Original Article

Clinical and Epidemiological Features of Patients With Confirmed Avian Influenza Presenting to Sulianti Saroso Infectious Diseases Hospital, Indonesia, 2005-2007

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Abstract

Introduction: Since the first human cases of H5N1 avian influenza virus infection were detected in Indonesia in 2005, the Sulianti Saroso Infectious Diseases Hospital in Jakarta has managed 27 confirmed cases from September 2005 to December 2007. Materials and Methods: We reviewed the clinical and epidemiological data of these patients. Results: Clinical and radiological features were not specific. Most patients were young and had indirect contact with infected poultry. The majority of cases presented to the Infectious Diseases hospital late when the patients already had features of the systemic inflammatory response syndrome (SIRS). The mortality was high at 77%. Conclusion: There is clearly an urgent need for better field diagnostics and therapeutics for the management of this emerging pathogen.

Ann Acad Med Singapore 2008;37:454-7

Key words: H5N1, Severity of illness

Introduction

The first human cases of H5N1 avian influenza (AI) virus infection were reported in Indonesia in July 2005.[1] On 19 September 2005, the Ministry of Health of Indonesia confirmed an established outbreak of AI in humans in Indonesia. This highly fatal infection has occurred across Indonesia with a fatality rate of around 80%. Since the occurrence of AI, the Sulianti Saroso, Infectious Diseases Hospital, a tertiary referral hospital specialising in Infectious Diseases that covers the western part of Jakarta, Indonesia, has treated 27 confirmed cases from 2005 until December 2007.

This report aims to discuss the clinical and epidemiological features of AI in humans caused by the influenza A (H5N1) virus at the Sulianti Saroso, Infectious Diseases Hospital, Jakarta, Indonesia.

Materials and Methods

A retrospective case series review was conducted among patients admitted to the Sulianti Saroso Infectious Diseases Hospital. Some of these data have already been reported as part of a larger national database.[2] This study, however, reports one hospital's experience and allows for a more detailed analysis of the data.

A clinically c*onfirmed case* of H5N1 AI in humans, as determined by the Director-General, Communicable Disease Control and Environmental Health, Indonesia, was defined as a suspect or probable case with acute respiratory disease symptoms such as fever (temperature >38ºC), cough, sore throat and or has shortness of breath or difficulty in breathing.

A *suspect case* was defined as a patient with a contact history of possible sources of AI in the environment (e.g. poultry-derived fertiliser), including a visit within a week to an animal husbandry that had had an AI outbreak in birds, had contact with a confirmed case of AI in humans during the period of transmission or who had worked in a laboratory that did human or animal specimen processing for suspected AI.

A *probable case* was defined as a patient with highly suggestive clinical and epidemiological features of H5N1 influenza but who had died before laboratory samples could be obtained for confirmation of diagnosis. This was infrequently encountered, as we were able to obtain samples from the vast majority of cases.

A *laboratory confirmed case* was defined as a clinically confirmed case with a positive result on a specific H5N1 virus test done at a World Health Organization (WHO) reference laboratory, either reverse transcription polymerase chain reaction (RT-PCR) positive for H5N1 or a 4-fold rise in H5 antibody titres on 2 serum specimens collected at least 2 weeks apart.

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Laboratory confirmation was done in Hong Kong and Indonesia. All cases were further confirmed by the WHO.

Direct contact history referred to a patient who had direct contact with sick or dead poultry. *Indirect contact* referred to a patient who had contact with contaminated environments including fertiliser or animal markets.

Results

There were a total of 27 laboratory confirmed cases of H5N1 AI in humans out of the 296 suspect cases managed at Sulianti Saroso Infectious Diseases Hospital in Jakarta between September 2005 and December 2007. The positive yield was 9.1%. Twenty-one of these confirmed cases had a fatal outcome, with 6 survivors.

Age and Gender

The youngest patient with H5N1 AI at our hospital was 1 year old and the oldest was 40 years old. The mean age of the confirmed cases was 16.9 years, with a standard deviation (SD) of 11.6. There were 14 (51.9%) females and 13(48.1%) males (Table 1). Younger age was protective [OR, 0.0; 95% confidence interval (CI), 0.0-0.78; $P = 0.016$] but there was no mortality difference between males and females (OR-1.1; 95% CI, 0.13-9.35; $P = 1.0$).

Spatio-temporal Distribution of Cases

All cases were referred by other hospitals or clinics from 3 provinces: Jakarta, West Java and Banten. In those provinces, 3 hospitals were designated to be the referral hospitals for AI.

The largest group of confirmed AI patients at Sulianti Saroso Infectious Diseases Hospital lived in Daerah Khusus Ibukota (DKI) Jakarta Province (44.4%). This included all 5 parts of DKI Jakarta. Another 22.2% of the patients lived in West Java Province and the remainder were from Banten Province (Fig. 1). The epidemic curve of cases presenting to Sulianti Saroso Infectious Diseases Hospital is shown in Figure 2. As can be seen from the figure, the peak of the epidemic appeared to have been in the early part of 2006; however, sporadic cases continued to occur.

Table 1. Demographics of Patients with H5N1 Avian Influenza at Sulianti Saroso Infectious Diseases Hospital, 2005-2007

Variable	Survived		Death		Total
	n	%	n	%	
Age (y)					
0-18	6	42.9	8	57.1	14
>18	0	0	13	100	13
Gender					
Male	3	23.1	10	76.9	13
Female	3	21.4	11	78.6	14

Contact History

The largest number of cases (12 or 44.4%) had indirect contact with poultry – predominantly by visiting markets or areas where outbreaks of poultry disease caused by H5N1 AI had been reported (Fig. 3). Unfortunately, for a significant number of cases, the contact history could not be definitively obtained partly because the disease was often rapidly fatal by the time the patients presented to our hospital.

Time from Onset of Symptoms to Presentation

The mean time to presentation at a healthcare facility from the onset of symptoms was 4.2 ± 2.9 days with a median of 4 days (range, 1 to 15). Six patients presented to the primary care practitioners, 1 patient was in a maternity hospital and the remainder presented to the district general hospitals. The mean time of transfer to the Sulianti Saroso Infectious Diseases Hospital, the designated infectious disease hospital, was 1.8 ± 3 days with a median of 1 day (range, 0 to 12).

Vital Signs at Presentation

For the 27 patients with confirmed H5N1 AI, the mean temperature at presentation was 37.5 ± 1.3°C with a median temperature of 37.8°C (range 35.8 to 40). The mean arterial pressure was 84.8 ± 11.6 mmHg with a median of 82 mmHg (range, 68 to 103). The mean respiratory rate at presentation was 36 ± 11/min with a median of 35/min (range, 15 to 60). The mean heart rate at presentation was 110 ± 24/min with a median of 104/min (range, 84 to 165). The highest heart rates and respiratory rates were recorded in children, as would be expected.

Radiological Findings

Twenty of the 27 patients had abnormal chest radiographs with the majority (19/20) showing evidence of bronchopneumonia or lobar pneumonia. Of note, 4 patients had pleural effusions at presentation. A representative set of chest radiographs is presented in Figure 4.

Outcomes

There was a total of 21 fatalities giving a case fatality rate of 77.8% overall. All the 27 patients, with confirmed AI at Sulianti Saroso Infectious Diseases Hospital, were treated with oseltamivir when they presented to our facility. All of the deaths occurred in the intensive care unit (ICU). The fatality rate of patients in our ICU (any underlying disease other than AI) for about the same period of time is about 65% (Sulianti Saroso Infectious Diseases Hospital Report, unpublished data). Comparing the mortality rate of the 2 groups of patients, the fatality rate of AI cases is higher than the non-AI group.

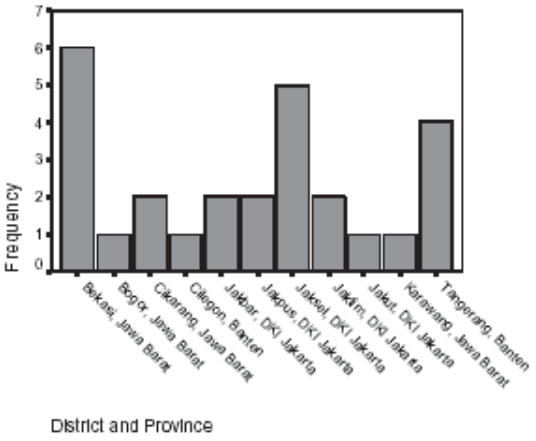

Fig. 1. Geographical distribution of confirmed cases of H5N1 avian influenza in patients at Sulianti Saroso Infectious Diseases Hospital.

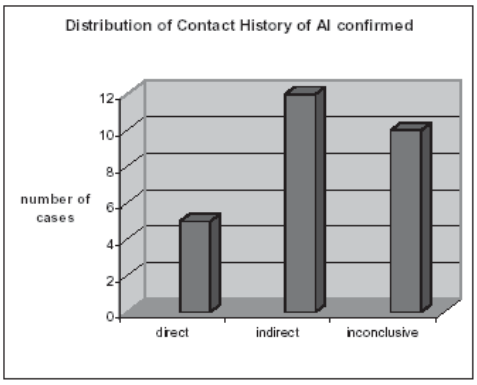

Fig. 3. Contact history of patients with laboratory confirmed H5N1 avian influenza.

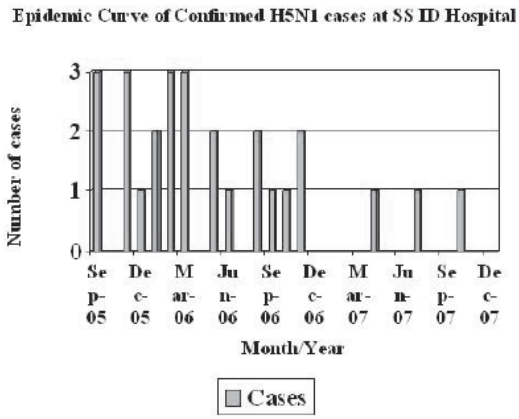

Fig. 2. Epidemic curve of human cases of H5N1 avian influenza presenting to Sulianti Saroso Infectious Diseases Hospital, September 2005 to December 2007.

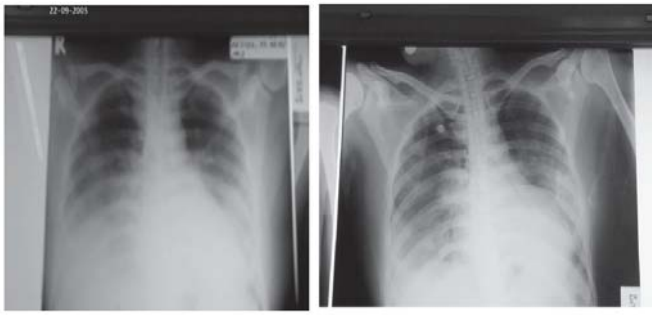

Fig. 4A. Initial chest radiograph of the first patient with H5N1 avian influenza managed at Sulianti Saroso Infectious Diseases Hospital.

Fig. 4B. Subsequent chest radiograph of the same patient 3 days after admission showing progression of pulmonary disease.

Discussion

There were 27 confirmed cases of AI managed at Sulianti Saroso Infectious Diseases Hospital from September 2005 to December 2007. The positivity rate among suspect cases is low (<10%). This may suggest the need to develop more reliable criteria for suspect cases or to a certain extent underdiagnosis, since some cases showed clinical features highly suggestive of viral pneumonia were negative by PCR. The timing of sampling at the later stage in the clinical course of the disease will most likely decrease the sensitivity of the test due to the lower viral load at that time.

AI in humans is predominantly a disease of young adults and adolescents; the mean age among our patients was 16 years with the oldest patient being 40 years old. This is probably due to a combination of factors including exposure to sick or dead poultry or contaminated markets where younger people are more likely to live and work. Paradoxically, older individuals who are more likely to succumb to seasonal influenza were less likely to be affected by H5N1 influenza. The reasons for this are not entirely clear but the same protective effect of age was noted in the 1918 influenza pandemic in which the elderly had a lower mortality rate than the young adult population worldwide.[3] It has been speculated that older individuals might have had pre-existing exposure to and hence persistent immunity to some novel strains of influenza including H5 now and H1 in 1918, although this has not been shown to be the case by serological studies published to date.

The peak of the H5N1 AI epidemic at the Sulianti Saroso Infectious Diseases Hospital appears to have been in the early part of 2006 before intense efforts by the Indonesian government to control H5N1 in poultry began. While there continue to be sporadic cases throughout the country and in the region served by our hospital, the epidemic curve at this point of time does not suggest a rising rate of infection. The same is true of the national data according to the WHO.[4] Of course, all this could change with a mutation in the virus and there are concerns that without complete eradication of the disease in humans and birds, the possibility of a mutation which makes the virus more easily transmissible could occur at any time.

Surprisingly, we found more patients with an indirect contact history than with a direct contact history. This is

possibly because of transmission through fertilisers made from chicken manure. Japanese researchers have reported the detection of highly pathogenic H5N1 AI viruses in blowflies near infected poultry farms.[5] The role of the contaminated environment in the transmission and propagation of H5N1 in humans and animals needs to be more clearly defined. It is also possible that some of the patients or their relatives might not have been forthcoming with their contact histories and this is borne out by the lack of contact data in about a third of the cases – one of the limitations of this study.

Most patients presented to local hospitals after a few days of illness and there was often a further delay in transfer to the tertiary care facility. As in most developing countries, few primary or secondary care facilities are equipped with the protocols[6] or the isolation or cardio-respiratory support resources needed for the management of critically ill patients with H5N1 influenza. This is probably the largest single contributor to the high mortality recorded. Unfortunately, the early signs and symptoms of H5N1 influenza are not specific and thus busy primary care physicians would find it extremely difficult to predict which of their dozens of patients with influenza-like illness is going to turn out to have highly pathogenic H5N1 influenza in a few days time. Even the radiographic appearances of our patients with laboratory confirmed H5N1 influenza were not specific and could mimic many far more common conditions seen in Indonesia such as pneumococcal pneumonia or tuberculosis. Early recognition is critical as it has been recognised from a global review of cases of H5N1 influenza that delays in treatment with antiviral agents result in much higher mortality.[7] For a large and diverse country such as Indonesia, this is likely to remain a challenge for some time. The only conceivable solution is the development of cheap, effective point-of-care tests for H5N1 influenza that are as easy to use as a pregnancy test for example. These could be used by a rural primary healthcare clinic or district hospital in any developing country. This is clearly a challenge for the global scientific community. Even if such tests were available, however, the next challenge would be ensuring that they are widely distributed and that the resources are available for primary and secondary healthcare providers to have immediate access either to antivirals or to rapid evacuation to tertiary facilities that can treat these patients to achieve good outcomes.

As a result of the delay in reaching definitive care, the majority of our patients were severely ill at presentation. Although their blood pressures were largely normal at presentation mainly because they were young individuals who were able to compensate physiologically, the vast majority had evidence of the systemic inflammatory response syndrome (SIRS) with marked tachycardia and tachypnoea. The recognition of SIRS and its complications is a critical step in the management of critically ill patients. Many of the interventions proven to improve[8] the outcomes of SIRS and the sepsis syndrome causing SIRS are not out of reach of tertiary care centres in developing countries. Investment in training and basic equipping of tertiary care facilities in developing countries to ensure at least basic circulatory and respiratory support could potentially result in good outcomes even in some individuals who present late. The psychological impact of such "saves" is likely to be multiplied in boosting the morale of the healthcare providers as well as the confidence of the local population in their own local tertiary care facilities.

Conclusion

Our experience with H5N1 AI in humans has taught us many lessons. The disease is rapidly progressive with a high fatality rate once severe symptoms or SIRS sets in. There are considerable challenges to controlling the epidemic and preventing the emergence of a human pandemic virus. Good clinical and epidemiological investigations and management together with a balanced approach by the global community[9] are critical to achieving this goal.

Acknowledgement

We would like to thank A/Prof Paul Ananth Tambyah of the National University of Singapore for assistance in preparing this manuscript.

REFERENCES

1. Kandun IN, Wibisono H, Sedyaningsih ER, Yusharmen , Hadisoedarsuno W, Purba W, et al. Three Indonesian clusters of H5N1 virus infection in 2005. N Engl J Med 2006;355:2186-94.
2. Sedyaningsih ER, Isfandari S, Setiawaty V, Rifati L, Harun S, Purba W, et al. Epidemiology of cases of H5N1 virus infection in Indonesia, July 2005-June 2006. J Infect Dis 2007;196:522-7.
3. Luk J, Gross P, Thompson WW. Observations on mortality during the 1918 influenza pandemic.Clin Infect Dis 2001;33:1375-8
4. World Health Organization. Cumulative Number of Confirmed Human Cases of Avian Influenza Reported to the WHO. Available at: http://www.who.int/csr/disease/avian_influenza/country/cases_table_2008_04_30/en/index.html. Accessed 1 May 2008.
5. Sawabe K, Hoshino K, Isawa H, Sasaki T, Hayashi T, Tsuda Y, et al. Detection and isolation of highly pathogenic H5N1 avian influenza A viruses from blow flies collected in the vicinity of an infected poultry farm in Kyoto, Japan, 2004. Am J Trop Med Hyg 2006;75:327-32.
6. Lye DC, Nguyen DH, Giriputro S, Anekthananon T, Eraksoy H, Tambyah PA. Practical management of avian influenza in humans. Singapore Med J 2006;47:471-5.
7. Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus, (2008). Update on Avian Influenza A (H5N1) Virus Infection in Humans. N Engl J Med 2008;358:261-73.
8. Mackenzie I, Lever A. Management of sepsis. BMJ 2007;335:929-32.
9. Enserink M. Avian influenza. Indonesia earns flu accord at World Health Assembly Science 2007;316:1108.