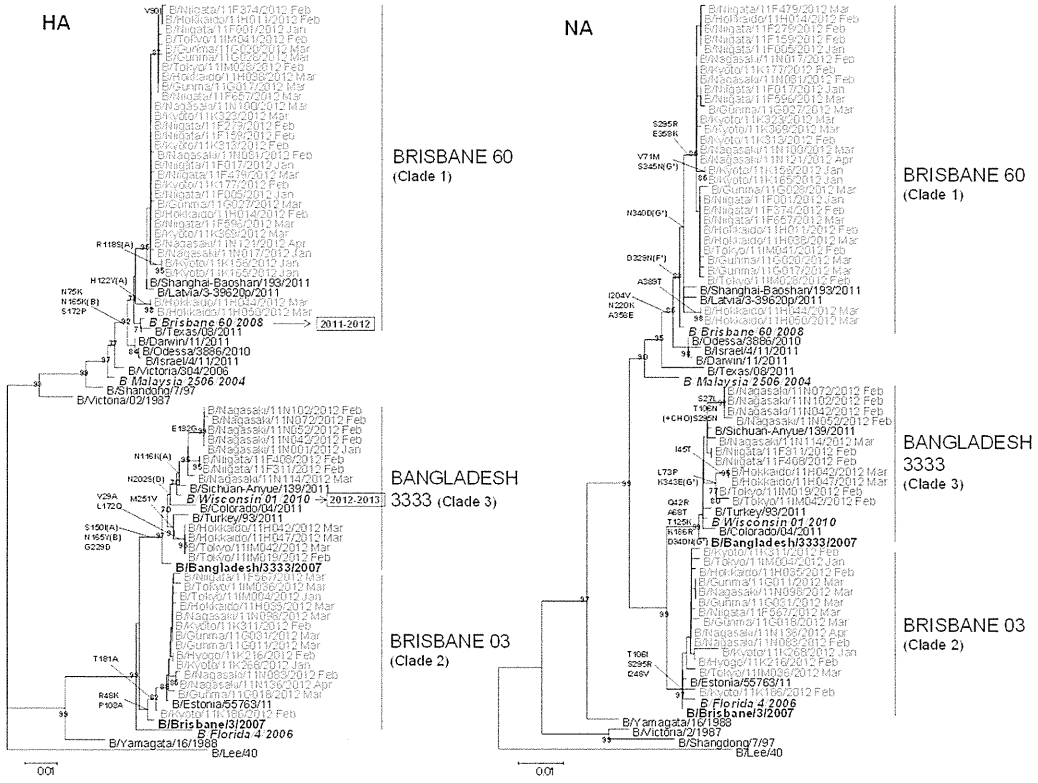

図５．2011－2012 年シーズンに日本各地で採取された B 型インフルエンザの HA 遺伝子および NA 遺伝子解析

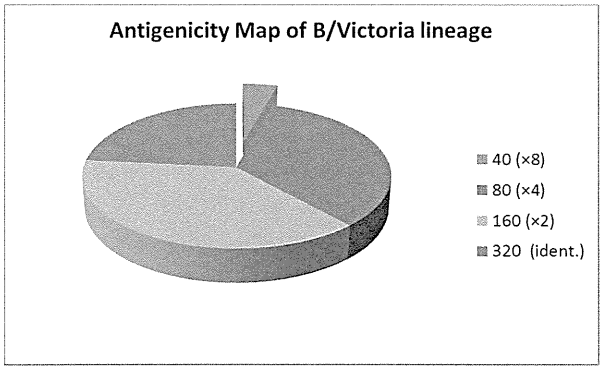

図６　2011-2012 年シーズンに採取された B/ビクトリア系統の HAI 抗原解析。ワクチン株の B/Brisbane/60/2008（ホモ価　320 倍）に対する HI 価の分布を示す。

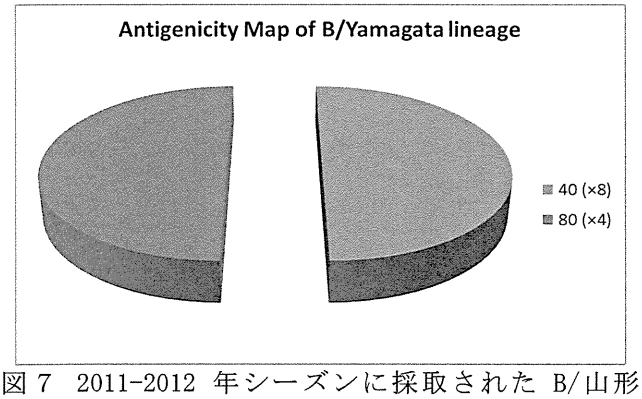

図７　2011-2012 年シーズンに採取された B/山形系統の HAI 抗原解析。2008/2009 年ワクチン株の B/Florida/4/2006（ホモ価　320 倍）に対する HI 価の分布を示す。

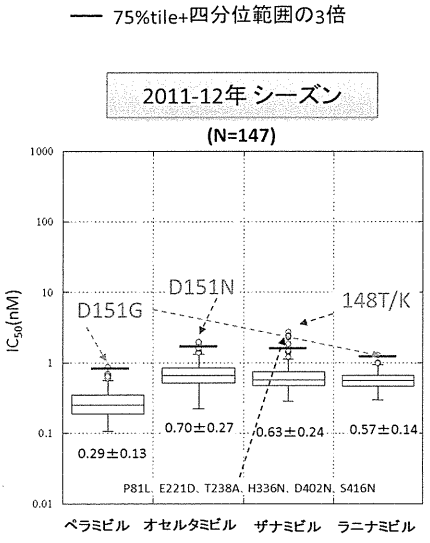

図８．2011－2012 年の A/H3N2 初診時株における NA 阻害剤 4 剤に対する IC50 値と、外れ値を示した検体に認められた NA 遺伝子変異
はずれ値は各薬剤の 75%タイル＋3IQR 以上と定義した。
平均値は 75%タイル＋3IQR 以上のはずれ値を除き算出した。

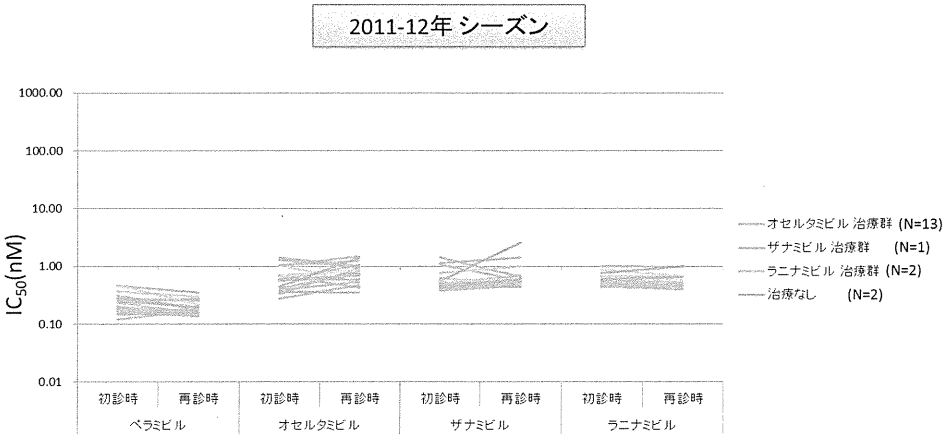

図９．2011－2012 年シーズンに初診時と薬剤治療後の再診時に採取された A/H3N2(n=18)の NA 阻害剤 4 剤に対する IC50 値の変化

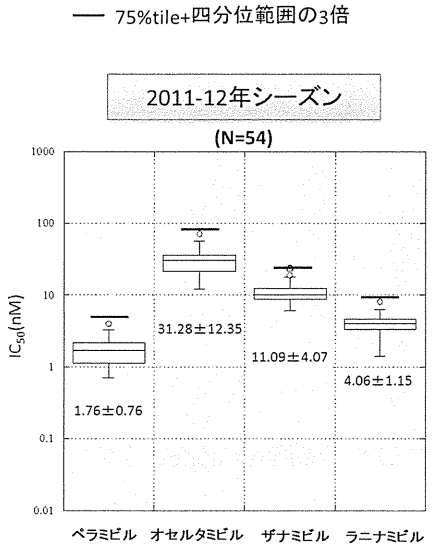

図 10. 2011－2012 年の B 型初診時株における NA 阻害剤 4 剤に対する IC50 値
はずれ値は各薬剤の 75%タイル＋3IQR 以上と定義した。
平均値は 75%タイル＋3IQR 以上のはずれ値を除き算出した。

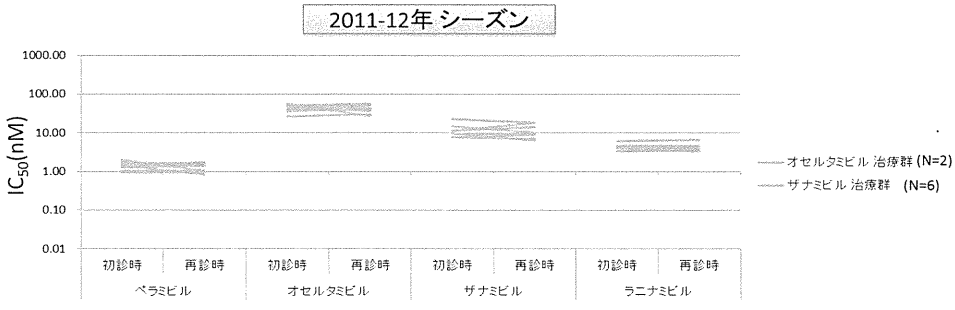

図 11. 2011－2012 年シーズンに初診時と薬剤治療後の再診時に採取された B(n=8)の NA 阻害剤 4 剤に対する IC50 値の変化

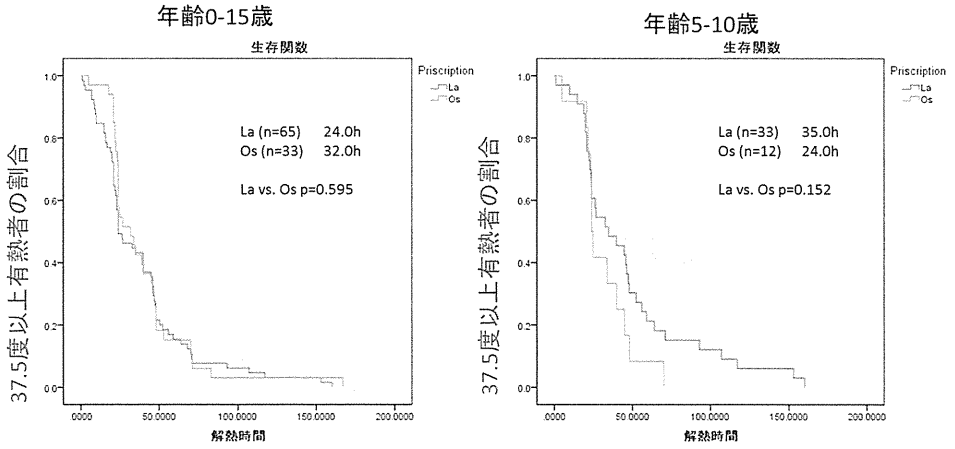

図 12. A/H3N2 型に罹患した 0-15 歳、5-10 歳児が 37.5 度以下に解熱するまでの時間の比較（カプランマイヤー法による）

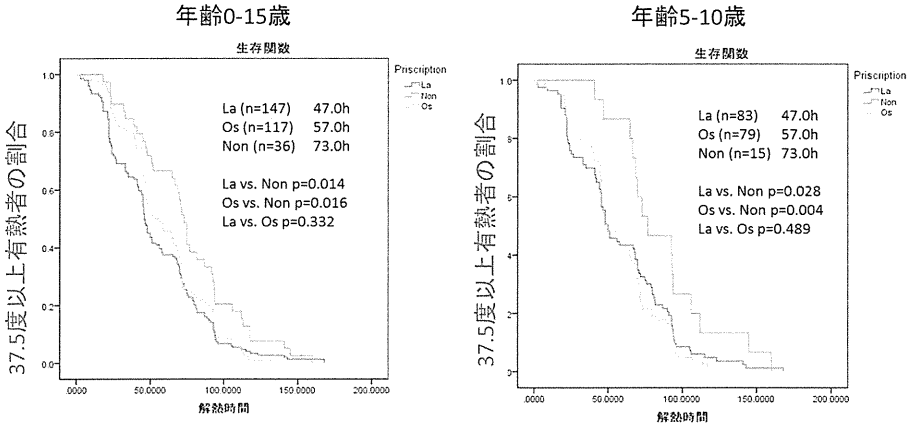

図 13.　B 型に罹患した 0-15 歳、5-10 歳児が 37.5 度以下に解熱するまでの時間の比較（カプランマイヤー法による）

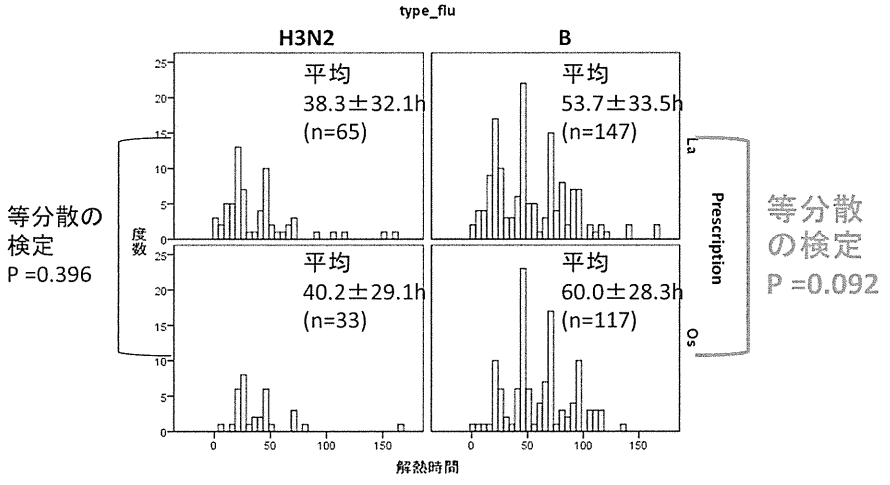

図 14. A/H3N2 と B 型罹患児の治療群（上段ラニナミビルと下段オセルタミビル）別の解熱時間の度数分布（0-15 歳）

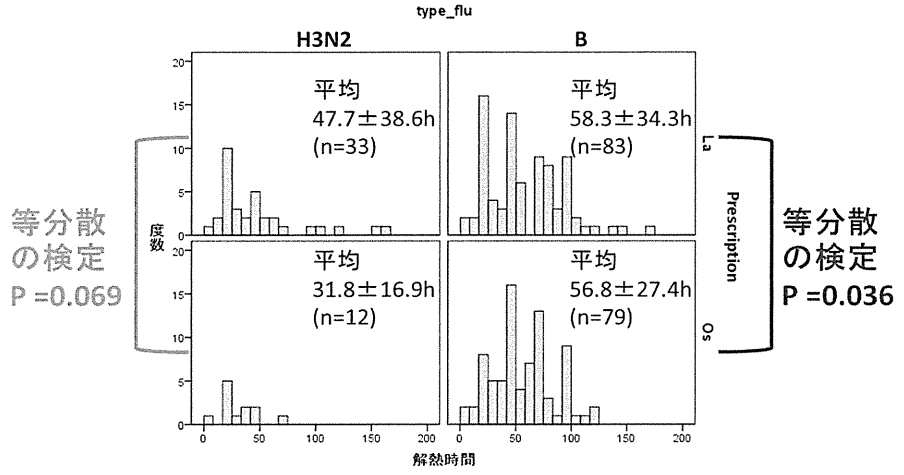

図１５．A/H3N2 と B 型罹患児の治療群（上段ラニナミビルと下段オセルタミビル）別の解熱時間の度数分布（5-10 歳）

研究成果の刊行に関する一覧

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
河合直樹 廣津伸夫 池松秀之	インフルエンザ診療マニュアル2012-2013年シーズン版	柏木征三郎	インフルエンザ診療マニュアル（2012－2013年版）	一般社団法人日本臨床内科医会	東京	2012	

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kudo K, Binh NG, Manabe T, Co DX, Tuan ND, Izumi S, Takasaki J, Minh DH, Thuy PTP, Van TT, Hanh TT, Chau NQ	Clinical preparedness for severe pneumonia with highly pathogenic avian influenza A (H5N1): Experiences with cases in Vietnam	Respiratory Investigation	50	140-150	2012
Manabe T, Higera Iglesias AL, Vazquez Manriquez ME, Alfaro Ramos L, Leticia Valadez MEM, Takasaki J, Kudo K	Socioeconomic Factors Influencing Hospitalized Patients with Pneumonia Due to Pandemic (H1N1) 2009 in Mexico	PLoS ONE	7(7)	e40529	2012
Manabe T, Hanh TT, Lam MD, Thuy TPP, Huyen TTD, Phuong TTM, Minh DH, Takasaki J, Chau GQ, Toan QL, Kudo K	Knowledge, Attitude, Practices and Emotional Reactions among Residents of Avian Influenza (H5N1) Hit Communities in Vietnam	PLoS ONE	7(10)	e47560	2012
Kudo K, Takasaki J, Manabe T, Uryu H, Yamada R, Kuroda E, Kobayashi N, Matsushita T	Systemic Corticosteroids and Early Administration of Antiviral Agents for Pneumonia with Acute Wheezing due to Influenza A(H1N1)pdm09 in Japan	PLoS ONE	7(2)	e32280	2012
Fukushi M, Yamashita M, Miyoshi-Akiyama T, Kubo S, Yamamoto K, Kudo K	Laninamivir Octanoate and Artificial Surfactant Combination Therapy Significantly Increases Survival of Mice Infected with Lethal Influenza H1N1 Virus	PLoS ONE	7(8)	e42419	2012
Manabe T, Thuy PTP, Kudo K, Van VTT, Takasaki J, Tuan ND, Co DX, Minh DH, Izumi S, Binh NG, Chau NQ, Hanh TT	Impact of Education and Network for Avian Influenza H5N1 in Human: Knowledge, Clinical Practice, and Motivation on Medical Providers in Vietnam	PLoS ONE	7(1)	e30384	2012
Vazquez-Manriquez ME, Makino A, Tanaka M, Abe Y, Yoshida H, et al	Emergence of HA mutants during influenza virus penumonia	Int J Clin Exp Pathol	5(8)	787-95	2012
Ukimura A, Ooi Y, Kanzaki Y, Inomata T, Izumi T	A National survey on myocarditis associated with Influenza H1N1pdm2009 in the pandemic and post-pandemic season in Japan	J Infect Chemother	19(3)	426-31	2013

Ukimura A, Satomi H, Ooi Y, Kanzaki Y	Myocarditis Associated with Influenza A H1N1pdm2009 (Review)	Influenza Res Treat		doi: 10.1155/2012/351979	2012
Kawai N, Ikematsu H, Kawashima T, Maeda T, Ukai H, Hirotsu N, Iwaki N, Kashiwagi S	Increased symptom severity but unchanged neuraminidase inhibitor effectiveness for A(H1N1)pdm09 in the 2010-2011 season: comparison with the previous season and with seasonal A(H3N2) and B	Influenza Other Respi Viruses	7(3)	448-55	2013
Ikematsu H, Kawai N, Kashiwagi S	In vitro neuraminidase inhibitory activities of four neuraminidase inhibitors against influenza viruses isolated in the 2010-2011 season in Japan	J Infect Chemother	18(4)	529-33	2012
Dapat IC, Dapat C, BaranovichT, Suzuki Y, Kondo H, Shobugawa Y, Saito R, Suzuki H; the Japanese Influenza Collaborative Study Group	Genetic Characterization of Human Influenza Viruses in the Pandemic (2009-2010) and Post-Pandemic (2010-2011) Periods in Japan	PLoS One	7(6)	e36455	2012
Shobugawa Y, Saito R, Sato I, Kawashima T, Dapat C, Dapat IC, Kondo H, Suzuki Y, Saito K, Suzuki H	Clinical effectiveness of neuraminidase inhibitors-oseltamivir, zanamivir, laninamivir, and peramivir-for treatment of influenza A(H3N2) and A(H1N1)pdm09 infection: an observational study in the 2010-2011 influenza season in Japan	J Infect Chemother	18(6)	858-864	2012
工藤宏一郎	高病原性鳥インフルエンザ(H5N1)の現状	THE LUNG perspectives	20(4)	387-391	2012
河合直樹、前田哲也 川島 崇、廣津伸夫 池松秀之、柏木征三郎	４種のノイラミニダーゼ阻害薬の使い方.	インフルエンザ	12	13:105-110	2012
河合直樹、池松秀之、柏木征三郎	抗ウイルス薬治療の実際. インフルエンザ	臨床と研究	89	1369-73	2012
河合直樹	検査・投薬のポイント.インフルエンザ診療マニュアルから	メディカル朝日	41:11号	19-21	2012
河合直樹、池松秀之 柏木征三郎、石黒信久	インフルエンザ診療 2012-2013 の対策 (内科/小児科)	Physicians' Therapy Manual(PTM)	5(Nov)	1-4	2012
河合直樹、池松秀之 柏木征三郎	新型インフルエンザは再びおこるか. インフルエンザの治療－成人	臨床と研究	89	1645-49	2012
河合直樹、池松秀之 柏木征三郎	今シーズンにおける抗インフルエンザ薬の使い方	日経メディカル	1月号(542)	107-109	2013
河合直樹、池松秀之 柏木征三郎	今シーズンにおける抗インフルエンザ薬の使い方	日経メディカル	1月号	141-143	2012

研究成果の刊行物

RESPIRATORY INVESTIGATION 50 (2012) 140–150

Contents lists available at SciVerse ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

Clinical preparedness for severe pneumonia with highly pathogenic avian influenza A (H5N1): Experiences with cases in Vietnam

Koichiro Kudo[a,d,*], *Nguyen Gia Binh*[b], *Toshie Manabe*[a,d], *Dao Xuan Co*[b], *Nguyen Dang Tuan*[b], *Shinyu Izumi*[a], *Jin Takasaki*[a], *Dang Hung Minh*[b], *Pham Thi Phuong Thuy*[c], *Vu Thi Tuong Van*[b], *Tran Thuy Hanh*[b], *Ngo Quy Chau*[b]

[a]*National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan*
[b]*Bach Mai Hospital, 78 Giai Phong, Dong Da, Hanoi, Vietnam*
[c]*NCGM-BMH Medical Collaboration Center, 78 Giai Phong, Dong Da, Hanoi, Vietnam*
[d]*Waseda University, 1-21-1 Nishi-Waseda, Shinjuku-ku, Tokyo 169-0051, Japan*

ARTICLE INFO

Article history:
Received 30 March 2012
Received in revised form
22 June 2012
Accepted 21 August 2012
Available online 29 September 2012

Keywords:
Early intervention
Acute respiratory distress syndrome
Avian influenza
H5N1
Polymyxin B-immobilized hemoperfusion

ABSTRACT

Background: Avian influenza A (H5N1) in human presents a global pandemic threat, and preparedness is urgently required in high-risk countries.

Methods: A retrospective chart review was conducted on 8 patients with H5N1 infection (aged 2–30 years; 3 fatal) who were hospitalized in Bach Mai Hospital (BMH), Vietnam, or in affiliated hospitals with consultation by physicians in BMH between 2007 and 2010. Demographic background, chest radiographs, and clinical and laboratory data were evaluated to determine the critical issues in relation to clinical outcomes. Treatment of 4 patients with acute respiratory distress syndrome (ARDS) (2 fatal) was assessed for renal replacement therapy using continuous hemodiafiltration (CHDF), polymyxin B-immobilized (PMX) hemoperfusion, or their combination.

Results: Patients had direct contact with dead/sick poultry infected with H5N1 virus or lived in areas where H5N1 poultry outbreaks had been reported at the same time as their illness. Time to initiation of oseltamivir from symptom onset was 2–6 days for survivors and 7–9 days for non-survivors. All patients except one had infiltrative shadows on chest radiographs on admission. Patients with delayed treatment developed ARDS. Renal replacement therapy contributed to patient survival, with improvement of oxygenation and a dramatic decrease in serum cytokine levels if initiated earlier.

Conclusions: Understanding local H5N1 poultry outbreaks and chest radiography assist early diagnosis and initiation of antiviral treatment. Developing a network among local and tertiary care hospitals can reduce the time to initiation of treatment. CHDF and PMX

Abbreviations: ARDS, acute respiratory distress syndrome; ALI, acute lung injury; CHDF, continuous hemodiafiltration; PMX, polymyxin B-immobilized; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in arterial blood; P/F, PaO_2/FiO_2; SOFA, Sequential Organ Failure Assessment

*Corresponding author at: Waseda University, Suite 613-6, #19 Build, 1-21-1 Nishi-Waseda, Shinjuku-ku, Tokyo 169-0051, Japan.
E-mail address: kudo@aoni.waseda.jp (K. Kudo).

2212-5345/$ - see front matter
http://dx.doi.org/10.1016/j.resinv.2012.08.005

hemoperfusion are possible candidates for effective treatment of ARDS with H5N1 if applied earlier.

1. Introduction

Avian influenza A (H5N1) virus infection in human presents a global pandemic threat. To date, H5N1 infection in human has been sporadic and related to exposure to zoonotic sources of the virus [1,2]. The recent unpredictable changes in H5N1 virus in human highlight the urgent need for clinical preparedness. H5N1 outbreaks among poultry and wild birds have occurred in Japan and worldwide [3]. It is necessary to implement a high alert for H5N1 in these high-risk countries.

H5N1 infection rapidly leads to severe pneumonia and acute respiratory distress syndrome (ARDS), which are pathologically characterized as diffuse alveolar damage [4,5]. Oseltamivir treatment is recommended for H5N1 patients [6–8], and the timing of antiviral treatment is vital for achieving a positive outcome [6,9]. The development of a clinical treatment system to administer oseltamivir as early as possible is crucial for H5N1 patients. In addition, the optimal dosage and duration of oseltamivir treatment need to be clarified for H5N1 patients [10,11]. Single treatment with oseltamivir is not sufficient for most H5N1 patients. Combination therapy with antiviral agents seems to be needed for severe pneumonia [2,11]. Without appropriate treatment for pneumonia due to H5N1 infection, ARDS can develop and often leads to death [4,12]. Since 2007, 30 confirmed human cases have been reported in Vietnam to date (63.3% of mortality). Despite the relatively low incidence of human H5N1 infections globally, H5N1 infection has been occurring continuously, with a high mortality rate [1]. This has rendered it difficult to conduct clinical studies to find effective treatment strategies. It has also resulted in a small number of physicians who have the experience and knowledge to treat H5N1 patients. Therefore, additional clinical data need to be collected.

The aims of the present study were to examine the clinical backgrounds and treatment methods of patients with H5N1 infection in Vietnam and to assess how the clinical system contributed to early initiation of oseltamivir treatment, how treatment affected patient survival, and whether renal replacement therapy was effective in H5N1 patients with ARDS. Experience in treating H5N1 patients can contribute to clinical preparedness for any future pandemic deriving from highly pathogenic influenza virus infection.

2. Materials and methods

2.1. Study site and subjects

Bach Mai Hospital (BMH) is a government hospital in Hanoi, Vietnam, that has played a central role in treating H5N1 patients in northern Vietnam since 2003. BMH has developed a cooperative network for treating H5N1 patients among provincial and district hospitals in 19 provinces (Fig. 1). Within the network, medical providers can exchange scientific information relating to H5N1 infection and clinical consultations by physicians in BMH who have treated H5N1 patients. The subjects of the present study were 8 patients with H5N1 infection between 2007 and 2010 who were hospitalized and treated in BMH (2 fatal), or hospitalized in

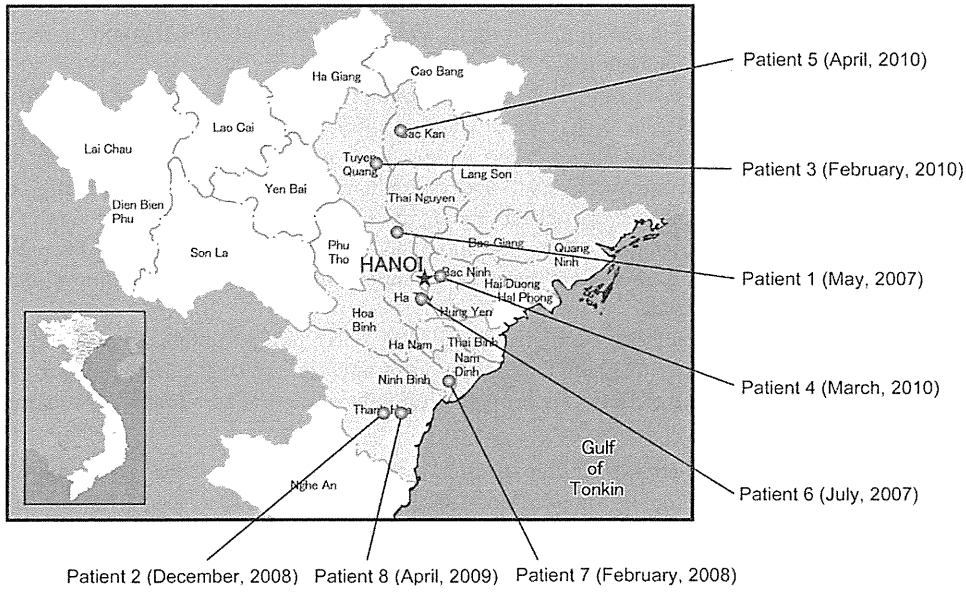

Fig. 1 – Map of Vietnam indicating the location of the study patients, as well as month and year of occurrence of H5N1 infection. Light gray area indicates the healthcare network among 19 provinces in this study.

local hospitals within the network and treated through consultations with physicians in BMH (one fatal). All patients tested positive for H5N1 virus by real-time reverse transcriptase-polymerase-chain-reaction (RT-PCR) at the National Institute of Hygiene and Epidemiology, Hanoi.

2.2. Study design

A retrospective chart review was conducted on 8 patients with H5N1 infection. Demographic background, clinical data, chest radiographs, and laboratory data were collected and assessed to determine the critical issues for treating H5N1 patients in relation to clinical outcomes. Renal replacement therapy was performed by using continuous hemodiafiltration (CHDF) [13], an absorbent column containing polymyxin B fiber (Toraymyxin/PMX, Toray Medical Co., Ltd., Tokyo, Japan) [14], or its combination, and was evaluated for treating ARDS due to H5N1 infection in 4 patients who were treated in the intensive care unit (ICU) of BMH. Partial pressure of oxygen in arterial blood/fraction of inspired oxygen (P/F) and Sequential Organ Failure Assessment (SOFA) score in 4 patients with ARDS as well as levels of serum inflammatory cytokines in a patient treated with PMX hemoperfusion were assessed at different time points during the ICU stay.

Hospital admission was defined as the time when treatment for H5N1 infection was initiated. ARDS and acute lung injury (ALI) were defined as $P/F \leq 200$ and 200–300, respectively [15].

2.3. Ethics

Ethical approvals were provided by the institutional review boards of Ministry of Health, Vietnam (No. 7998/BYT-K2DT, December 2011) and the National Center for Global Health and Medicine (No. 592, March 2011). Written informed consent was obtained from study patients or their relatives.

3. Results

3.1. General characteristics of study patients

Among the 8 patients (6 female, 2 male, aged 2–30 years) examined, four were initially treated at local hospitals and transferred and treated in the ICU, BMH. The remaining 4 patients were treated in local general hospitals (Fig. 1). The characteristics and clinical presentation on admission of each patient are shown in Table 1.

None of the patients had any underlying diseases. Two patients were chicken traders and another 2 reported cooking and eating infected (dead) poultry. One patient was a fish farmer who handled dried bird excrement as feed. The remaining 4 patients of young age (2, 8, 17, and 23 years old) had no history of direct contact with either sick or dead poultry; however, they lived in areas where H5N1 poultry outbreaks had been reported at the same time as their illness.

All patients had fever (≥ 38.0 °C) at the time of admission. Productive cough and dyspnea were common. Chest pain was observed in 5 patients. Upon admission, all patients, except Patient 5, had respiratory difficulty (median respiration rate, 30 breaths/min; range, 25–36); low oxygen saturation in arterial blood under oxygen administration with nasal, mask, or mechanical ventilation; and abnormal breath sounds (crackles) in the chest. Infiltration shadows on chest radiographs indicating pneumonia were observed at hospital admission for all patients except Patient 5. The primary laboratory tests were performed on admission (Table 1). Specific abnormalities in laboratory findings were not observed, except for tendencies toward leukopenia in peripheral blood and high levels of serum creatinine.

3.2. Clinical course and treatment of study patients

The clinical course and treatment for each patient are shown in Table 2. All patients, except Patient 5, sought primary medical assistance (primary care) in the local community before hospital admission. Time from symptom onset (fever) to primary care ranged 2–7 days. Patients were transferred to either a local general hospital or BMH, and treatment for H5N1 infection was initiated in accordance with positive results by RT-PCR. The time from primary care to hospital admission ranged 0–5 days, and total duration from symptom onset to initiation of treatment ranged 2–9 days.

ALI/ARDS was observed in all patients on admission, except Patient 5. Multiple organ failure developed in all non-survivors and 2 survivors during hospitalization. Patients 1 and 4 (survivors), who had long hospitalization, had nosocomial infections, as determined by sputum and blood cultures. Bacterial co-infection was detected in the sputum from Patient 2 on admission.

All patients were treated with oseltamivir, which is the only available antiviral agent in Vietnam. The basic dosage of oseltamivir was 150 mg/day in local general hospitals and 300 mg/day in BMH. The duration of treatment was 5–8 days, or until the patient's death. Other drug regimens and treatments included antibiotics, corticosteroids, oxygen including ventilation support, and renal replacement therapy including blood purification therapy. Between presentation to primary care and hospital admission, patients were empirically treated with antibiotics. Corticosteroids were administered to all patients with pneumonia concomitantly with oseltamivir. Antibiotics were administered during the entire treatment period.

3.3. Chest radiographs

Chest radiographs are shown upon admission (before oseltamivir administration), at the time of worst condition, and during the recovery period in Fig. 2. With Patients 6, 7, and 8 (non-survivors), consolidation shadows rapidly expanded to the entire lung fields within a few days after hospital admission (but were not critical at admission in Patients 6 and 7). consolidation shadows for survivors eventually diminished, although 2 patients exhibited exacerbated conditions after admission. Patients 1, 4, 6, and 7 developed pneumothorax during mechanical ventilation support.

Table 1 – Background and clinical characteristics of patients on admission.

Variable	Survivors					Non-survivors		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
General background								
Year of illness	2007	2008	2010	2010	2010	2007	2008	2009
Place treated	BMH	Province	Province	BMH	Province	BMH	BMH	Province
Age (yr)/gender (M/F)	30/M	8/F	17/F	25/F	2/F	22/F	27/M	23/F
Route of exposure to virus	Handling chickens	Ate infected chicken	Backyard poultry died 5 days before onset	Cooked and ate infected chicken	Epidemic outbreak in poultry in residential area	Fish farmer, handled bird excrement	Chicken trader, handled dead chickens	Epidemic outbreak in poultry in residential area
Underlying disease	None	None	None	None	None	None	None	None
Clinical presentation								
Body temperature (°C)	40.1	38.5	38.0	39.5	37.5	38.1	39.8	39.0
Primary signs and symptoms	Fever, dyspnea, cough, sputum, chest pain	Fever, dyspnea, cough, sputum, chest pain	Fever, dyspnea, cough, sputum	Fever, dyspnea, cough, chest pain	Fever, cough	Fever, dyspnea, cough, chest pain	Fever, dyspnea, cough, chest pain	Fever, dyspnea, cough, chest pain, diarrhea
Respiration rate (per min)	30	25	NA	30	25	36	30	36
Crackles	+	+	+	+	NA	+	+	+
SpO_2[a] under oxygen administration (L/min)	74% 8 L mask	99% 3 L nasal	92% 5 L nasal	90% 8 L mask	No oxygen	65% 100% MV	70% 9 L mask	79% 100% MV
PaO_2/FiO_2[b]	119	NA	NA	207	NA	38.4	32.8	NA
Abnormal shadow on chest radiograph[c]	Unilateral mixed	Unilateral infiltration	Bilateral mixed	Bilateral mixed	Absence of pneumonia	Bilateral mixed	Bilateral consolidation	Unilateral consolidation
APACHE score[d]	23	NA	NA	22	NA	24	32	NA
SOFA[e]	11	NA	NA	9	NA	9	10	NA
Laboratory findings[f]								
Serum creatinine (mg/dL)	1.45	0.90	NA	0.90	NA	0.82	1.12	2.68
AST (U/L)	477	145	NA	94	NA	199	171	114
ALT (U/L)	131	66	NA	12	NA	45	36	32

Table 1 (*continued*)

Variable	Survivors					Non-survivors		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
LDH (IU/L)	NA	101	NA	1051	NA	NA	891	NA
Leukocyte (per mm^3)	2190	2000	6100	1670	4100	5400	1320	NA[¶]
Platelet (per mm^3) $\times 10^4$	8.7	2.7	NA	6.5	NA	11.9	13.6	NA

M, Male; F, female; NA, not available; MV, oxygen therapy using mechanical ventilation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.
[a] Oxygen saturation measured by pulse oximeter.
[b] PaO_2/FiO_2 ratio. PaO_2: partial pressure of oxygen in arterial blood (mmHg); FIO_2: fraction of inspired oxygen. Measured after the initiation of mechanical ventilation.
[c] Bilateral or unilateral lung abnormal shadow on chest radiograph. Mixed, abnormal shadows represent both infiltration and consolidation.
[d] APACHE II score: Acute Physiology and Chronic Health Evaluation score. Score range, 0–71; higher range indicates more severe disease.
[e] SOFA: Sequential Organ Failure Assessment. Score range, 0–24; higher values indicate more severe disease.
[f] Normal ranges were as follows: leukocyte count, 5000–10,000; platelet count ($\times 10^4$), 15–45; AST level, <37 U/L; ALT level, <41 U/L; LDH, 105–333 IU/L; serum creatinine, 0.7–1.2 mg/dL.

3.4. *Evaluation of renal replacement therapy including PMX hemoperfusion for ARDS due to H5N1 infection*

As a therapy for ARDS, renal replacement therapy and/or blood purification therapy were applied to Patients 1, 4, 6, and 7, who were treated in BMH, where CHDF/PMX treatments were provided. The *P/F* ratios for Patients 1, 4, 6, and 7 were <100 at the time of the initiation of renal replacement therapy (Table 3). Patient 1 (survivor) and Patient 7 (non-survivor) were treated with CHDF, and the time from ARDS onset to CHDF was <20 h in Patient 1 and >27 h in Patient 7. Patient 6 (non-survivor) was treated with PMX hemoperfusion, and the time from ARDS onset to PMX was >24 h. Patient 4 (survivor) was treated with PMX hemoperfusion followed by CHDF, and the time from ARDS to the initiation of sequential therapy was 10–15 h.

The available data for the sequential therapy with PMX hemoperfusion and CHDF in Patient 4 were assessed both with oxygenation and the measurement of five kinds of serum cytokine levels (interleukin [IL]-6, IL-8, interferon [IFN]-γ, IL-1β, tumor necrosis factor [TNF]-α) (Fig. 3). Immediately after ICU admission, the respiratory condition of Patient 4 rapidly deteriorated and the *P/F* ratio decreased to 43. PMX hemoperfusion was applied sequentially using 3 columns at a flow rate of 100 mL/min for 3 days. The *P/F* ratio increased to 128 at 24 h and to 203 at 3 days after the initiation of PMX hemoperfusion. Among the 5 serum cytokines examined, levels of IL-6, IL-8, and IFN-γ markedly decreased at 24 h after initiation of PMX hemoperfusion, whereas significant elevation of IL-1β and TNF-α was not observed at the time of initiation of PMX hemoperfusion (Fig. 3). Patient 4 was treated with CHDF after PMX hemoperfusion for 4 days. The patient was extubated and discharged 23 days after symptom onset. No serious adverse events were observed during the renal replacement therapy.

4. Discussion

The present study revealed that early initiation of antiviral treatment has a strong influence on the survival of patients with H5N1 infection, and that the healthcare network can assist in providing early medical intervention. Renal replacement therapy including PMX hemoperfusion, especially sequential therapy with PMX and CHDF, can be offered to treat H5N1 patients with ARDS. However, the timing is also crucial for a positive outcome.

Most human cases of avian influenza (H5N1) occur through direct or indirect contact with poultry or contaminated environments [16–18]. Previous reports from Vietnam, Thailand, Indonesia, and Cambodia have presented a relationship between human cases of H5N1 infection and a history of contact with sick and/or dead poultry [4,17,19]. In the present study, among 8 patients admitted to hospitals within the network (Fig. 1), some had direct contact with infected poultry because of their work or life habits. Others had no history of direct contact, but H5N1 outbreaks in poultry around these patients' residential areas were reported at the same time as their illness. An association between infection in wild birds and H5N1 outbreaks among poultry

Table 2 – Clinical course and treatment of study patients.

Variable	Survivors					Non-survivors		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Clinical time course								
Days from onset to primary care[a]	3	3	3	3	2	4	4	7
Days from onset to hospital admission[b]	6	6	4	5	2	7	9	8
Days from onset to treatment[c]	6	6	4	5	2	7	9	8
Days hospitalized	26	13	10	23	10	5	3	2
Days from onset to death	–	–	–	–	–	12	12	10
Clinical progression of organ dysfunction								
Respiratory failure on admission	ARDS	ALI	ALI	ARDS	None	ARDS	ARDS	ARDS
MOF (days from admission)	+ (day 1)	None	None	+ (day 1)	None	+ (day 1)	+ (day 1)	NA
Bacterial infection[d]								
On admission	ND	*Streptococcus pneumoniae*	ND	ND	ND	ND	ND	ND
During hospitalization (Days from admission)	*Acinetobacter* (day 4) *P. cepacia* (day 7) *P. aeruginosa* (day 11)	ND	ND	*Acinetobacter* (day 5)	ND	ND	ND	NA
Treatment								
Oseltamivir (duration: days)	300 mg/day (8)	150 mg/day (5)	150 mg/day (5)	300 mg/day (8)	75 mg/day (6)	300 mg/day (5, to death)	300 mg/day (3, to death)	150 mg/day (2, to death)
Corticosteroid (duration: days)	Hydrocortisone 300 mg/day (6) 200 mg/day (1)	Methylprednisolone 40 mg/day (1)	Methylprednisolone 80 mg/day (1)	Methylprednisolone 500 mg/day (4) 250 mg/day (2)	None	Hydrocortisone 300 mg/day (5)	Hydrocortisone 200 mg/day (3)	Hydrocortisone 200 mg/day (3)

Table 2 (*continued*)

Variable	Survivors					Non-survivors		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Antibiotic	100 mg/day (1) Cephalosporin, Aminoglycoside	Cephalosporin, Aminoglycoside	Cephalosporin	125 mg/day (1) Cephalosporin, Carbapenem, Fluoroquinolone	Cephalosporin	Carbapenem, Macrolide	Carbapenem, Macrolide, Aminoglycoside	Cephalosporin, Aminoglycoside, Tetracycline
Oxygen therapy (duration: days)	MV (8) Nasal cannula (5)	Nasal cannula (2)	Nasal cannula (1)	MV (7) Nasal cannula (3)	None	MV (5)	MV (3)	MV (2)

ARDS: P/F <200; ALI, P/F ≤300; MOF: ARDS with oliguria in Patient 1, hypotension and coagulopathy in Patient 4, hypotension and coagulopathy in Patient 6, hypotension in Patient 7.
ARDS, acute respiratory distress syndrome; P/F, partial pressure of oxygen in arterial blood/fraction of inspired oxygen ratio; ALI, acute lung injury; MOF, multiple organ failure; NA, not available; ND, not detected; MV, mechanical ventilation.
[a] Time interval from symptom onset to local healthcare organization (primary care).
[b] Time interval from symptom onset to local general hospital or tertiary care hospital.
[c] Time interval from symptom onset to initiation of treatment for H5N1.
[d] *Acinetobacter*, *Pseudomonas*, and *Streptococcus pneumoniae* were detected in sputum; *Sepacia* was detected in blood culture.

has been reported [20]. The main period of occurrence of H5N1 poultry outbreaks is around the *Tet* holiday (Lunar New Year) festival in January or February [21]. The distribution, trading, and consumption of chickens increase dramatically during this period [22] because chicken is a traditional dish for the celebration of *Tet*. Thus, the risk of H5N1 infection in humans increases around that time [21]. Illness in the study patients tended to be concentrated around the *Tet* festival. Therefore, understanding H5N1 poultry outbreaks and traditional habits, festivals, and celebrations that increase chicken consumption can aid in prediction of the time of occurrence of human H5N1 infections. It may also assist physicians' decision making for diagnosis and treatment if patients with pneumonia are presented.

Although the time to seeking healthcare reflects patients' knowledge about disease, socioeconomic difficulties, historical habits, and the healthcare system in each country, most of the previous studies in Vietnam documented a median duration from symptom onset to hospitalization for 6 days [4,23–25]. The WHO summarized 42 cases of H5N1 infection that were reported to the WHO in 2010, the median duration between symptom onset and hospital admission was 4 days (range 0–12) [26]. The present study observed a median of 6 days (range 2–9) from symptom onset to hospitalization (Table 2). The range was 2–6 days in survivors and 7–9 days in non-survivors. Based on the findings of the present study, it appears that 6 days is the critical period for patient survival. However, there were two distinct reasons that led to delayed initiation of oseltamivir treatment from symptom onset. In the present study, the average intervals from symptom onset to first access to primary care and from primary care to initiation of antiviral administration were 3.6 days (range 2–7) and 2.3 days (range 0–5), respectively (Table 2). Providing proper education to motivate people towards early access to healthcare and developing a network among the different healthcare settings that enables the transfer of H5N1 (suspected) patients from primary to tertiary care can shorten the total time interval to initiation of oseltamivir treatment [27,28]. In addition, waiting to receive a positive RT-PCR result for H5N1 virus leads to delayed diagnosis. All patients, except Patient 5, had infiltrative shadows on their chest radiographs on admission (Fig. 2). If a patient had a contact history with infected poultry or an H5N1 poultry outbreak around their residential area, he/she had the opportunity to receive early oseltamivir treatment even if the PCR result had not been obtained.

Variable symptoms and signs of the early stage of illness have been reported [4,12,17,18,23,24,29]. In the present study, lower respiratory tract symptoms were predominant at the early stage of disease. High fever, along with cough, was present in all study patients at the beginning of illness. This indicated that the viral infection began in the lower respiratory tract in most patients in the present study. At the time of hospital admission, all patients, except Patient 5, had already developed pneumonia. Patients who did not receive any treatment for >7 days from symptom onset (non-survivors) and in whom focal or unilateral shadows on chest radiographs were observed on admission rapidly progressed to severe conditions with bilateral and diffuse shadows (Fig. 2). In contrast, patients who received oseltamivir treatment by ≤6 days from symptom onset (survivors) did not experience rapid progression (Fig. 2).

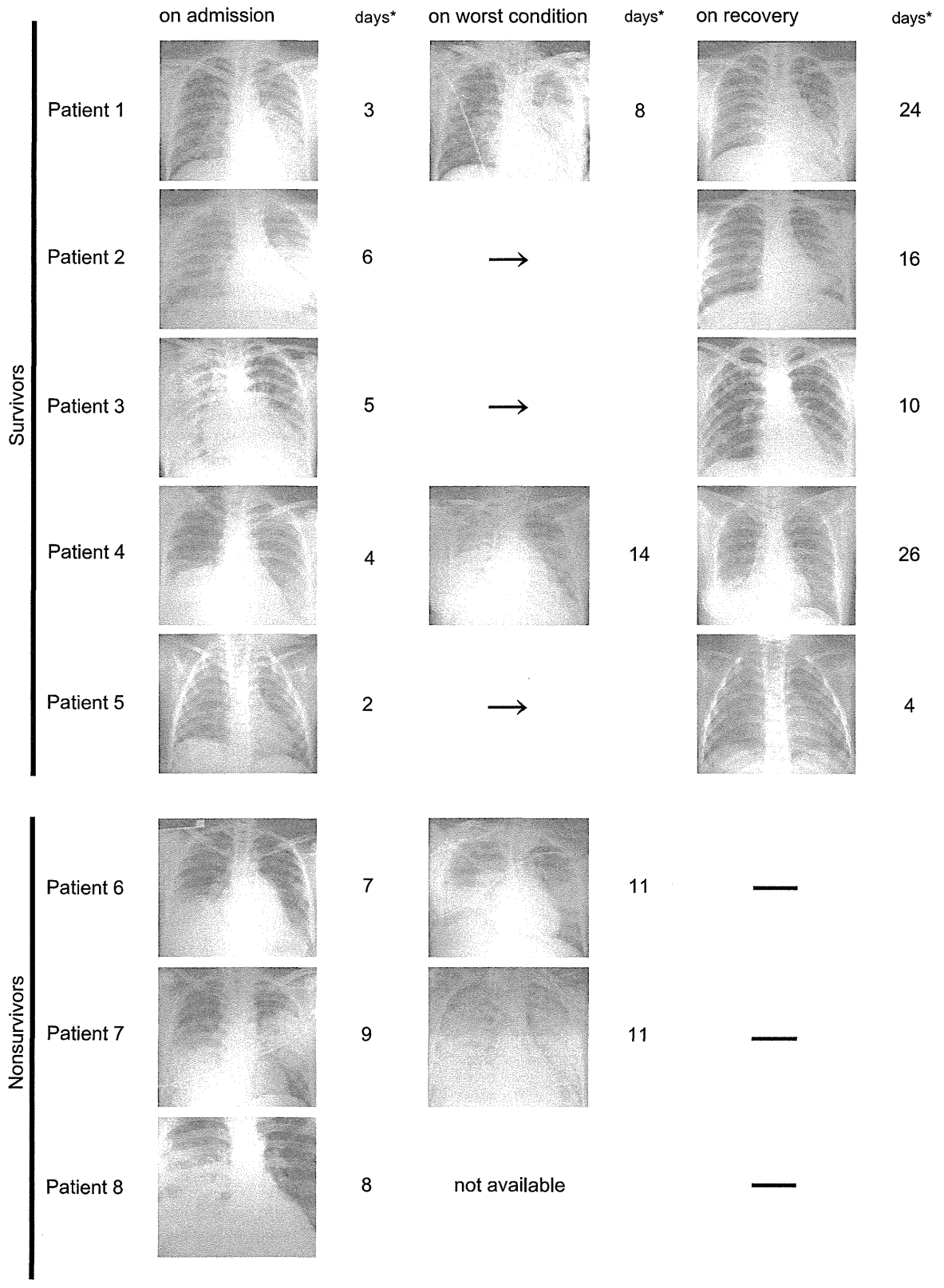

Fig. 2 – Chest radiographs of each patient upon admission (before oseltamivir administration), at the time of worst condition, and during the recovery period. All patients except Patient 5 had extensive consolidation shadows in unilateral or bilateral lung fields on admission. Patient 1: subcutaneous and mediastinal emphysema was observed (day 8). Patient 4: consolidations were observed all over the right lung and pneumothorax in the right thorax (day 14). Patient 5: no obvious shadows were observed on admission (day 2). *The number of days from symptom onset.

Table 3 – Condition of patients treated with renal replacement therapy.

Outcome	Patient 1 Survived	Patient 4 Survived	Patient 6 Died	Patient 7 Died
Renal replacement therapy				
Method	CHDF[a]	PMX/CHDF[b]	CHDF[a]	PMX[c]
Days from symptom onset	7	6	10	10
APACHE II score[d] on ICU admission	23	22	24	32
Time from occurrence of ARDS[e] to treatment (h)	<20	10–15	>27	>24
MOF[f] at the time of initiation of treatment	Yes	Yes	Yes	Yes
P/F ratio[g] from the initiation of treatment				
At the time of initiation	65	43	38	47
1 day	119	128	47	53
2 days	102	162	43	39
3 days	130	203	NA	NA
SOFA[h]				
At the time of initiation	10	13	11	9
1 day	8	10	12	13
2 days	7	11	NA	NA
3 days	7	11	Death	Death

ARDS, acute respiratory distress syndrome; NA, not available due to patient's death.
[a] Continuous hemodiafiltration.
[b] Sequential therapy with PMX hemoperfusion (3 columns, for 3 days) and CHDF.
[c] Polymyxin B fiber column.
[d] APACHE II score [20].
[e] ARDS was considered to be present if PaO_2/FiO_2 <200.
[f] MOF: ARDS with oliguria in Patient 1, shock and coagulopathy in Patient 4, shock and coagulopathy in Patient 6, shock in Patient 7.
[g] P/F: PaO_2/FiO_2 ratio; PaO_2: partial pressure of oxygen in arterial blood (mmHg); FIO_2: fraction of inspired oxygen.
[h] SOFA, Sequential Organ Failure Assessment.

Streptococcus bacterial infection was detected in one patient at the time of admission. Nosocomial bacterial infections were found in 2 survivors. Secondary bacterial infection was not detected in non-survivors. All non-survivors had developed ARDS at the time of hospital admission and were dead within 2–5 days following admission. It was not clear if secondary bacterial infection developed between the onset of illness and death under treatment with multiple antibiotics. Antibiotics were administered to all patients. However, once viral infection has been diagnosed, antibiotics administration should be limited appropriately to reduce the incidence of nosocomial bacterial infections, which are partly caused by the large amount or variety of antibiotics.

Although the WHO recommends against administering systemic corticosteroids, except for septic shock with adrenal insufficiency [6–8], systemic corticosteroids were administered to survivors and non-survivors in the present study, with the exception of the patient without pneumonia. The dose of corticosteroids for survivors and non-survivors did not differ significantly, whereas the time to initiation of corticosteroid treatment from symptom onset was later in non-survivors than in survivors. The results suggest that corticosteroid treatment did not negatively affect survivors who received oseltamivir earlier and who had less severe pneumonia than the non-survivors did. Therefore, the timing appears to be crucial for obtaining clinical benefits from corticosteroid treatment of H5N1 patients. However, further investigations and discussions are required.

Four out of 8 patients developed ARDS and received renal replacement therapy using CHDF, PMX hemoperfusion, or both sequentially in the ICU at BMH (Table 3). PMX column is a medical device initially developed to bind blood endotoxin in sepsis caused by gram-negative bacilli [14]. PMX hemoperfusion can effectively improve the P/F ratio and mortality rate [14,30,31]. Furthermore, a report on an animal model indicated that PMX hemoperfusion could improve the oxygenation associated with non-endotoxic lung injury and reduce the serum level of IL-8 [32]. Hypercytokinemia is thought to be one of the main causes of severe pneumonia associated with influenza (H5N1) virus infection [5,6,33]. PMX hemoperfusion and CHDF can both reduce plasma cytokine levels [30,31] and absorb activated neutrophils [34,35]. In addition, PMX hemoperfusion improves hemodynamics [31,36,37]. There has been no report on H5N1 patient who was treated with PMX. Some successful cases of ARDS with influenza A(H1N1)pdm09 infection treated with PMX have been reported in Japan [38,39], including evaluation of blood cytokine levels [40]. In the present study, Patient 4 was treated with PMX columns and sequential CHDF (Fig. 3). At 24 h after initiation of PMX hemoperfusion, levels of IL-6, IL-8, and IFN-γ in the peripheral blood had markedly decreased, with improvement of the *P/F* ratio. We believe that the improved *P/F* ratio was a reflection of decreased serum cytokine levels, which resulted in suppression of the inflammatory mechanism for ARDS in the lungs by PMX hemoperfusion.

The previous reports have indicated that early initiation of PMX hemoperfusion in patients with ALI and in patients with abdominal septic shock improves pulmonary oxygenation [35,41]. In the present study, patients treated with PMX hemoperfusion within 20 h from the time of ARDS onset

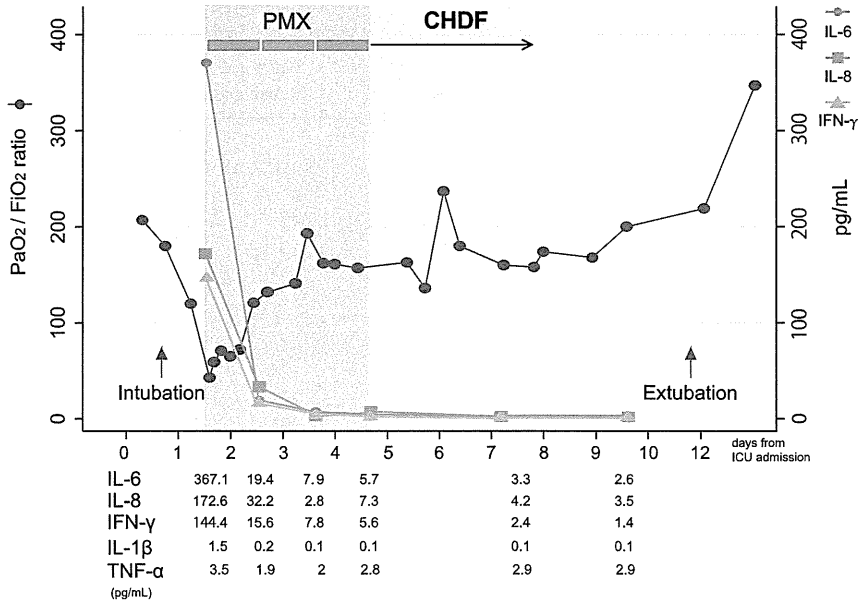

Fig. 3 – Clinical course of Patient 4 receiving sequential therapy with PMX and CHDF. The P/F ratio increased from 43 to 128 at 24 h and to 203 after 3 days, and serum levels of IL-6, IL-8, and IFN-γ markedly decreased 24 h after initiation of PMX hemoperfusion. No significant elevation in IL-1β and TNF-α was observed at the time of initiation of PMX hemoperfusion. Sequential CHDF maintained and improved the respiratory conditions of the patient.

survived, but those treated after 24 h died (Table 3). It was suggested that the early initiation of PMX hemoperfusion is also crucial for the survival of patients with ARDS caused by H5N1 infection. In addition, sequential CHDF maintained and improved respiratory conditions in patients. PMX/CHDF treatment appears to be a candidate for treating ARDS with H5N1 infection if applied early in the illness. To date, PMX columns are only commercially available in Japan and Europe [14,30,31]. Single treatment with CHDF can also contribute to survival if PMX is not available (as in Patient 1). The results were obtained from four patients, including evaluation of blood cytokine levels in one patient, thus further investigation of the effect of PMX/CHDF on the treatment of H5N1 patients with ARDS is required.

The present study was limited by the small study population of only eight patients. However, our experiences with these cases in Vietnam could contribute to clinical preparedness for severe pneumonia with highly pathogenic avian influenza A (H5N1).

5. Conclusions

Careful monitoring of local H5N1 poultry outbreaks, creating a healthcare network, and using chest radiographs can reduce the time to medical intervention for early diagnosis and early initiation of antiviral treatment. Renal replacement therapy using sequential therapy with PMX hemoperfusion and CHDF are possible candidates for treating ARDS due to H5N1 infection if applied early.

Conflict of interest

The authors have no potential conflict of interest.

Acknowledgments

Authors would like to thank provincial hospitals in Thanh Hoa, Thinh Quang, and Bac Kan provinces for their cooperation. This study was supported by a Grant from the Japan Initiative for Global Research Network (J-GRID) by the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

REFERENCES

[1] World Health Organization. Cumulative number of confirmed human cases of avian influenza A (H5N1) reported to WHO. Available from: 〈http://www.who.int/influenza/human_animal_interface/H5N1_cumulative_table_archives/en/index.html〉; January 2012 [accessed January 30, 2012].

[2] Adams S, Sandrock C. Avian influenza: update. Med Princ Pract 2010;19:421–32.

[3] World Organization for Animal Health OIE daily update on avian influenza situation in birds. Available from: 〈http://www.oie.int/animal-health-in-the-world/update-on-avian-influenza/2011/〉; January 2012 [accessed January 30, 2012].

[4] Hien TT, Liem NT, Dung NT, et al. The World Health Organization International Avian Influenza Investigative Team: avian influenza A (H5N1) in 10 patients in Vietnam. N Engl J Med 2004;350:1179–88.

[5] 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.

[6] Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus. Update on avian influenza A (H5N1) virus infection in humans. N Engl J Med 2008;358:261–73.

[7] World Health Organization. Clinical management of human infection with avian influenza A (H5N1) virus. Available from: 〈http://www.who.int/csr/disease/avian_influenza/guidelines/ClinicalManagement07.pdf〉; August 2007 [accessed January 10, 2011].
[8] Schünemann HJ, Hill SR, Kakad M, et al. WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus. Lancet Infect Dis 2007;7:21–31.
[9] Adisasmito W, Chan PKS, Lee N, et al. Effectiveness of antiviral treatment in human influenza A (H5N1) infections: analysis of a global patient registry. J Infect Dis 2010;202: 1154–60.
[10] White NJ, Webster RG, Govorkova EA, et al. What is the optimal therapy for patients with H5N1 influenza? PLoS Med 2009;6:e1000091.
[11] Uyeki TM. Human infection with highly pathogenic avian influenza A (H5N1) virus: review of clinical issues. Clin Infect Dis 2009;49:279–90.
[12] Kandun N, Tresnaningsih E, Purba WH, et al. Factors associated with case fatality of human H5N1 virus infections in Indonesia: a case series. Lancet 2008;372:744–9.
[13] Bellomo R, Tipping P, Boyce N. Continuous veno-venous hemofiltration with dialysis removes cytokines from the circulation of septic patients. Crit Care Med 1993;21:522–6.
[14] Hisataka S. Extracorporeal endotoxin removal for the treatment of sepsis: endotoxin adsorption cartridge (Toraymyxin). Ther Apher Dial 2003;7:108–14.
[15] Bernard GR, Artigas A, Brigham KL, et al. The American–European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818–24.
[16] Pham ND, Hoang TL, Nguyen KT, et al. Risk factors for human infection with avian influenza A H5N1, Vietnam, 2004. Emerg Infect Dis 2006;12:1841–7.
[17] Chotpitayasuondh T, Ungchusak K, Hanshaoworakul W, et al. Human disease from influenza A (H5N1), Thailand, 2004. Emerg Infect Dis 2005;11:201–9.
[18] Kandun IN, Wibisono H, Sedyaningsih ER, et al. Three Indonesian clusters of H5N1 virus infection in 2005. N Engl J Med 2006;355:2186–94.
[19] Vong S, Ly S, Mardy S, et al. Environmental contamination during influenza A virus (H5N1) outbreaks, Cambodia, 2006. Emerg Infect Dis 2008;14:1303–5.
[20] Keawcharoen J, van den Broek J, Bouma A, et al. Wild birds and increased transmission of highly pathogenic avian influenza (H5N1) among poultry, Thailand. Emerg Infect Dis 2011;17:1016–22.
[21] World Health Organization Western Pacific Region. WHO representative office in Viet Nam speeches TET celebration. Available from: 〈http://www.wpro.who.int/vietnam/media_centre/speeches/speech_16012009.htm〉; 2009 [accessed October 6, 2011].
[22] Magalhaes RJS, Oriz-Pelaez A, Kim LLT, et al. Associations between attributes of live poultry trade and HPAI H5N1 outbreaks: a descriptive and network analysis study in northern Vietnam. BMC Vet Res 2010;6:10.
[23] Le MTQ, Wertheim HFL, Nguyen HD, et al. Influenza A H5N1 Clade 2.3.4 Virus with a different antiviral susceptibility profile replaced Clade 1 Virus in humans in Northern Vietnam. PLoS ONE 2008;3:e3339.
[24] 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.
[25] Hien ND, Ha NH, Van NT, et al. Human infection with highly pathogenic avian influenza virus (H5N1) in northern Vietnam, 2004–2005. Emerg Infect Dis 2009;15:19–23.
[26] World Health Organization. Update on human cases of highly pathogenic avian influenza A (H5N1) virus infection, 2010. Wkly Epidemiol Rec 2011;86:161–6.
[27] Manabe T, Thuy PTP, Can VV, et al. Impact of educational intervention concerning awareness and behaviors relating to Avian Influenza (H5N1) in a high-risk population in Vietnam. PLoS ONE 2011;6:e23711.
[28] Manabe T, Thuy PTP, Kudo K, et al. Impact of education and network for avian influenza H5N1 in human: knowledge, clinical practice, and motivation on medical providers in Vietnam. PLoS ONE 2012;7:e30384.
[29] Buchy P, Mardy S, Vong S, et al. Influenza A/H5N1 virus infection in human in Cambodia. J Clin Virol 2007;39:164–8.
[30] Cruz DN, Perazella MA, Bellomo R, et al. Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review. Crit Care 2007;11:137.
[31] Cruz DN, Antonelli M, Fumagalli R, et al. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. JAMA 2009;301:2445–52.
[32] Tsushima K, Koizumi T, Yoshikawa S, et al. Polymyxin B immobilized column is effective for hydrochloric acid induced lung injury in rats. Eur J Pharmacol 2006;535:270–9.
[33] Korteweg C, Gu J. Pathology, molecular biology, and pathogenesis of avian influenza A (H5N1) infection in humans. Am J Pathol 2008;172:1155–70.
[34] Abe S, Seo Y, Hayashi H, et al. Neutrophil adsorption by polymyxin B-immobilized fiber column for acute exacerbation in patients with interstitial pneumonia: a pilot study. Blood Purif 2010;29:321–6.
[35] Kushi H, Miki T, Okamoro K, et al. Early hemoperfusion with an immobilized polymyxin B fiber column eliminates humoral mediators and improves pulmonary oxygenation. Crit Care 2005;9:R653–61.
[36] Mitaka C, Tomita M. Polymyxin B-immobilized fiber column hemoperfusion therapy for septic shock. Shock 2011;36: 332–8.
[37] Ruberto F, Pugliese F, D'Alio A, et al. Clinical effects of use polymyxin B fixed on fibers in liver transplant patients with severe sepsis or septic shock. Transplant Proc 2007;39: 1953–5.
[38] Yokoyama T, Tateishi K, Tsushima, et al. A case of severe ARDS caused by novel swine-origin influenza (A/H1N1pdm) virus: a successful treatment with direct hemoperfusion with polymyxin B-immobilized fiber. J Clin Apher 2010;25: 350–3.
[39] Yatera K, Yamasaki K, Kawanami T, et al. A case of successful treatment with polymyxin B-immobilized fiber column direct hemoperfusion in acute respiratory distress syndrome after influenza A infection. Intern Med 2011;50:601–5.
[40] Takeda S, Munakata R, Abe S, et al. Hypercytokinemia with 2009 pandemic H1N1 (pH1N1) influenza successfully treated with polymyxin B-immobilized fiber column hemoperfusion. Intensive Care Med 2010;36:906–7.
[41] Suyama H, Kawasaki Y, Morikawa S, et al. Early induction of PMX-DHP improves oxygenation in severe sepsis patients with acute lung injury. Hiroshima J Med Sci 2008;57:79–84.

Socioeconomic Factors Influencing Hospitalized Patients with Pneumonia Due to Influenza A(H1N1)pdm09 in Mexico

Toshie Manabe[1], Anjarath Lorena Higuera Iglesias[2], Maria Eugenia Vazquez Manriquez[3], Eduarda Leticia Martinez Valadez[4], Leticia Alfaro Ramos[2], Shinyu Izumi[1], Jin Takasaki[1], Koichiro Kudo[1]*

1 Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan, **2** Department of Clinical Epidemiology Investigation, Research Institute, National Institute of Respiratory Diseases, Mexico City, Mexico, **3** Department of Pathology, National Institute of Respiratory Diseases, Mexico City, Mexico, **4** Department of Epidemiology, National Institute of Respiratory Diseases, Mexico City, Mexico

Abstract

Background: In addition to clinical aspects and pathogen characteristics, people's health-related behavior and socioeconomic conditions can affect the occurrence and severity of diseases including influenza A(H1N1)pdm09.

Methodology and Principal Findings: A face-to-face interview survey was conducted in a hospital in Mexico City at the time of follow-up consultation for hospitalized patients with pneumonia due to influenza virus infection. In all, 302 subjects were enrolled and divided into two groups based on the period of hospitalization. Among them, 211 tested positive for influenza A(H1N1)pdm09 virus by real-time reverse-transcriptase-polymerase-chain-reaction during the pandemic period (Group-pdm) and 91 tested positive for influenza A virus in the post-pandemic period (Group-post). All subjects were treated with oseltamivir. Data on the demographic characteristics, socioeconomic status, living environment, and information relating to A(H1N1)pdm09, and related clinical data were compared between subjects in Group-pdm and those in Group-post. The ability of household income to pay for utilities, food, and health care services as well as housing quality in terms of construction materials and number of rooms revealed a significant difference: Group-post had lower socioeconomic status than Group-pdm. Group-post had lower availability of information regarding H1N1 influenza than Group-pdm. These results indicate that subjects in Group-post had difficulty receiving necessary information relating to influenza and were more likely to be impoverished than those in Group-pdm. Possible factors influencing time to seeking health care were number of household rooms, having received information on the necessity of quick access to health care, and house construction materials.

Conclusions: Health-care-seeking behavior, poverty level, and the distribution of information affect the occurrence and severity of pneumonia due to H1N1 virus from a socioeconomic point of view. These socioeconomic factors may explain the different patterns of morbidity and mortality for H1N1 influenza observed among different countries and regions.

Citation: Manabe T, Higuera Iglesias AL, Vazquez Manriquez ME, Martinez Valadez EL, Ramos LA, et al. (2012) Socioeconomic Factors Influencing Hospitalized Patients with Pneumonia Due to Influenza A(H1N1)pdm09 in Mexico. PLoS ONE 7(7): e40529. doi:10.1371/journal.pone.0040529

Editor: Malcolm Gracie Semple, University of Liverpool, United Kingdom

Received October 3, 2011; **Accepted** June 12, 2012; **Published** July 11, 2012

Funding: This work was supported by the Japan Initiative for Global Research Network on Infectious Diseases from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: kudo@dcc.go.jp

Introduction

In March 2009, Mexico was the first country to raise the international alert about the outbreak of influenza A(H1N1)pdm09 virus infection [1]. The pandemic spread rapidly worldwide; however, the number of severe and fatal cases differed among different countries and regions [2]. In Mexico, there were large numbers of hospitalized patients with acute and severe illness, and fatalities occurred [1,2,3,4,5]. Many patients with influenza-like symptoms, including pneumonia, presented to the National Institute of Respiratory Disease (INER), Mexico City, Mexico; a number of these required hospitalization owing to the severity of the illness, and there were fatalities, especially at the early stage of the pandemic [1]. After the announcement of the post-pandemic period for influenza A(H1N1)pdm09 by the World Health Organization (WHO) [6], effective management of the influenza pandemic continued to be a major concern. Clinical preparedness for A(H1N1)pdm09 was based on an understanding of the pathogenic characteristics of the virus and host immune-response patterns as well as the ability to undertake clinical interventions and ordinary individuals' knowledge about prevention; all of these factors were thought to have been at a developed stage in Mexico following the experiences of the 2009 influenza pandemic. However, a similar number of hospitalized patients with influenza-associated pneumonia presented again to the INER in the post-pandemic period [7].

Various factors affecting occurrence of pneumonia, disease severity, and mortality associated with A(H1N1)pdm09H1N1 have been reported from a clinical viewpoint [8,9,10,11]. Other

underlying conditions, including such environmental and socioeconomic factors as education and poverty, are also thought to affect the disease morbidity and mortality [12,13]. However, only limited data are available regarding the influence of socioeconomic factors on the occurrence of pneumonia related to influenza virus infection. Previously, we reported that the number of days between symptom onset and oseltamivir treatment affects the occurrence and severity of pneumonia due to H1N1 influenza [14]. Delayed treatment is associated with socioeconomic difficulties of INER patients [14]. A study in Canada also showed that delayed antiviral treatment is independently associated with disease severity [15]. We hypothesize that some risk factors affecting the continued occurrence of pneumonia in the post-pandemic period in Mexico, including delay in seeking healthcare, need to be addressed from the socioeconomic rather than clinical point of view. These factors may explain the different mortality and morbidity patterns for A(H1N1)pdm09 in different countries and regions.

The aim of the present study was to assess how socioeconomic and living conditions relate to the disease severity of H1N1 influenza, including pneumonia, in Mexico.

Materials and Methods

Study design

The survey was conducted at the INER, Mexico City between December 2010 and April 2011, and it included follow-up consultation with subjects or their relatives using structured questionnaires administered by physicians or trained medical staff. The subjects were former patients hospitalized in the INER for pneumonia due to A(H1N1)pdm09 who tested positive by real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) during the pandemic period; patients hospitalized for pneumonia who tested positive for influenza A virus during the post-pandemic period served as a comparison group. Patients with pneumonia caused by primary bacterial infection were excluded. All subjects were treated with oseltamivir. The pandemic period was defined as April 2009 to July 2010, and the post-pandemic period was defined as August 2010 to March 2011, in accordance with the declaration of the post-pandemic period by the WHO [9]. No subjects were hospitalized in both the pandemic and post-pandemic periods.

The questionnaire was designed to collect data on the demographic characteristics of subjects, socioeconomic status, living environment, and information relating to A(H1N1)pdm09, as well as related clinical data. Socioeconomic status was classified in terms of daily income while living environment was defined in terms of numerous factors associated to living conditions, including area in which subjects lived (i.e., location), house size and construction material, among other factors. All questions were either closed-ended or multiple choice. Each variable was compared between subjects hospitalized in the pandemic period (Group-pdm) and those hospitalized in the post-pandemic period (Group-post). In addition, factors affecting access to health care were evaluated. Socioeconomic level was classified based on daily income and on the ability of household income to pay for utilities, food, and medical services according to the Social Gap Index by the CONEVAL (Consejo Nacional de Evaluación de la Política de Desarrollo Social) [16]. Location was defined by the accessibility to public service which was also evaluated according to the Social Gap Index.

All subjects provided written informed consent. Ethical approval was provided by the Institutional Review Board of the National Institute of Respiratory Diseases, Mexico City and the National Center for Global Health and Medicine, Tokyo. The investigators maintained the datasets in password-protected systems and have preserved the anonymity of the subjects when presenting data.

Statistical Analysis

Data from the surveys were double-entered and analyzed using SPSS ver. 19 (IBM, Armonk, NY, USA). For categorical variables, frequencies were compared using the chi-square test and Fisher's exact test. For determination of independent factors for the time to seeking healthcare, multivariate regression analysis was conducted using a stepwise selection method included all variables in baseline characteristics, socioeconomic status, living environment, and information relating to A(H1N1)pdm09, and related clinical data, if $p < 0.1$ in univariate analysis. For all analyses, significance levels were two-tailed, and p value of <0.05 was considered significant.

Results

General and health-related backgrounds for study subjects

In all, 302 subjects who were hospitalized with pneumonia between April 2009 and March 2011 and received follow-up consultation during the study period agreed to participate in the present survey. Among them, 211 (69.9%) were hospitalized during the pandemic period (Group-pdm) and 91 (30.3%) in the post-pandemic period (Group-post). The general backgrounds of subjects are listed (Table 1). The median ages of subjects in Group-pdm and Group-post were 38.5 (range, 0–90) years and 42.0 (range, 2–91) years, respectively. There was a higher percentage of younger subjects in Group-pdm than in Group-post ($p = 0.001$). There was no significant sex difference between the groups ($p = 0.354$). Approximately 17% of the subjects had received no education, and there was no significant difference in education level between the groups ($p = 0.356$). Although unemployment was higher in Group-post (18.7%) than in Group-pdm (8.6%), the occupations were not significantly different between the groups ($p = 0.437$). The socioeconomic level of 70.5% of all subjects was low, whereas 29.5% were of middle socioeconomic level ($p = 0.332$).

The health-related background details of subjects are presented in Table 1. The rate of seasonal influenza vaccination was approximately 20% in both groups in 2010; however, the vaccinated populations in 2009 and 2011 were smaller than in 2010. There were significantly more smokers in Group-post (23.1%) than in Group-pdm (8.1%) ($p = 0.002$). Medication for chronic respiratory illness was being taken by 2.8% of Group-pdm subjects and 44.0% of Group-post subjects ($p<0.001$). The median number of days to initiation of oseltamivir administration from symptom onset for all subjects was 6 days (range, 0–35) and there was no significant difference between the groups ($p = 0.379$).

Economic factors

The detailed economic situation of the subjects was defined by the Social Gap Index of COVEVAL (Table 2). The ability of household income to pay for all utility services (light, gas, water, sewerage, and telephone) or some (two or three of the five) was significantly lower in Group-post than in Group-pdm ($p<0.001$). The ability of household income to pay for all foods (meat, egg, milk, cereals, vegetables) or some foods (two or three of the five) was 59.7% and 40.3%, respectively, in Group-pdm vs. 27.8% and 56.7%, respectively, in Group-post ($p<0.001$); 15.6% of the subjects in Group-post stated that could not pay for any food from their income. The ability of household income to pay for all health