

ORIGINAL ARTICLE

Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection

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ABSTRACT

BACKGROUND

During the spring of 2013, a novel avian-origin influenza A (H7N9) virus emerged and spread among humans in China. Data were lacking on the clinical characteristics of the infections caused by this virus.

METHODS

Using medical charts, we collected data on 111 patients with laboratory-confirmed avian-origin influenza A (H7N9) infection through May 10, 2013.

RESULTS

Of the 111 patients we studied, 76.6% were admitted to an intensive care unit (ICU), and 27.0% died. The median age was 61 years, and 42.3% were 65 years of age or older; 31.5% were female. A total of 61.3% of the patients had at least one underlying medical condition. Fever and cough were the most common presenting symptoms. On admission, 108 patients (97.3%) had findings consistent with pneumonia. Bilateral ground-glass opacities and consolidation were the typical radiologic findings. Lymphocytopenia was observed in 88.3% of patients, and thrombocytopenia in 73.0%. Treatment with antiviral drugs was initiated in 108 patients (97.3%) at a median of 7 days after the onset of illness. The median times from the onset of illness and from the initiation of antiviral therapy to a negative viral test result on real-time reverse-transcriptase–polymerase-chain-reaction assay were 11 days (interquartile range, 9 to 16) and 6 days (interquartile range, 4 to 7), respectively. Multivariate analysis revealed that the presence of a coexisting medical condition was the only independent risk factor for the acute respiratory distress syndrome (ARDS) (odds ratio, 3.42; 95% confidence interval, 1.21 to 9.70; $P=0.02$).

CONCLUSIONS

During the evaluation period, the novel H7N9 virus caused severe illness, including pneumonia and ARDS, with high rates of ICU admission and death. (Funded by the National Natural Science Foundation of China and others.)

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ON MARCH 30, 2013, THREE PATIENTS with fatal cases of rapid, progressive pneumonia were confirmed to be infected with a novel avian-origin influenza A (H7N9) virus that had not been detected in humans and animals previously.^{1,2} The new human H7N9 viruses are the product of reassortment of viruses that are of avian origin.

Global attention was soon focused on the situation because of the increasing number of new cases and the high rate of death associated with these infections.³ As of May 9, the World Health Organization (WHO) had reported 131 laboratory-confirmed cases, including 32 deaths.⁴ However, data on the clinical characteristics of the illnesses and risk factors for severe illness among patients who were hospitalized for the treatment of H7N9 virus infection were still lacking. In this report, we describe clinical characteristics and laboratory abnormalities in 111 of the cases of H7N9 virus infection in China that had been confirmed as of May 10, 2013.

METHODS

DATA SOURCES

We conducted a retrospective study focusing on the clinical characteristics of confirmed cases of the novel H7N9 virus infection. The strategy of new case identification in Beijing was different from that used in other areas in China. In Beijing, all patients with fever and influenza-like illness or pneumonia who had been visiting Shanghai, Zhejiang, or Jiangsu or who had a history of poultry exposure within 2 weeks before the onset of illness were required to be screened for H7N9 virus. In other areas, only patients with fever and rapidly progressing pneumonia who had no response to antibiotic therapy were tested for H7N9 virus.

The case definitions of confirmed human infection with the novel H7N9 virus have been described by Li et al.⁵ and are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. Only patients with laboratory-confirmed infection were enrolled in this study.

The medical records of patients were copied and sent to the data-collection center in Beijing. A team of physicians who had been taking care of patients with H7N9 virus infection reviewed the data. Our data collection and analysis, which

were independent and differed from those described by Li et al.,⁵ were coordinated by the National Health and Family Planning Commission. The research ethics board at First Affiliated Hospital at Zhejiang University approved the study design. The requirement for informed consent was waived because of the urgent need to collect data on this emerging pathogen.

We used a standardized case-report form to collect clinical data. All data were entered in duplicate into a computerized database. If information was not clear, the working group in Beijing contacted the clinician responsible for the care of the patient for clarification. Definitions of moderate-to-severe acute respiratory distress syndrome (ARDS), rhabdomyolysis, pneumonia, acute kidney injury, and exposure to live poultry are provided in the Supplementary Appendix.

LABORATORY CONFIRMATION

Laboratory confirmation of the novel H7N9 virus was performed with the use of the same protocols described previously by Gao et al.¹ and Li et al.⁵ (see the Supplementary Appendix for details). Three methods of laboratory diagnosis were used: real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, viral isolation, and H7N9 serologic testing with the use of modified hemagglutination-inhibition assays. In most cases, other viruses, including seasonal influenza viruses (H1, H3, or B), H5N1, severe acute respiratory syndrome coronavirus (SARS-CoV), and human coronavirus–Erasmus Medical Center (HCoV-EMC), were also detected by means of real-time RT-PCR.

Blood cultures were performed for patients presenting with chills and shivering. Sputum or endotracheal aspirates were sent for identification of possible causative bacteria or fungi. Urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae* (Binax) were also performed on all samples.

STATISTICAL ANALYSIS

Continuous variables were summarized as either means and standard deviations or medians with interquartile ranges. For categorical variables, the percentages of patients in each category were calculated. We used an unpaired Student's t-test, chi-square test, or Fisher's exact test, as appropriate, to compare the clinical characteristics of subgroups of patients who had moderate-to-severe ARDS and those who did not.

We used multiple logistic-regression analysis to identify independent predictors of moderate-to-severe ARDS and death. The outcome was predicted with the use of factors such as age, sex, severity of symptoms (e.g., fever, cough, sputum production, and hemoptysis), and the interval between symptom onset and the initiation of antiviral therapy (≤ 3 days or > 3 days). A P value of less than 0.05 was considered to indicate statistical significance. No adjustment for multiple testing was performed. All analyses were performed with the use of SPSS software for Windows (release 17.0).

RESULTS

EPIDEMIOLOGIC CHARACTERISTICS

This report describes 111 patients with confirmed H7N9 virus infection as of May 10, 2013 (Fig. S1 in the Supplementary Appendix). We included in our study all 82 patients described in our previous report on the epidemiology of the H7N9 virus outbreak.⁵ The patients in our case series included 111 of the 131 patients (84.7%) with laboratory-confirmed H7N9 virus infection as of May 10, 2013, in China (Table 1).

H7N9 virus infection was diagnosed by means of serologic analysis alone in only 1 patient, in Shanghai, with negative results on real-time RT-PCR assay and viral culture. In 2 patients, the diagnosis was confirmed on both real-time RT-PCR assay and serologic analysis. In another 20 patients, the diagnosis was confirmed on both real-time RT-PCR assay and viral culture. All the other diagnoses were confirmed only on real-time RT-PCR assay.

The median age of the patients was 61 years (range, 3 to 88); 42.3% of the patients were 65 years of age or older. Male patients predominated in number over female patients, with a sex ratio of approximately 2:1. A total of 61.3% of the patients had one or more coexisting medical conditions. Coronary heart disease, hypertension, diabetes, and chronic obstructive pulmonary disease were the most common coexisting conditions. Two patients were pregnant, one in the first trimester and the other in the second trimester. On the basis of data from 62 patients (55.9%) for whom a definite date of exposure to live poultry was available, we estimated that the incubation period was 5 days (interquartile range, 2 to 8) (Table 1, and Fig. S2 in the Supplementary Appendix).

Table 1. Demographic and Epidemiologic Characteristics of 111 Patients Infected with H7N9 Virus in China.

Characteristic	Value
Age	
Median (range) — yr	61 (3–88)
Subgroup — no. (%)	
0–4 yr	1 (0.9)
5–14 yr	1 (0.9)
15–49 yr	28 (25.2)
50–64 yr	34 (30.6)
≥ 65 yr	47 (42.3)
Female sex — no. (%)	35 (31.5)
Coexisting condition — no. (%)	
Any	68 (61.3)
Hypertension	51 (45.9)
Diabetes	18 (16.2)
Coronary heart disease	11 (9.9)
Immunosuppression*	10 (9.0)
Chronic obstructive pulmonary disease	8 (7.2)
Cancer†	6 (5.4)
Cerebrovascular disease	4 (3.6)
Hepatitis B infection‡	4 (3.6)
Chronic renal disease	2 (1.8)
Pregnancy	2 (1.8)
Current smoker — no. (%)	27 (24.3)
Exposure to live poultry	
In previous 14 days — no. (%)	62 (55.9)
Median incubation time since exposure (interquartile range) — days	5 (2–8)
Hospitalization — no. (%)	109 (98.2)

* Immunosuppression may have been caused by the presence of human immunodeficiency virus infection, chemotherapy or radiotherapy within 1 month before the onset of illness, or glucocorticoid therapy (equivalent of 30 mg of prednisone per day) for 15 days before the onset of illness.

† Cancers included breast cancer, colorectal cancer, thyroid cancer, thymoma, and lymphoma. Of these cancers, only one case of lymphoma was active, whereas the other cases were stable disease.

‡ Hepatitis B infection was defined as a positive assay for hepatitis B surface antigen, with or without an elevated level of alanine aminotransferase.

CLINICAL FEATURES AND LABORATORY ABNORMALITIES

The clinical characteristics of the patients are shown in Table 2. Fever and cough were the most common symptoms. Diarrhea or vomiting was reported in 13.5% of the patients. On admission, 98 of the 111 patients (88.3%) had lymphocytopenia, and 44 (39.6%) had thrombocytopenia. The

Table 2. Clinical Characteristics and Selected Laboratory Abnormalities of 111 Patients Infected with H7N9 Virus *

Characteristic	Value
Fever	
Any — no. (%)	111 (100.0)
Maximal temperature — °C	39.2±0.8
Subgroup — no. (%)	
37.3–38.0°C	11 (9.9)
38.1–39.0°C	43 (38.7)
>39.0°C	57 (51.4)
Fatigue — no. (%)	40 (36.0)
Conjunctivitis — no. (%)	0
Cough — no. (%)	100 (90.1)
Sputum production — no. (%)	62 (55.9)
Hemoptysis — no. (%)	27 (24.3)
Shortness of breath — no. (%)	62 (55.9)
Diarrhea or vomiting — no. (%)	15 (13.5)
White cells	
Median — per mm ³	4450
Interquartile range — per mm ³	2900–6230
Subgroup — no. (%)	
>10,000 per mm ³	5 (4.5)
<4000 per mm ³	51 (45.9)
Lymphocytes — per mm³	
Median	460
Interquartile range	320–700
Lymphocytopenia — no. (%)	98 (88.3)
Hemoglobin — g/dl	12.9±3.1
Platelets — per mm³	
Median	115,500
Interquartile range	82,000–149,500
Thrombocytopenia — no. (%)	81 (73.0)
C-reactive protein >10 mg/liter — no. (%)	85 (76.6)
Procalcitonin >0.5 ng/ml — no. (%)	28 (37.3)
Aspartate aminotransferase >40 U/liter — no. (%)	73 (65.8)
Creatinine >133 μmol/liter (1.5 mg/dl) — no. (%)	10 (9.0)
Lactate dehydrogenase >250 U/liter — no. (%)	91 (82.0)
Creatine kinase >200 U/liter — no. (%)	49 (44.1)
Myoglobin >80 μg/ml — no. (%)	16 (55.2)
PaO₂:FiO₂	
Median	144.0
Interquartile range	107.1–226.9
Potassium — mmol/liter	3.8±0.5
Sodium — mmol/liter	136.8±6.0
D-dimer >0.5 mg/liter — no. (%)	47 (90.4)
Chest radiologic findings — no. (%)	
Involvement of both lungs	60 (54.1)
Ground-glass opacity	62 (55.9)
Consolidation	99 (89.2)

* Plus–minus values are means ±SD. A complete list of ranges of laboratory measures in this table is provided in Table S4 in the Supplementary Appendix. Lymphocytopenia was defined as a lymphocyte count of less than 1500 per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter. Procalcitonin was measured in 75 patients, myoglobin was measured in 29 patients, and total D-dimer was measured in 52 patients. PaO₂:FiO₂ denotes the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.

white-cell count was normal or slightly decreased in most patients. Elevated levels of aspartate aminotransferase, creatine kinase, and lactate dehydrogenase were observed in nearly all the patients (Table 2, and the Supplementary Appendix).

All 111 patients underwent chest radiography on admission; 108 (97.3%) had findings that were consistent with pneumonia. Bilateral ground-glass opacities and consolidation were the most common radiologic findings.

Representative radiologic findings for one 68-year-old man with hypertension were followed from his admission to the hospital (on day 7 after the onset of symptoms) until discharge (day 42). Unilateral ground-glass opacities and partial consolidation were observed in the left lung on admission (Fig. 1A). Noninvasive ventilation was initiated, but there was rapid deterioration. The patient was intubated and underwent mechanical ventilation on day 9. Computed tomography showed rapid progression of ground-glass opacities and consolidation with involvement of both lungs (Fig. 1B). On day 16, the patient's condition was still serious, with an increase in bilateral ground-glass opacities and areas of consolidation (Fig. 1C). He was extubated on day 36, and reticular changes were noticed on day 42, before discharge (Fig. 1D).

Klebsiella pneumoniae was isolated from both blood and sputum samples in five patients and methicillin-resistant *Staphylococcus aureus* from blood and sputum samples in one patient.

A single pathogen was isolated from sputum or endotracheal samples in 18 patients, including 12 with *Acinetobacter baumannii*, 2 with *Burkholderia cepacia*, 1 with *Pseudomonas aeruginosa*, 1 with *Enterobacter aerogenes*, 1 with *K. oxytoca*, and 1 with *P. putida*. Two pathogens — *K. pneumoniae* and *A. baumannii* — were isolated from sputum or endotracheal samples obtained from 5 patients. All the bacterial pathogens were identified at least 48 hours after admission to the hospital.

TREATMENT AND VIRAL-LOAD KINETICS

A total of 108 patients (97.3%) were treated with antiviral drugs (Table 3). The median time from the onset of illness to the initiation of antiviral therapy was 7 days (range, 1 to 23); 9.9% of the patients received antiviral therapy within 48 hours after the onset of symptoms. Among the 108 patients for whom dates of admission and the initiation of antiviral therapy were available, the therapy was started before hospitalization in 17 patients

(15.3%), within 24 hours after admission in 72 patients (64.9%), and more than 24 hours after admission in 19 patients (17.1%).

Data with respect to viral-load kinetics were available for 41 patients who had received antiviral agents (oseltamivir at a daily dose of 150 to 300 mg in 38 patients and oseltamivir followed by peramivir at a daily dose of 600 mg in 3 patients). The median times from the onset of illness and from the initiation of antiviral therapy to a negative test result on daily real-time RT-PCR assay were 11 days (interquartile range, 9 to 16) and 6 days (interquartile range, 4 to 7), respectively.

Seventy-nine patients (71.2%) also received antibiotic therapy within 6 hours after admission. Commonly used antibiotics included fluoroquinolones (in 34 patients), piperacillin (in 28 patients), imipenem or meropenem (in 21 patients), cephalosporins (in 21 patients), azithromycin (in 7 patients), and vancomycin (in 6 patients). One patient was treated with caspofungin on admission.

Sixty-nine patients (62.2%) were treated with at least one glucocorticoid, with the administration of intravenous methylprednisolone (median dose, 80 mg per day; range, 40 to 320 mg per day) in 64 patients, intravenous dexamethasone (5 mg per day) in 5 patients, and intravenous hydrocortisone (range, 100 to 200 mg per day) in 2 patients.

COMPLICATIONS AND CLINICAL OUTCOMES

Of the 111 patients we evaluated, 85 (76.6%) were admitted to an intensive care unit (ICU); of these patients, 54 were directly admitted to the ICU, and 31 were admitted during hospitalization. Moderate-to-severe ARDS was the most common complication (in 79 patients), followed by shock (in 29 patients), acute kidney injury (in 18 patients), and rhabdomyolysis (in 11 patients). The median time from the onset of illness to ARDS was 7 days (range, 1 to 19). The median time from the onset of illness to shock was 8 days (range, 3 to 55) (Fig. S2 in the Supplementary Appendix). Of the patients with ARDS, 65 required invasive mechanical ventilation, and of these patients 20 received extracorporeal membrane oxygenation.

Univariate analysis showed that the risk factors for moderate-to-severe ARDS were an age of 65 years or older and the presence of at least one coexisting medical condition, a lymphocyte count of less than 1000 per cubic millimeter, an aspartate aminotransferase level of more than 40 U per

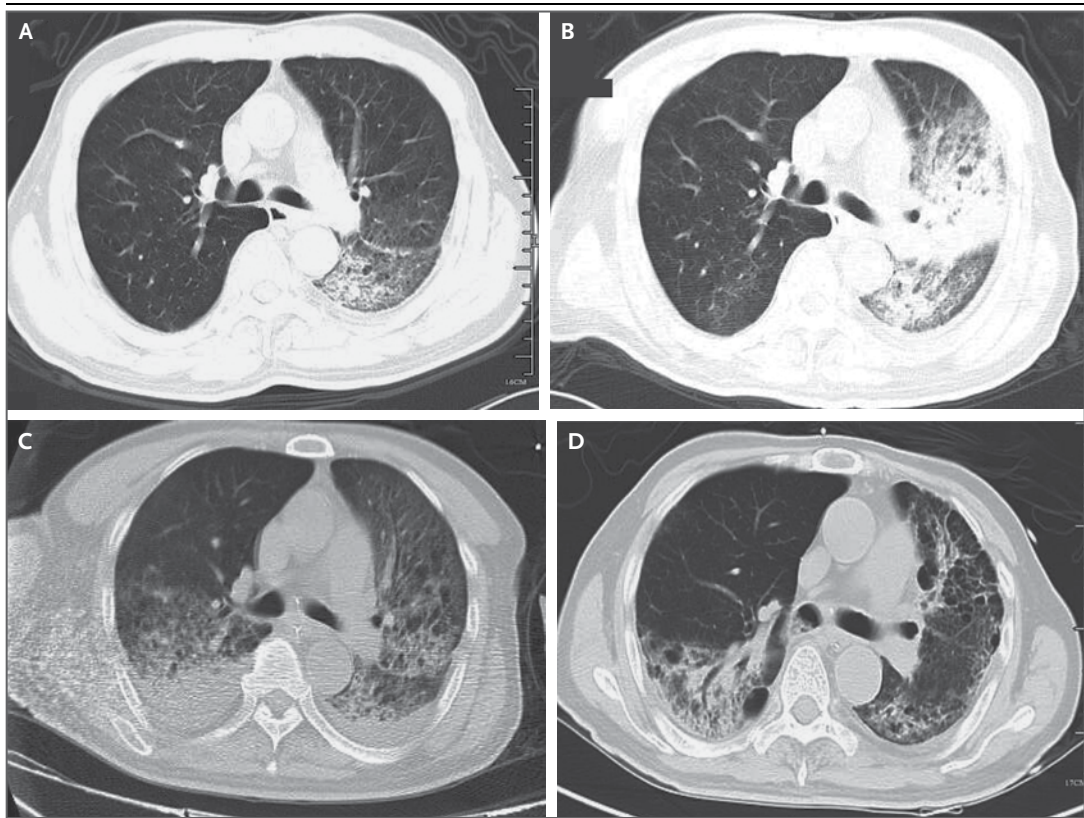


Figure 1. Computed Tomographic Scans of the Chest in a 68-Year-Old Man with Pneumonia Caused by Avian Influenza A (H7N9) Virus.

On day 7 after the onset of illness, at the time of hospital admission (Panel A), unilateral ground-glass opacities and partial consolidation were observed in the upper and lower portions of the left lung at the tracheal carina level. On day 9 (Panel B), there was rapid progression of the ground-glass opacities, which were observed in the posterior segment of the right lower lobe (not shown), along with consolidation in the left lung. On day 16 (Panel C), there were increased ground-glass opacities in the left lung and increased consolidation in both lungs. On day 42 (Panel D), when the patient was discharged from the hospital, ground-glass opacities and consolidation in both lungs had begun to resolve, with predominant reticular changes and distortion of the previously involved areas of parenchyma. Scans showing areas below the carina level, obtained on days 7, 9, 16, and 42, are provided in Figure S3 in the Supplementary Appendix.

liter, and a creatine kinase level of more than 200 U per liter; patients were less likely to have been treated with oseltamivir or peramivir within 3 days after the onset of illness (Table S1 in the Supplementary Appendix). However, on multivariate analysis, the presence of coexisting medical conditions was the only independent risk factor for moderate-to-severe ARDS (odds ratio, 3.42; 95% confidence interval, 1.21 to 9.70; $P=0.02$) (Table 4).

Univariate analysis showed that the risk of death was increased among patients who were 65 years of age or older; among those who had a coexisting medical condition, shortness of breath

at presentation, ARDS, shock at any point during the illness, or acute kidney injury; and among those in whom antiviral therapy was initiated more than 5 days after the onset of symptoms (Table S2 in the Supplementary Appendix). However, in multivariate analysis, shock was the only predictor of death (odds ratio, 6.51; 95% CI, 1.09 to 38.92; $P=0.04$) (Table S3 in the Supplementary Appendix).

As of May 10, a total of 30 patients had died, 49 patients had been discharged from the hospital with full recovery, and 30 patients remained hospitalized; of the patients who were still in the hospital, 24 were in an ICU. One of the

2 pregnant patients had been discharged with full recovery, and the other remained hospitalized in stable condition. Of the 2 patients who were not hospitalized, 1 died 7 days after symptom onset, and 1 had a full recovery. The median time from the onset of illness to death was 14 days (interquartile range, 8 to 24) (Fig. S2 in the Supplementary Appendix). All patients with fatal infections had pneumonia and ARDS.

DISCUSSION

The findings in this series of patients suggest that the novel H7N9 virus can cause severe illness, including pneumonia and ARDS; 76.6% of patients required admission to an ICU and 27.0% died. It is possible that a larger number of patients have had infections that were not diagnosed because their symptoms were less severe.

Patients who were hospitalized with H7N9 virus infection had an uneven age distribution, with 42.3% who were 65 years of age or older. The age distribution was similar to that for seasonal influenza⁶ but differed from the age distribution among patients who were hospitalized with H5N1 virus infection or those with pandemic H1N1 virus infection. In 2009, among 1461 Chinese patients who were hospitalized with pandemic H1N1 pneumonia, the mean age was 23 years (range, 27 days to 99 years).⁷ According to a study by Yu et al.,⁸ the median age of 26 patients with confirmed H5N1 virus infection was 29 years (range, 6 to 62). A possible explanation for the predominance of elderly patients in this outbreak of H7N9 virus infection is that retired persons have more opportunities to shop in live-animal markets and are therefore more likely to be exposed to live poultry. Other possibilities are that elderly persons have an increased risk of coexisting illnesses and are more susceptible to severe forms of disease than are younger persons, even after the same exposure.⁹

The clinical features of hospitalized patients with H7N9 virus infection were generally similar to patients with severe pandemic H1N1 virus infection¹⁰ or H5N1 virus infection.¹¹ Patients usually presented with fever and cough, with early sputum production, and the illness progressed rapidly to severe pneumonia, moderate-to-severe ARDS, and shock. As compared with hospitalized patients with seasonal influenza A,

Table 3. Complications, Treatment, and Clinical Outcomes in 111 Patients Infected with H7N9 Virus.*

Variable	Value no. of patients (%)
Complications	
Pneumonia	108 (97.3)
Acute respiratory distress syndrome	79 (71.2)
Shock	29 (26.1)
Acute kidney injury	18 (16.2)
Rhabdomyolysis	11 (9.9)
Treatment	
Bacteria isolation from culture	29 (26.1)
Administration of oseltamivir or peramivir	108 (97.3)
Timing from onset of illness to administration of antiviral therapy	
0–2 days	11 (9.9)
3–5 days	32 (28.8)
≥6 days	65 (58.6)
Oxygen therapy	111 (100)
Mechanical ventilation	
Noninvasive	31 (27.9)
Invasive	65 (58.6)
Admission to an intensive care unit	85 (76.6)
Extracorporeal membrane oxygenation	20 (18.0)
Continuous renal-replacement therapy	29 (26.1)
Artificial-liver-support-system therapy*	17 (15.3)
Antibiotics	79 (71.2)
Antifungal drugs	1 (0.9)
Glucocorticoids	69 (62.2)
Intravenous immune globulin	59 (53.2)
Clinical outcome	
Death	30 (27.0)
Cause of death	
Refractory hypoxemia	22 (73.3)
Shock	1 (3.3)
Acute heart failure	2 (6.7)
Secondary bacterial or fungal infection	3 (10)
Arrhythmia	2 (6.7)
Discharge from hospital†	49 (44.1)

* The main form of artificial-liver-support-system therapy was plasma exchange combined with continuous venovenous hemofiltration. It was used in patients with severe H7N9 virus infection when the condition deteriorated rapidly and a cytokine storm was detected.

† The median length of the hospital stay for patients who were discharged was 21 days (interquartile range, 16 to 27).

Table 4. Multivariate Analysis of Risk Factors for the 79 Patients with the Acute Respiratory Distress Syndrome.

Risk Factor	Odds Ratio (95% CI)*	P Value
Age \geq 65 yr	1.01 (0.99–1.03)	0.30
Coexisting medical condition	3.42 (1.21–9.70)	0.02
Lymphocyte count $<$ 1000 cells/mm ³	2.73 (0.60–12.52)	0.20
Aspartate aminotransferase level $>$ 40 U/liter	1.37 (0.42–4.43)	0.60
Creatine kinase level $>$ 200 U/liter	1.80 (0.59–5.48)	0.30
Time from symptom onset to initiation of antiviral therapy $>$ 3 days	2.42 (0.49–11.99)	0.28

* The reference groups were patients under the age of 65 years, those who did not have a coexisting medical condition, those with a lymphocyte count of 1000 cells per cubic millimeter or more, those with an aspartate aminotransferase level of 40 U per liter or less, those with a creatine kinase level of 200 U per liter or less, and those with a delay in the initiation of antiviral therapy of 3 days or less.

patients with H7N9 virus infection were more likely to have severe symptoms: of 327 hospitalized adults with seasonal influenza, 52 (15.9%) required ICU admission and 27 (8.3%) died within 15 days after symptom onset.¹²

Like patients with other avian influenza infections,¹³ patients with H7N9 virus infection were not reported to have a sore throat or rhinorrhea. Conjunctivitis, a common finding with H7 human infections,¹⁴ was also not reported among the patients in our study. Diarrhea or vomiting was reported in 13.5% of patients in our study, as compared with 42 to 70% of patients with H5N1 virus infection.¹⁵ Rhabdomyolysis, which was present in 9.9% of the patients in our study, has also been reported in children infected with pandemic H1N1 virus.¹⁶

The laboratory findings for pandemic H1N1 and H5N1 viruses — including leukopenia, lymphocytopenia, thrombocytopenia, and increased levels of aspartate aminotransferase, creatine kinase, and lactate dehydrogenase — were also commonly seen in our patients. It has been reported that lymphocytopenia and thrombocytopenia were common findings in case series of patients with H5N1 virus infection, and these conditions were prognostic indicators for ARDS and death.^{17,18}

The development of refractory hypoxemia was the leading cause of death in patients with H7N9 virus infection, as was reported in the H5N1 virus case series. The case fatality rates for the two H5N1 series in Vietnam and Thailand ranged

from 67 to 80%, and the time from the onset of symptoms until death ranged from 4 to 30 days (median, 8 and 23 days in the two studies).^{17,18} Among the patients in our study, the median time from the onset of illness to death was 14 days and ranged from 6 to 58 days. But since one third of patients still remained in the hospital at the time of this report, the death rate of 27.0% (30 of 111 patients) may be an underestimate.

The analysis of the initial patients infected with H7N9 virus revealed that antiviral therapy was initiated at a median of 7 days (range, 1 to 23) after the onset of illness, and patients with moderate-to-severe ARDS were less likely to have been treated within 5 days. WHO guidelines recommend the early initiation of antiviral therapy for patients who are infected with H5N1 virus or pandemic H1N1 virus, guidelines that we believe should be followed for patients infected with H7N9 virus.^{15,19}

Our study has several limitations. First, our case series probably represents the more severe end of the disease. Since the retrospective nature of our study called for a focus on patients with symptoms severe enough to present for medical care, we cannot describe the full spectrum of this illness. However, we did include a small number of patients with mild cases who did not have pneumonia. An asymptomatic virus carrier was found in Beijing, the mother of a 7-year-old girl infected with H7N9 virus. We believe a wide serologic surveillance study is needed to determine how many persons in affected areas in China have had H7N9 virus infection with no symptoms or only mild symptoms. Second, our study was limited by the observational nature of the investigation, and since confounding may have occurred as a result of the administration of antiviral therapy on the basis of clinical decisions, we can provide no insights regarding the effects of various doses of antiviral agents or glucocorticoids, the timing of administration of therapy, or the duration of therapy on clinical outcomes. Third, at the time of submission of the manuscript, many patients still remained in the hospital, so we were unable to estimate either the rate of death or predictors of death. Fourth, we have included data for most but not all patients with laboratory-confirmed illness. Finally, we did not have data for some patients with respect to potential exposures to swine, wild birds, or other vectors or the potential for human transmissibility, so more epidemiologic investigation is required

to identify the source of infection and the mode of transmission.

In conclusion, among the patients in our study, H7N9 virus infection caused severe illness, including rapidly progressive pneumonia and ARDS, which was characterized by bilateral ground-glass opacities and consolidation and by high mortality.

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APPENDIX

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REFERENCES

- Gao R, Cao B, Hu Y, et al. Human infection with a novel avian-origin influenza A (H7N9) virus. *N Engl J Med* 2013; 368:1888-97.
- Chen Y, Liang W, Yang S, et al. Human infections with the emerging avian influenza A H7N9 virus from wet market poultry: clinical analysis and characterisation of viral genome. *Lancet* 2013 April 25 (Epub ahead of print).
- Uyeki TM, Cox NJ. Global concerns regarding novel influenza A (H7N9) virus infections. *N Engl J Med* 2013;368:1862-5.
- Number of confirmed human cases of avian influenza A(H7N9) reported to WHO. Geneva: World Health Organization, May 2013 (http://www.who.int/influenza/human_animal_interface/influenza_h7n9/05_Report-WebH7N9Number.pdf).
- Li Q, Zhou L, Zhou M, et al. Preliminary report: epidemiology of the avian influenza A (H7N9) outbreak in China. *N Engl J Med* 2013. DOI: 10.1056/NEJMoa1304617.
- Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA* 2004; 292:1333-40.
- Yang SG, Bin Cao B, Liang RL, et al. Antiviral therapy and outcomes of patients with pneumonia caused by influenza A pandemic (H1N1) virus. *PLoS One* 2012;7(1):e29652.
- Yu H, Gao Z, Feng Z, et al. Clinical characteristics of 26 human cases of highly pathogenic avian influenza A (H5N1) virus infection in China. *PLoS One* 2008;3(8):e2985.
- 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(6):e6051.
- Bai L, Gu L, Cao B, et al. Clinical features of pneumonia caused by influenza A (H1N1) virus in Beijing, China. *Chest* 2011;139:1156-64.
- Liem NT, Tung CV, Hien ND, et al. Clinical features of human influenza A (H5N1) infection in Vietnam: 2004-2006. *Clin Infect Dis* 2009;48:1639-46.
- McGeer A, Green KA, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis* 2007; 45:1568-75.
- Wong SSY, Yuen K. Avian influenza virus infections in humans. *Chest* 2006; 129:156-68.
- Belser JA, Bridges CB, Katz JM, Tumpey TM. Past, present, and possible future human infection with influenza virus A subtype H7. *Emerg Infect Dis* 2009;15:859-65.
- The Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. Avian influenza A (H5N1) infection in humans. *N Engl J Med* 2005;353:1374-85.
- D'Silva D, Hewagama S, Doherty R, Korman TM, Buttery J. Melting muscles: novel H1N1 influenza A associated rhabdomyolysis. *Pediatr Infect Dis J* 2009; 28:1138-9.
- Chotpitayasunondh T, Ungchusak K, Hanshaoworakul W, et al. Human disease from influenza A (H5N1), Thailand, 2004. *Emerg Infect Dis* 2005;11:201-9.
- Tran TH, Nguyen TL, Nguyen TD, et al. Avian influenza A (H5N1) in 10 patients in Vietnam. *N Engl J Med* 2004; 350:1179-88.
- Clinical management of human infection with pandemic (H1N1) 2009: revised guidance. Geneva: World Health Organization, 2009 (http://www.who.int/csr/resources/publications/swineflu/clinical_management_h1n1.pdf).

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