Clinical Infectious Diseases

MAJOR ARTICLE

Benefit of Early Initiation of Neuraminidase Inhibitor Treatment to Hospitalized Patients With Avian Influenza A(H7N9) Virus

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Background. The significance of early neuraminidase inhibitor (NAI) therapy for treating influenza A(H7N9) is currently unknown.

Methods. The duration of viral shedding was monitored by reverse-transcription polymerase chain reaction after patients with confirmed H7N9 infection were admitted to the First Affiliated Hospital, Zhejiang University, during April 2013–April 2017. Indices such as the length of hospitalization and mortality were collected, and the correlation between the time of administration of NAI and the severity of disease was systematically analyzed.

Results. One hundred sixty patients with confirmed H7N9 infection were divided into 3 groups according to NAI starting time. Three of 20 (15%) patients for whom NAI was administered within 2 days died compared with 12 of 52 (23.1%) patients who received treatment within 2–5 days and 33 of 88 (37.5%) patients who were treated after 5 days ($P < .05$). The median durations of viral shedding from NAI therapy initiation was 4.5 days (interquartile range [IQR], 3–9 days) for patients who took antiviral medication within 2 days, which was significantly different from that for patients who took medication within 2–5 days (7.5 days [IQR, 4.25–12.75 days]) or after 5 days (7 days [IQR, 5–10 days]) ($P < .05$). We found that the duration of viral shedding from NAI therapy was the shortest in spring 2013 (5.5 days) and the longest in winter–spring 2016–2017 (8.5 days) ($P < .05$), showing a prolonged trend.

Conclusions. Early NAI therapy within 2 days of illness shortened the duration of viral shedding and improved survival in patients with H7N9 viral infection.

Keywords. influenza; H7N9; neuraminidase inhibitor treatment; viral shedding.

During the spring of 2013, a novel and highly virulent avian-origin influenza A subtype virus, H7N9, emerged among humans in eastern China [1]. H7N9 virus caused severe human illness, which was characterized by pneumonia that rapidly developed into acute respiratory distress syndrome (ARDS), multiple-organ dysfunction, and shock [2–4]. Overall, 1161 people were infected by the end of January 2017, with 433 deaths; the death rate was as high as 37.3% [5].

Due to intrinsic adamantane resistance, H7N9 influenza virus infections are treated primarily with neuraminidase inhibitors (NAIs), particularly oseltamivir and, to some extent, intravenous administration of peramivir or zanamivir [6, 7]. The guideline for diagnosis and treatment of H7N9 issued by the World Health Organization and the National Health and Family Planning Commission of China recommends that NAI antiviral therapy be administered at the early stage of H7N9; however, this is not always accomplished [8, 9].

The present study of a cohort of critically ill patients infected with H7N9 aimed to investigate the relationship between the time of NAI administration and mortality as a primary endpoint and to determine whether early administration of NAI treatment affects the duration of viral shedding and hospital length of stay (LOS).

METHODS

Study Design

This was an observational study of patients with laboratory-confirmed avian influenza A(H7N9) viral infection admitted to the First Affiliated Hospital, School of Medicine, Zhejiang University, from 1 April 2013 to 1 April 2017. Five major waves of human influenza A(H7N9) viral infections have occurred in Zhejiang since the

Received 24 April 2017; editorial decision 15 October 2017; accepted 24 October 2017; published online October 23, 2017.

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Clinical Infectious Diseases® 2018;66(7):1054–60

DOI: 10.1093/cid/cix930

first human case was identified in April 2013: spring 2013; winter–spring 2013–2014; winter–spring 2014–2015; winter–spring 2015–2016; and winter–spring 2016–2017 (winter:from December to February, spring:from march to may). The hospital is a large-scale general hospital, which serves as a designated hospital for H7N9 avian influenza in the Zhejiang Province. Written informed consent was obtained from all participants or their guardians. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of the First Affiliated Hospital of Zhejiang University.

Laboratory Confirmation

After admission, respiratory specimens (nasopharyngeal swabs, sputum, or endotracheal aspirates) were collected daily to determine the amount of H7N9 viral RNA by polymerase chain reaction (PCR) analysis. According to the guideline for diagnosis and treatment of H7N9 issued by the National Health and Family Planning Commission of China, patients who have tested negative for H7N9 for 3 consecutive days are considered H7N9 negative and will not be tested further.

All laboratory procedures for respiratory secretions have been previously reported [4]. In brief, we used TaqMan real-time reverse-transcription PCR (RT-PCR) under standard thermocycling conditions to detect the M, H7, and N9 genes. The detection limit of the M, H7, and N9 RT-PCR assays was approximately 100 copies of RNA/mL. Specimens with cycle threshold (Ct) values ≤38.0 were considered positive, specimens with Ct >38.0 were repeated, specimens with repeated results of Ct values <38 were considered positive, and specimens with Ct >38.0 and undetectable Ct values after repeated tests were considered negative.

Data Collection

The clinical data collected included demographic data, medical comorbidities, date of symptom onset, symptoms and signs, timing of antiviral therapy, progression and resolution of clinical illness, and duration of viral shedding. Medical comorbidities documented included diabetes mellitus, heart disease, chronic lung disease, renal failure, liver disease, human immunodeficiency virus infection, cancer, and receipt of immunosuppressive therapy, including corticosteroids. We consider that the symptoms started when any of fever, cough, chills, dizziness, headache, or fatigue appeared. The severity of illness was evaluated according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score on the day of admission. Moderate-to-severe ARDS was diagnosed by the ARDS Berlin definition—that is, severe hypoxemia (partial pressure arterial oxygen/fraction of inspired oxygen [PaO_2/FiO_2] ≤200 mm Hg with positive end expiratory pressure (PEEP) ≥5 cmH_2O), in addition to bilateral opacities on chest radiograph that could not be fully explained by cardiac failure or fluid overload.

Statistical Analysis

For most variables, descriptive statistics, such as the mean standard deviation (for data with normal distribution), median with interquartile range (IQR; for data with skewed distribution), and proportion (%), were calculated. The *t* test, analysis of variance, Mann-Whitney *U* test, and Kruskal-Wallis test were used for continuous variables. The χ^2 test and Fisher exact test were used for categorical variables. The Kruskal-Wallis test was used to evaluate the duration of viral shedding among groups, Kaplan-Meier curves were used to analyze survival, and logistic regression was used for multivariable analysis. Statistical analyses were performed using SPSS software, version 16.0. In all analyses, a *P* value <.05 was considered significant. All probabilities were 2-tailed.

RESULTS

Patient Description

In total, 160 patients confirmed H7N9 infection with specific NAI therapy timing were admitted to the clinical diagnosis and treatment center from 1 April 2013 to 1 April 2017. Of these cases, 94 were male and 66 were female. The median age of all patients was 58.5 years (IQR, 50–67 years), and 74 patients (46.3%) were >60 years of age. The majority of patients developed fever (96.9%) and cough (81.9%). In 103 cases (64.4%), there were underlying comorbid diseases, and 39 cases (24.4%) had ≥2 comorbidities. The most common underlying comorbidities were hypertension (43.8%) and diabetes mellitus (18.1%). With disease progression, 118 cases (73.8%) developed ARDS, and 30 cases (18.8%) developed shock. Among all subjects, 48 patients (30%) ultimately died. The average hospital LOS for surviving patients was 18 days (IQR, 11–34.3 days) (Table 1).

Clinical Illness and the Effect of Antiviral Treatment

For all the patients, the median dosage was 150 mg/day for the first oseltamivir dose and 300 mg/day for the maximum oseltamivir dose. The median oseltamivir duration was 9 days. One hundred one patients received a combination therapy of oseltamivir and peramivir. The median dosage of peramivir was 300 mg/day (Table 1).

Based on when the antiviral medication was given, all patients were divided into 3 subgroups: patients taking NAI therapy within 2 days (20 cases) from symptom onset, 2–5 days (52 cases) from symptom onset, and 5 days after symptom onset (88 cases). There was no difference among the 3 groups with regard to age, sex, or underlying diseases. Among all the complications, only the incidence of ARDS in the group taking NAI therapy within 2 days was significantly lower than that of other groups. Among clinical and laboratory features, only the level of serum aspartate aminotransferase in the group taking NAI therapy within 2 days was significantly lower than that of other groups. The usage rate of mechanical ventilation for the 3 groups of patients was 25% (antiviral therapy within 2 days), 40.4% (antiviral therapy within 2–5 days), and 63.6% (antiviral therapy after 5 days), respectively (*P* < .001). Among survivors, the median LOS was 23 days (IQR, 13–51 days) for the group of patients taking medication after 5 days, significantly longer than the 15 days (IQR, 12–46.5 days)

Table 1. Demographics and Clinical Characteristics of 160 Patients With Avian-Origin Influenza A(H7N9) Infection

Variable	All Patients (N = 160)
Demographics	
Age, y, median (IQR)	58.5 (50–67)
Sex, male/female, %	65.6/34.4
Signs or symptoms at early stage, No. (%)	
Fever	155 (96.9)
Cough	131 (81.9)
Weakness	74 (46.3)
Muscle soreness	41 (25.6)
Other	62 (38.8)
Underlying disease, No. (%)	
Hypertension	70 (43.8)
Diabetes mellitus	29 (18.1)
Coronary heart disease	19 (11.8)
COPD	14 (8.8)
Cancer	3 (1.9)
Chronic kidney disease	9 (1.9)
Hematological disorder	5 (3.1)
Pregnancy	2 (1.3)
Autoimmune disorder	5 (3.1)
Complications, No. (%)	
ARDS	118 (73.8)
Shock	30 (18.8)
Heart failure	37 (23.1)
Liver damage	31 (19.4)
Acute kidney injury	34 (21.3)
Rhabdomyolysis	13 (8.1)
Clinical and laboratory features, median (IQR)	
APACHE II score	17 (13–21)
PSI score	84 (51–115)
WBC count, cells/L	4.4 (3–7.1)
C-reactive protein, mg/dL	87.3 (40.3–132.2)
Creatine kinase, IU/L	194.5 (77–423.5)
Aspartate aminotransferase, IU/L	59 (37–105)
Creatinine, IU/L	68 (57–86)
Treatment, No. (%)	
Mechanical ventilation	82 (51.3)
Extracorporeal membrane oxygenation	39 (24.4)
Corticosteroid treatment	134 (83.8)
Administration of antiviral treatment	
Initial dosage of oseltamivir, mg/d, median (IQR)	150 (150–150)
Initial dosage of peramivir, mg/d, median (IQR)	300 (300–600)
Duration of NAI treatment, d, median (IQR)	9 (7–13)
Oseltamivir-peramivir combination therapy, No. (%)	101 (63.1)
Clinical outcome	
Death, No. (%)	48 (30.0)
Days from admission to death, median (IQR)	16.5 (7–40)
Discharge from hospital, No. (%)	112 (70.0)
Length of stay in hospital, d, median (IQR)	18 (11–34.3)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NAI, neuraminidase inhibitor; PSI, Pneumonia Severity Index; WBC, white blood cell.

for the group of patients taking medication within 2 days and 12 days (IQR, 11–17 days) for the group of patients taking medication within 2–5 days ($P = .042$; Table 2).

After 6 months of symptom onset, 3 of 20 (15%) patients for whom NAI treatment was administered within 2 days died, compared with 12 of 52 (23.1%) patients who received NAI therapy within 2–5 days and 33 of 88 (37.5%) patients who received treatment >5 days after symptom onset. The Kaplan-Meier survival analysis indicated that the long-term mortality of H7N9-infected patients who received NAI therapy within 2 days of symptom onset was significantly lower than that of patients who received NAI therapy within 2–5 days or >5 days after symptom onset ($P < .05$; Figure 1). Using logistic regression analysis, we further discovered that administration of NAI therapy within 2 days of symptom onset was associated with a clinically and significantly decreased risk of death (odds ratio, 0.511 [95% confidence interval, .291–.899]; $P = .018$; Table 3).

Duration of Viral Shedding and Effect of Antiviral Treatment

Among the 160 patients, >2000 combined nasal and throat swab specimens were obtained for avian influenza A(H7N9) virus PCR assay. Six H7N9 patients were still positive for the H7N9 virus when they died. Among the 6 cases, 1 died of multiple organ failure, 1 died of arrhythmia, and the other 4 died of hypoxemia. The virus duration was 4.5 days (IQR, 3–9 days) after NAI therapy for the group of patients who received medication within 2 days, which was significantly different from 7.5 days (IQR, 4.25–12.75 days) for those who received medication within 2–5 days and 7 days (IQR, 5–10 days) for those who received medication >5 days ($P < .05$). However, there was no significant difference between the groups of patients taking medication within 2–5 days or >5 days ($P = .653$; Figure 2*A*). We compared viral load of first pathogen test after antiviral therapy between different groups of patients and found that the viral load in the group of patients taking medication within 2 days was significantly lower than that of the other 2 groups of patients ($P < .05$), whereas there was no difference between the groups of patients taking medication within 2–5 days and >5 days ($P = .680$; Figure 2*B*).

Duration of Viral Shedding in Different Waves of H7N9 Virus Epidemics

In these 5 waves of H7N9 virus epidemics, there were 44, 42, 22, 22, and 30 patients with H7N9 infection admitted to our center. The average patient age in the latest wave was 53 years (IQR, 44–64.8 years), which made this group the youngest and was significantly different from the other groups ($P = .034$). The median time of NAI therapy administration after disease confirmation in each of the 5 epidemics was 6, 6, 7, 6.5, and 4 days, respectively. The duration of viral shedding from antiviral therapy initiation of the 5 waves were 5.5, 8, 8, 6.5, and 8.5 days, respectively, being shortest for the first wave and longest for the last wave ($P = .027$; Table 4).

Table 2. Demographic and Clinical Characteristics of Patients With Avian-Origin Influenza A(H7N9) Who Were Prescribed a Neuraminidase Inhibitor, by Time From Onset

Characteristic	Antiviral Therapy Within 2 d From Onset (n = 20)	Antiviral Therapy 2–5 d From Onset (n = 52)	Antiviral Therapy >5 d From Onset (n = 88)	*P* Value
Demographics				
Age, y, median (IQR)	58.5 (50.8–65)	57.5 (50.8–66)	59.5 (49.3–68)	.890[a]
Sex, male/female, %	65/35	69.2/30.8	63.6/36.4	.796[b]
Underlying disease, No. (%)				
Hypertension	11 (55)	22 (42.3)	37 (42.0)	.555[b]
Diabetes mellitus	4 (20)	10 (19.2)	15 (17.0)	.923[b]
Coronary heart disease	2 (10)	8 (15.4)	9 (10.2)	.732[b]
COPD	3 (15)	3 (5.8)	8 (9.0)	.456[b]
Cancer	0 (0)	1 (1.9)	2 (2.3)	.795[b]
Chronic kidney disease	2 (10)	3 (5.8)	4 (4.5)	.632[b]
Hematological disorder	1 (5)	2 (3.8)	2 (2.3)	.861[b]
Pregnancy	0 (0)	1 (1.9)	1 (1.1)	.797[b]
Autoimmune disorder	1 (5)	1 (1.9)	3 (3.4)	.675[b]
Complications, No. (%)				
ARDS	11 (55)	32 (61.5)	75 (85.2)	**.001**[b]
Shock	4 (20)	8 (15.4)	18 (20.5)	.773[b]
Heart failure	3 (15)	9 (17.3)	25 (28.4)	.227[b]
Liver damage	2 (10)	11 (21.2)	18 (20.5)	.523[b]
Acute kidney injury	2 (10)	8 (15.4)	24 (27.3)	.106[b]
Rhabdomyolysis	1 (5)	4 (7.7)	8 (9.0)	.825[b]
Clinical and laboratory features, median (IQR)				
APACHE II score	15 (13–17.5)	15 (11–21)	17 (13–22)	.212[a]
PSI score	65 (52.5–88)	67 (51.8–122)	89 (54.3–112)	.367[a]
WBC count, cells/L	5.1 (3.1–7.4)	5.3 (3.9–8.6)	3.9 (2.5–6.8)	.061[a]
C-reactive protein, mg/dL	103.9 (48.2–175.8)	81.4 (32.4–146.2)	90.9 (44.2–126.1)	.830[a]
Creatine kinase, IU/L	158 (66–326)	132 (66–396)	211 (89.5–540)	.235[a]
AST, IU/L	33.5 (23–58)	65 (38.3–92.8)	61.5 (41–119)	**.001**[a]
Creatinine, IU/L	67 (58.3–77.5)	67 (56.3–88.5)	70.7 (57–88.8)	.686[a]
Treatment, No. (%)				
Mechanical ventilation	5 (25)	21 (40.4)	56 (63.6)	**.001**[b]
Extracorporeal membrane oxygenation	2 (10)	13 (25)	24 (27.3)	.265 [b]
Corticosteroid treatment	16 (80)	45 (86.5)	73 (83.0)	.762[b]
Administration of antiviral treatment				
Initial dosage of oseltamivir, mg/d, median (IQR)	150 (150–150)	150 (150–150)	150 (150–150)	.492[a]
Initial dosage of peramivir, mg/d, median (IQR)	300 (300–600)	300 (300–600)	300 (300–600)	.477[a]
Duration of oseltamivir treatment, d, median (IQR)	7 (5–11)	9.5 (6.25–14.75)	9.5 (7–12)	.090[a]
Oseltamivir-peramivir combination therapy, No. (%)	13 (65.0)	33 (63.5)	55 (62.5)	.977[b]
Clinical outcome				
Death, No. (%)	3 (15)	12 (23.1)	33 (37.5)	**.021**[b]
Days from admission to death, median (IQR)	15 (4–67)	27 (4–46)	15 (7–23)	.575[a]
Discharge from hospital, No. (%)	17 (85)	40 (76.9)	55 (62.5)	**.021**[b]
Length of stay in hospital, d, median (IQR)	15 (12–46.5)	12 (11–17)	23 (13–51)	**.042**[a]

Values in boldface indicate statistical significance ($P < .05$).

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PSI, Pneumonia Severity Index; WBC, white blood cell.

[a] *P* value calculated using analysis of variance for continuous variables (normal distribution) or Kruskal-Wallis test for continuous variables (abnormal distribution).

[b] *P* value calculated using χ^2 or Fisher exact test for categorical variables.

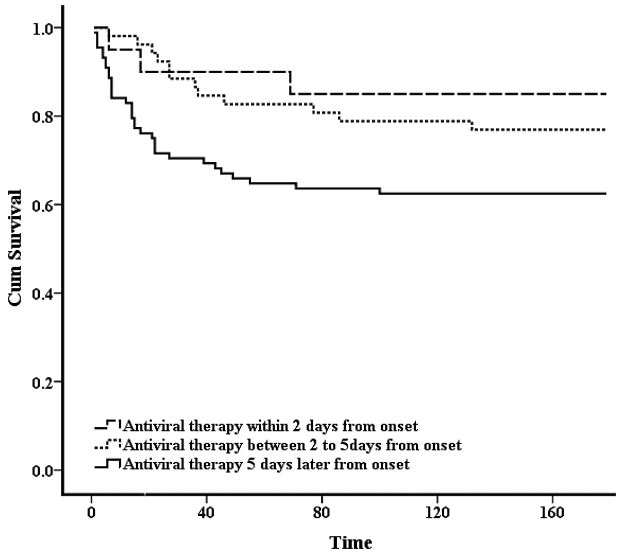

Figure 1. Kaplan-Meier survival curves according to the time of illness at initiation of antiviral treatment.

Table 3. Multivariable Analysis of the Impact of Antiviral Therapy on Mortality Associated With Laboratory-Confirmed Avian-Origin Influenza A(H7N9)

Variable	OR (95% CI)	*P* Value
Age	1.044 (1.014–1.075)	.018
Antiviral therapy	0.511 (.291–.899)	.018
Sex	1.103 (.51–2.384)	.804
Underlying disease	1.281 (.559–2.937)	.558

Abbreviations: CI, confidence interval; OR, odds ratio.

DISCUSSION

Our finding that NAI treatment was associated with a significantly lower mortality rate indicates that the use of NAI therapy might improve patient outcomes for H7N9 virus infection. Early use of antiviral drugs can reduce the risk of death in patients with H7N9 virus infection by nearly half. These data are congruent with evidence from observational studies in hospitalized patients, indicating that therapy with NAI reduces symptom duration, complications, LOS, and mortality for influenza among adult outpatients [10–12].

Our findings also agree with a previous study among adults, in whom early initiation of NAI treatment was strongly associated with a shorter duration of influenza [13, 14]. These findings are plausible, considering our understanding of the mechanism of action of oseltamivir and the pathogenesis of influenza. The efficacy of oseltamivir lies in the ability to prevent infection of new host cells by interfering with the release of progeny influenza viruses from infected cells [15]. Because the replication of influenza viruses peaks at 24–72 hours after the onset of symptoms and the viral load correlates positively with the severity of symptoms [16, 17], administering oseltamivir as early as possible after the onset of symptoms could provide the greatest clinical benefits.

Whether it is effective to take antiviral drugs after 2 days of symptom onset remains controversial. Adisasmito et al found that H5N1 patients could still benefit from the initiation of oseltamivir up to 6–8 days after the onset of symptoms [18]. However, in this current study, although we confirmed that taking antiviral drugs within 2 days from onset could reduce the mortality of H7N9 patients dramatically, there was no significant difference in mortality between the 2 groups of patients taking medication within either 2–5 days or >5 days of symptom onset. Therefore, it is difficult to evaluate whether taking antiviral drugs after 2 days also works.

The guideline for diagnosis and treatment of H7N9 issued by the World Health Organization and the National Health and Family Planning Commission of China recommends that NAI therapy can be initiated empirically as soon as possible. However, in this study, we found that only 12.5% of the patients were able to take NAI therapy within 2 days of the onset of

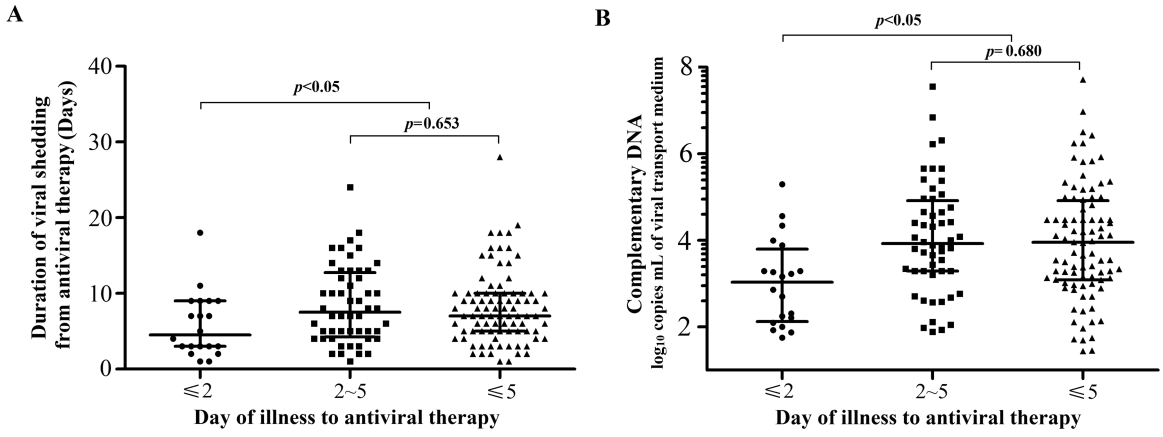

Figure 2. Duration of avian influenza A(H7N9) viral shedding (*A*) and viral load of first pathogen test after antiviral therapy (*B*), according to the time of illness at initiation of antiviral treatment.

Table 4. Demographics and Clinical Characteristics of Patients in Different Waves of Avian-Origin Influenza A(H7N9) Virus Epidemics

Characteristic	Spring 2013 (n = 44)	Winter–Spring 2013–2014 (n = 42)	Winter–Spring 2014–2015 (n = 22)	Winter–Spring 2015–2016 (n = 22)	Winter–Spring 2016–2017 (n = 30)	*P* Value
Age, y, median (IQR)	63 (50.3–73)	55 (43.8–63.3)	61 (53.8–68)	61 (55–68)	53 (44–64.8)	**.034**[a]
Sex, male/female, %	65.9/34.1	73.8/26.2	77.3/32.7	54.4/45.6	53.3/46.7	.219[b]
ARDS, No. (%)	29 (65.9)	32 (76.2)	17 (77.3)	18 (81.8)	22 (73.3)	.754[b]
Time of antiviral therapy from onset, d, median (IQR)	6 (3.25–8)	6 (3.75–8)	7 (5.5–11.3)	6.5 (3.8–9)	4 (3–6.25)	.098[b]
Duration of viral shedding from antiviral therapy, d, median (IQR)	5.5 (3–8)	8 (4–10)	8 (4.8–13.3)	6.5 (5–10.3)	8.5 (5–15.3)	**.027**[a]

Value in boldface indicates statistical significance ($P < .05$).

Abbreviations: ARDS, acute respiratory distress syndrome; IQR, interquartile range.

[a] *P* value calculated using analysis of variance for continuous variables (normal distribution) or Kruskal-Wallis test for continuous variables (abnormal distribution).

[b] *P* value calculated using χ^2 or Fisher exact test for categorical variables.

symptoms, and the timely administration of NAI therapy was lower than that during the H1N1 influenza outbreak in 2009. Many reasons might contribute to this result. First, the majority of H7N9 patients are farmers, who do not generally seek formal clinical treatment in a timely manner [19]. Second, the onset of symptoms of H7N9 influenza is typically subtle, with common initial symptoms such as fever and cough; thus, the diagnosis is likely to be delayed [2]. Therefore, strengthening the training of primary healthcare personnel is necessary.

By study of animal models, researchers have found that the use of corticosteroids could promote viral replication and prolong duration of the virus [20]. Currently, Cao et al discovered that low dosage (25–150-mg/day methylprednisolone or its equivalent) of corticosteroid had no effect on the duration of H7N9 virus, whereas high dosage (>150 mg/day methylprednisolone or its equivalent) of corticosteroid could significantly increase the duration of H7N9 virus in the body [21]. In this study, low dosage of corticosteroid (40 mg/day methylprednisolone or its equivalent) was used. According to Cao et al's report, we also believe that the effect of low-dose corticosteroids on the duration of H7N9 virus was insignificant, and therefore did not affect our result.

Resistance of neuraminic acid inhibitor is a serious challenge in clinical antiviral therapy. Previous studies have discovered that NA-R292K, NA-E119V, NA-I222K, NA-I222R and other site mutations of H7N9 virus were directly related to resistance of neuraminic acid, leading to duration of viral shedding prolonged [22, 23]. In this study, compared with the first wave in 2013, viral duration time after antiviral therapy was significantly increased in latter waves of patients, which we considered to be related with NAI resistance and needs further research. Ilyushina et al have verified that combination of the second type of anti-influenza virus drug could reduce the occurrence of influenza A virus resistance [24]. Although research has found that combination therapy of oseltamivir and peramivir was not significantly superior to oseltamivir monotherapy for influenza A(H7N9) infection [25], the exploration of combination antiviral therapy to reduce resistance remains essential.

There are several limitations to our study. First, this study is a single-center retrospective analysis, which could lead to the unbalanced distribution of confounders when we evaluate the efficacy of the antiviral therapy. Some factors may affect viral duration time or mortality, such as age, severity of the disease, or use of corticosteroids. Through comparison, we found that there were no significant differences in the above indices among the 3 groups. Second, as H7N9 influenza is a serious disease with high mortality, patients with confirmed H7N9 will always take antiviral therapy as soon as a diagnosis is made. Therefore, we did not have a group of patients who did not receive antiviral therapy in this study, and we could not comprehensively evaluate the clinical effectiveness of antiviral therapy on H7N9 avian influenza infection. Third, the sample size was insufficient to compare treatment effects in different subgroups. Finally, we used the method of PCR in this study, which could not recognize nonviable virus and was not able to reflect the replication level of the virus in vivo. However, PCR has higher sensitivity and is easier to use, and thus we still choose the method of PCR, as done in other studies [17, 20].

In conclusion, this study showed that NAI therapy might improve survival in patients with avian influenza A(H7N9) viral infections. Early treatment, especially within the first 2 days of illness, shortened the duration of viral shedding. Therefore, early treatment of suspected or confirmed cases is strongly encouraged.

Notes

Acknowledgments. We acknowledge the contributions of other clinical and technical staff of the First Affiliated Hospital, College of Medicine, Zhejiang University.

Financial support. This work was supported by the China National Mega-Projects for Infectious Diseases (grant number 2017ZX10103008);

the National Key Research and Development Program of China (grant number 2016YFC1200200); and the National Natural Science Foundation of China (grant numbers 81672014 and 81702079).

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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