dexamethasone [$n = 11$], methyl prednisolone [$n = 3$], or both [$n = 3$]) during the first 72 hours, 24% (4/17) were admitted to hospitals coincident with their first glucocorticoid dose, and 24% (16/66) of the other 66 case-patients had also been admitted directly during the first 72 hours. The remaining 76% (13/17) received glucocorticoids in outpatient facilities and were sent home. Case-patients who received glucocorticoids did not differ in the timing of ILI onset to first encounter with medical care or to hospital admission. The types of clinics where case-patients received their first treatment for ILI did not differ between case-patients who received early glucocorticoids and those who did not. Patients who received early glucocorticoids did not differ from other patients by age or gender distribution, ethnicity, frequency of underlying diseases, obesity, or pregnancy. Glucocorticoids were used to reduce fever ($n = 14$) or prevent complications of pneumonia ($n = 3$). For adults, the median daily dose (in equivalents of methyl prednisolone) of glucocorticoids was 50 mg (range, 25–90 mg) for fever reduction and 61 mg (range, 37–133 mg) for pneumonia. All glucocorticoids were given parenterally.

Of the 17 case-patients who received early glucocorticoids before onset of critical disease, 71% (12/17) subsequently developed critical disease, nearly doubling the risk compared with those who received late or no glucocorticoid treatment (39%, 26/66) ($RR_{M\text{-}H} = 1.8$, 95% CI = 1.2–2.8, after adjustment for presence of underlying diseases and known risk factors). In the sensitivity analysis, the risk for patients who received early glucocorticoid treatment tripled that for patients who received no glucocorticoid treatment ($RR_{M\text{-}H} = 3.3$, 95% CI = 1.6–6.8) (Table 3). For every 10 mg increase in the total glucocorticoid dose in the first 72 hours of ILI onset, the OR was 1.3 (95% CI = 1.04–1.4) using logistic regression. The first major intervention for critical disease occurred a median of 6 days (range, 2–11 days) after ILI onset in the early glucocorticoid group compared with 9 days (range, 3–15 days) in other patients. The median interval from first use of glucocorticoids to intervention for critical illness was 4 days (range, 1–11 days). Eighty-eight percent (15/17) of the patients who received early glucocorticoids continued to receive them after 72 hours.

Table 1. Characteristics of Patients Who Used Glucocorticoids ≤72 Hours and >72 Hours After Disease Onset and Those Who Never Used These Drugs: Shenyang, China 2009

	Glucocorticoids use time before critical disease intervention[a,b]			
	≤72 h	>72 h	Either	No use
Age, median years (range)	40 (6–58)	45 (3–70)	43 (3–70)	38 (5–75)
Males	71 (12)	59 (17)	63 (29)	49 (18)
Ethnicity				
Han	94 (16)	90 (26)	91 (42)	92 (34)
Others	5.9 (1)	10 (3)	8.7 (4)	8.1 (3)
≥1 known risk factors	35 (6)	52 (15)	46 (21)	57 (21)
Underlying disease	12 (2)	38 (11)	28 (13)	35 (13)
1 kind	12 (2)	14 (4)	13 (6)	19 (7)
2–3 kinds	0 (0)	24 (7)	15 (7)	16 (6)
Obesity	18 (3)	28 (8)	24 (11)	14 (5)
Pregnancy	5.9 (1)	0 (0)	2.2 (1)	16 (6)
Gestational weeks, median weeks (range)	33 (33–33)	…	33 (33–33)	26 (6–40)
Fever	100 (17)	100 (29)	100 (46)	100 (37)
Temperature (°C) at first clinic visit, median (range)	38 (37.5–40)	38.5 (38–40)	38.3 (37.5–40)	39 (37.5–40)
Cough	100 (17)	97 (28)	98 (45)	97 (36)
Productive cough	41 (7)	69 (20)	59 (27)	59 (22)
Sore throat	41 (7)	28 (8)	33 (15)	22 (8)
First treatment received at				
Village or town clinics	29 (5)	41 (12)	37 (17)	16 (6)
Primary hospitals	24 (4)	21 (6)	22 (10)	24 (9)
Secondary or tertiary hospitals	47 (8)	38 (11)	41 (19)	59 (22)
Days from onset to first clinic visit, median days (range)	1 (0–2)	1 (0–7)	1 (0–7)	0 (0–5)
Days from first clinic visit to hospitalization, median days (range)	4 (0–10)	4 (0–19)	4 (0–19)	4 (0–10)
Highest PMEWS ≤72 h after illness onset, median scores (range)	2 (1–5)	2 (0–3)	2 (0–5)	2 (0–5)
PMEWS at the time when glucocorticoids used, median scores (range)	NA	2 (1–9)	NA	2 (0–9)

NOTE. Data are % (*n*) unless otherwise indicated. PMEWS = Pandemic Medical Early Warning Score; NA = not applicable.

[a] Exact χ^2 or nonparametric Kruskal–Wallis test for differences among treatment arms. All test results were not significant ($P > .05$).

[b] We selected glucocorticoids using time randomly from patients who used glucocorticoids before critical disease as the equivalent using time of patients who did not use glucocorticoids.

Pyrazolones given in the first 72 hours were not significantly associated with increased risk of developing critical illness. Only 2 case-patients had received oseltamivir, a neuraminidase inhibitor, in the first 48 hours of illness.

Glucocorticoids More Than 72 Hours of Influenza-Like Illness Onset and Critical Disease

After 72 hours, an additional 29 case-patients received glucocorticoids before the first intervention for critical disease or, for patients who did not develop critical disease, hospital discharge. All of those 29 patients were diagnosed with pneumonia, of whom 28% (8/29) received glucocorticoids before, 35% (10/29) on the same day of, and 35% (10/29) after pneumonia diagnosis. The time of pneumonia diagnosis was unavailable for 1 patient. Among those 29 case-patients, 55% (16/29) developed critical disease, doubling the risk compared with those who received no glucocorticoids (27%, 10/37) ($RR_{M\text{-}H} = 2.1$, 95% CI = 1.1–4.1, after adjusting for presence of underlying disease, and presence of known risk factors) (Table 3). For every 10 mg increase in the cumulative dose of glucocorticoids (adjusted for equivalency to methyl prednisolone) before intervention for critical disease, the OR was 1.04 (95% CI = 1.0–1.08) using logistic regression. Of those 29 patients, 93% (27/29) were given oseltamivir; 25 of the patients received oseltamivir >48 hours after illness onset.

Time-to-Event Estimation of Risk of Glucocorticoid Use

The Kaplan–Meier time-to-event estimator of risk of developing critical pH1N1 infection was consistently higher among patients who received glucocorticoids than among patients who received no glucocorticoids over the course of disease. Using proportional hazards modeling, glucocorticoid use was associated with near tripling of the risk of developing critical illness (hazard ratio = 2.8, 95% CI = 1.3–5.9; log rank test: $\chi^2 = 7.82$, $P = .0052$) (Figure 1). When we controlled for the 2 summary variables (ie, presence of underlying diseases and known risk factors), this association was virtually unchanged (hazard ratio = 2.9, 95% CI = 1.3–6.2).

Table 2. Clinical Characteristics of Critical and Noncritical Patients Infected With Pandemic (H1N1) Influenza Virus: Shenyang, China, October–November 2009

	Critical patients		
	Yes (n = 38)	No (n = 45)	P [a]
Highest PMEWS >72 h after illness onset, median scores (range)	6.5 (2–16)	2.0 (0–8)	<.001
Males	53 (20)	60 (27)	.500
Obesity	21 (8)	18 (8)	.706
Age, median years (range)	43 (3–75)	40 (5–70)	.416
Age ≥65 years	5.3 (2)	8.9 (4)	.834
Pregnancy	11 (4)	6.7 (3)	.528
Gestational weeks, median weeks (range)	34 (6–37)	17 (12–40)	>.999
Underlying disease			
0	68 (26)	69 (31)	.622
1 kind	18 (7)	13 (6)	
2–3 kinds	13 (5)	18 (8)	
Any underlying diseases or known risk factors[b]	55 (21)	47 (21)	.435
Complications			
Pneumonia	100 (38)	89 (40)	.059
Respiratory failure	87 (33)	0.0 (0)	<.001
Mechanical ventilation	37 (14)	0.0 (0)	<.001
Acute respiratory distress syndrome	58 (22)	2.2 (1)	<.001
Failure or insufficiency of ≥2 other organs	34 (13)	0.0 (0)	<.001
Hepatic insufficiency	45 (17)	4.4 (2)	.001
Renal insufficiency	26 (10)	2.2 (1)	<.001
Heart failure	29 (11)	2.2 (1)	<.001
Septic shock	5.3 (2)	0.0 (0)	<.001
Intensive care unit admission	71 (27)	0.0 (0)	<.001
Death	37 (14)	0.0 (0)	<.001

NOTE. Data are % (n), unless otherwise indicated. P = Probability that there was no difference between critical and non-critical patients; PMEWS = Pandemic Medical Early Warning Score.

[a] Exact χ^2 or nonparametric Kruskal–Wallis test for differences among treatment arms.

[b] Presence of any of the 19 underlying diseases or 3 known risk factors (age ≥65, pregnancy, obesity) examined in this study.

Table 3. Risk of Developing Critical Disease After Infection With pH1N1 Influenza Virus, by Timing of Glucocorticoid Treatment After Onset of Influenza-Like Illness: Shenyang, China, October–November 2009

Timing of glucocorticoid treatment after ILI onset	Patients (n)	Critical illness attack rate (%)	Risk ratio (95% CI)	Risk ratio$_{M\text{-}H}$[a] (95% CI)
Compared with late (>72 h) or never				
Early (≤72 h)	17	71	1.8 (1.2–2.8)	1.8 (1.2–2.8)
Late (>72 h) or never[b]	66	39	Ref	Ref
Compared with never[b]				
Early (≤72 h) or late (>72 h)	46	61	2.3 (1.3–4.0)	2.4 (1.3–4.4)
Early (≤72 h)	17	71	2.6 (1.4–4.8)	3.3 (1.6–6.8)
Late (>72 h)	29	55	2.0 (1.1–3.8)	2.1 (1.1–4.1)
Never[b]	37	27	Ref	Ref

NOTE. CI = confidence interval.

[a] Adjusted (using the Cochran–Mantel–Haenszel method) for 2 summary variables: (1) presence of any of the 19 underlying diseases examined, and (2) presence of any of the 3 known risk factors for severe influenza infection examined (ie, age ≥65 years, pregnancy, obesity).

[b] No glucocorticoids administered before first intervention for critical disease or for patients who did not develop critical disease, before hospital discharge.

DISCUSSION

In this retrospective cohort investigation, we found that parenteral use of glucocorticoids for fever treatment during the early, mild stages of pH1N1 infection increased the risk of developing subsequent critical illness or death. This finding had a dose–response effect and specificity of the effect to glucocorticoids rather than to other drugs or underlying conditions. Further, to address potential confounding by indication, we used a very conservative approach by comparing early glucocorticoid use to a reference group that contained a substantial proportion of patients who received glucocorticoids later in the course of illness but before the first indicator of critical disease, which would have biased the association toward the null. Extending the analysis to patients who received glucocorticoids after 72 hours, often to prevent pneumonia or its complications, revealed the opposite effect—a subsequent deterioration of the patient and a greater risk of a critical outcome.

Although outside of China glucocorticoids are not widely used to lower fever or to prevent severe pneumonia, they are widely accepted as immunosuppresants for the management of underlying illnesses and conditions. Used in this manner, they are described as a risk factor for severe influenza and as an indication for influenza vaccine [18, 19]. However, these review articles report only 1 study supporting these warnings and recommendations—a meta-analysis covering all infectious diseases, without specific data on influenza [20]. A study of seasonal influenza showed higher viral titers and prolonged viral excretion with glucocorticoid-treated pneumonia, but it did not evaluate the contribution of glucocorticoids to severe or critical illness [21]. Of the many studies on the pH1N1 virus, 2 examined the relationship between glucocorticoid use and critical disease [6, 22]. Both studies showed associations of critical disease and death with glucocorticoid use. However, neither study differentiated between glucocorticoids given for underlying disease, for treatment of pneumonia, or for ARDS or

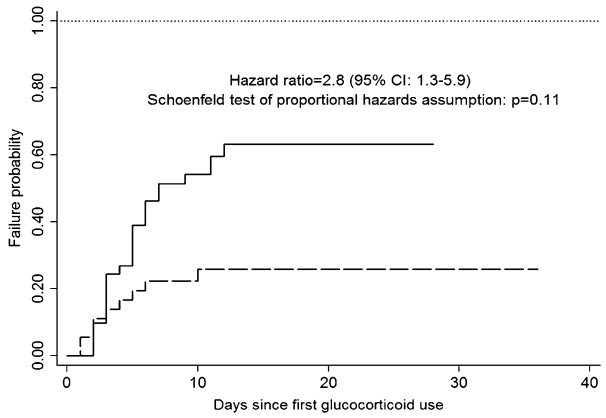

Figure 1. Estimated probability of developing critical illness after pandemic (H1N1) infection by parenteral glucocorticoid use: Shenyang, China, October–November 2009.

other complications of pneumonia. Glucocorticoid treatment of pneumonia from another influenza virus, H5N1 avian influenza, has been associated with a fatal outcome [23]. Other studies showed associations between immunosuppression and critical pH1N1 infection but did not differentiate glucocorticoids from other sources of immunosuppression [5, 24–26].

Experimental studies on mice from the 1950s showed that cortisone and hydrocortisone given during the first 4 days of influenza A infection lowered the median lethal dose (LD_{50}) of the viral innoculum and increased the viral titer in the lungs [27]. Both effects occurred during the first week of infection before antibodies against influenza were detectable. A more modern animal model evaluation of glucocorticoids on influenza, although rare, also indicates poor survival [28–30].

Treatment of pneumonia with glucocorticoids is less clear cut. During the severe acute respiratory syndrome (SARS) epidemic, observational studies from China and Hong Kong reported a beneficial effect [31, 32] whereas others showed associations of glucocorticoids with a deterioration of patient conditions [33]. Use of glucocorticoids to prevent ARDS in community-acquired pneumonia patients has actually increased the risk of ARDS [34]. The World Health Organization advised against treatment of pH1N1 virus with glucocorticoids except in cases of septic shock requiring vasopressors or suspected adrenal insufficiency [35].

Of the Chinese textbooks we reviewed (including those of pharmacology, pediatrics, and internal medicine), none mentioned using glucocorticoids to treat fever; guidance on glucocorticoids for pneumonia was limited to certain special circumstances [36, 37]. Nonetheless, the use of glucocorticoids to treat acute fever and pneumonia in China is a widespread practice, as shown in both current investigations and a previously published one [38], as well as publications in the Chinese literature [39–50].

Although most hospitalized patients received oseltamivir, only 2 patients received this drug <48 hours of illness, greatly limiting its effectiveness. Early, point-of-care diagnostic techniques should be developed for early, more effective treatment.

This study had at least 3 limitations. First, outpatient clinic records had incomplete documentation of the components of the PMEWS at the specific time that glucocorticoids were given. Accordingly, we used all data from the first 72 hours. Second, since 88% of the patients who received early glucocorticoids continued to receive them after 72 hours, the critical illness could also have been due to later use of glucocorticoids. Third, our investigation was hospital-based; hence the findings may not be generalizable to the community at large. We began the investigation with the intent to include nonhospitalized persons with pH1N1 infection as a control group. However, community virologic surveillance for pH1N1 was designed to select children with ILI whereas most of our confirmed, hospitalized cases were adults. Accordingly, we were unable to estimate the community-based prevalence of using glucocorticoids to treat fever from pH1N1 virus in this outbreak. Had this been a community-based investigation, the risk ratio might have been even greater.

In summary, the use of glucocorticoids during early pH1N1 infection was associated with an increased risk of subsequent critical disease or death. The findings of this study, combined with experimental data and clinical experiences in other countries, suggest that glucocorticoids should not be used to treat fever or prevent complications of pneumonia. We recommend that guidelines against the use of glucocorticoids for fever treatment should be established in China. Similarly, glucocorticoid treatment of uncomplicated pneumonia from influenza should be restricted to limited situations where glucocorticoids have proven benefit.

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