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Literature Review

THE CLINICAL PROFILES OF AVIAN INFLUENZA IN ENDEMIC AND NON-ENDEMIC REGIONS IN INDONESIA. HOSPITAL-BASED STUDIES AND ITS IMPLICATION ON CLINICAL MANAGEMENT IN THE FUTURE

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ABSTRACT

Indonesia is a greatest burden country of H5N1 avian influenza (AI) virus infection in the world, since first outbreak in Central Java 2005 until August 2010 there was 168 confirmed cases and 138 dead cases. The incidence increasing rapidly in widespread area endemic in Java, Sumatera, Bali and Sulawesi, and sporadic outbreaks in other areas. The World Health Organization stated that AI still became a treat in the next pandemic. H5N1 AI virus infection spreads in almost all provinces, but its endemic in Jakarta, Tangerang and Banten and in other area such Surabaya, Bali were sporadic outbreaks. There are 27 confirmed H5N1 AI infection cases in Jakarta from 296 suspected cases, while in Surabaya only 5 confirmed H5N1 AI infection cases from 12 suspected cases. The age of patient mean with H5N1 AI infection was 16.9 ± 11.6 yo in Jakarta and 24 ± 8.51 yo in Surabaya. There was no difference between male and female. Mortality rate was 77.7% in Jakarta and 60% in Surabaya. A large number of case has indirect contact history, predominantly by visiting market or areas where outbreaks of poultry disease. The clinical feature H5N1 AI virus infection could manifest as mild until severe pneumonia that often progress rapidly to ARDS. In Jakarta, 74% case showed abnormality chest radiography as bilateral pneumonia, while in Surabaya showed lobar pneumonia and bilateral pneumonia. Management patient of H5N1 AI infection is supportive therapy and antiviral, whereas a large number of cases needed mechanical ventilator support.

Key words: *clinical profile, avian influenza, H5N1, epidemiology avian*

BACKGROUND

Highly pathogenic avian H5N1 influenza viruses (HPAI) now appear to be endemic among bird and poultry populations in Eurasia.[1,2] Sporadic transmission to humans raises concern that the H5N1 virus may mutate or combine with genetic material from coinfecting human influenza viruses to generate a novel strain capable of sustained human-to-human transmission with pandemic potential.[2] The World Health Organization has described the threat from H5N1 as a "public health crisis", and declared that the world is as close as ever to the next pandemic.[3]

Avian influenza H5N1 — Highly pathogenic avian H5N1 influenza viruses are endemic among bird and poultry populations in Asian countries. The first association of avian influenza H5N1 with clinical respiratory disease were occurred in Hong Kong in 1997, when 18 human cases were occurred during a poultry outbreak of highly pathogenic H5N1 influenza in live-bird markets. This outbreak was associated with a high mortality rate (33 percent), a high incidence of pneumonia (61 percent), and a high rate of intensive care (51 percent).[3,4]

In Indonesia, the first human case of H5N1 avian influenza (AI) virus infection were reported in July 2005. 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%. Until August 2010, there are 168 human cases H5N1 AI virus infection in Indonesia with mortality 136 cases.[5]

H5N1 HPAI spreads endemic in Java, Sumatera, Bali and Sulawesi, and sporadic outbreaks in other areas. H5N1 HPAI prevalence by village varies widely. Only

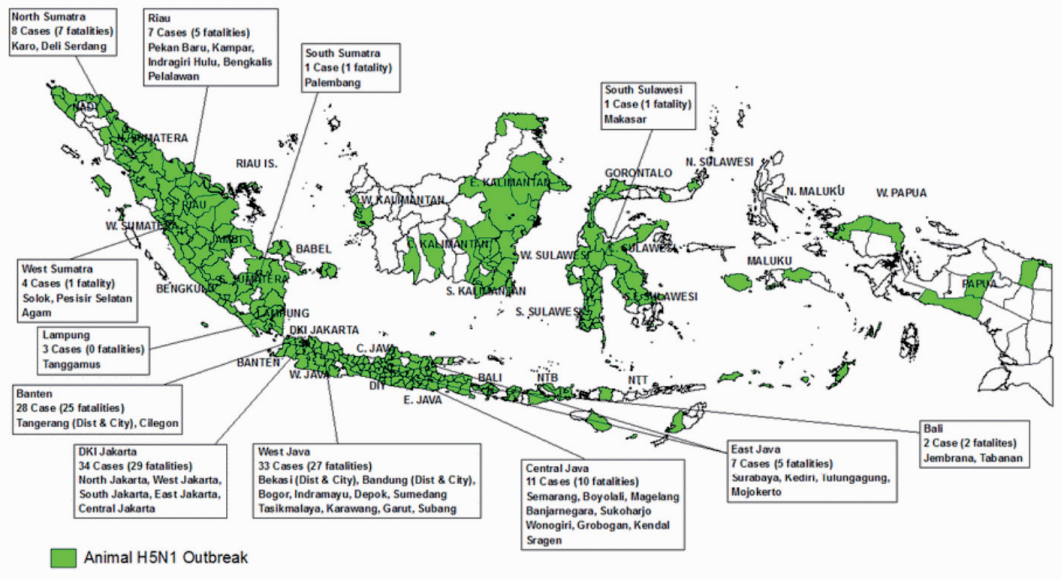

Figure 1. Location of Human H5N1 Avian Influenza Cases and Animal Outbreaks at 10 December 2008 Adapted from reference no 5.

two of Indonesia's 33 provinces have never reported the occurrence of H5N1 HPAI.[6]

Participatory Disease Surveillance and Response (PDSR) is program that targets village poultry production systems (mainly backyard) and reports evidence of virus circulation in the village. During March 2010, PDSR officers visited 1.984 villages, of which 137 (6.9%) were infected (98 were newly found, while the remaining 39 carried over the infection status from the previous month). This infection rate was lower than the February 2010 infection rate of 16.6%, which was expected as Indonesia emerged from the usual wet season peak. During the previous 12 months, PDSR officers visited 20 117 villages (30.0%) in the 349 districts under PDSR surveillance.[5]

Endemic and Non-endemic Region

Indonesia is consisting a thousand islands, the highest population density is in a Java island. Since first outbreak in 2005, H5N1 HPAI spreads endemic in Java and sporadic outbreaks in other area. The most H5N1 HPAI human cases were found in DKI Jakarta, Banten, West Java whereas these areas were endemic region. While other areas as East Java (Surabaya), Sumatera, Bali and others were non-endemic region.

PATHOGENESIS OF HPAI

Influenza viruses are spherically or longitudinally shaped enveloped particles with an up to eight-fold segmented, single-stranded RNA genome of negative polarity. Influenza viruses hold generic status in the *Orthomyxoviridae* family and were classified into types A, B or C based on antigenic differences of their nucleo- and matrix proteins. Avian influenza viruses (AIV) belong to type A.[1,8]

Influenza A and B viruses have two major antigenic surface glycoproteins embedded into the membrane, the hemagglutinin (HA) and neuraminidase (NA) that induce antibody responses in humans. Influenza virus strains were classified by their core proteins (ie, A, B, or C), species of origin (eg, avian, swine), geographic site of isolation, serial number, and for influenza A, by subtypes of HA and NA.[1,4]

Influenza A is responsible for frequent, usually annual outbreaks or epidemics of varying intensity, and occasional pandemics; while influenza B causes outbreaks every two to four years. Although 16 HA (H1-H16) and nine NA (N1-N9) virus subtypes has occured in their natural reservoir of aquatic birds, only three hemagglutinin subtypes have caused widespread human respiratory infection (H1, H2, and H3), suggesting a degree of host specificity.[1,3]

Human influenza H1 and H3 subtypes currently circulating continuously undergo variability or "antigenic drift." Inefficient proofreading by influenza viral RNA polymerase results in a high incidence of transcription errors and amino acid substitutions in the hemagglutinin or neuramidase, allowing new variants to evade preexisting humoral immunity and cause interpandemic outbreaks.[3]

Simultaneous infection of a cell by two influenza viruses may allow recombination of RNA segments and result in the generation of a new "reassorted" virus with novel surface proteins to which there was little population immunity. Pandemic influenza viruses arise by this process called "antigenic shift."[3]

It has been hypothesised that the HA gene of the H5 and H7 subtypes harbour distinct secondary RNA structures which favour insertional mutations (codon duplications) by a re-copying mechanism of the viral polymerase unit at a

purine-rich sequence stretch encoding the endoproteolytic cleavage site of these HA proteins.[2,3]

Pigs may play an important role in the evolution of human pandemic strains. Pig's trachea contain receptors for both avian and human influenza viruses and the domestic pig supports the growth of viruses of both human and avian origin. Thus, it has been proposed that genetic reassortment between avian and human virus may occur in pigs, leading to a novel strain.[4]

The incubation periods for H5N1 avian influenza may be longer than normal seasonal influenza, which is around two to three days. Current datas for H5N1 infection indicate an incubation period ranging from two to eight days and possibly as long as 17 days. However, the possibility of multiple exposure to the virus makes it difficult to define the incubation period precisely. WHO currently recommends that an incubation period of seven days be used for field investigations and the monitoring of patient contacts.[2,3]

Clinical Manifestation

Initial symptoms include a high fever, usually with a temperature higher than 38° C, and influenza-like symptoms. Diarrhoea, vomiting, abdominal pain, chest pain, and bleeding from the nose and gums have also been reported as early symptoms in some patients. Watery diarrhoea without blood appears to be more common in H5N1 avian influenza than in normal seasonal influenza. The spectrum of clinical symptoms may, however, be broader, and not all confirmed patients have presented with respiratory symptoms.[3,9]

***Case definition* (WHO 2006)**

Person under investigation is a person whom public health authorities have decided to investigate for possible H5N1 infection.

Suspected H5N1 case is a person presenting with unexplained acute lower respiratory illness with fever (> 38° C) and cough, shortness of breath or difficulty breathing and > 1 of the following exposures in the 7 days prior to symptom:

a. Close contact with a person who is a suspected, probable or confirmed H5N1 case.
b. Exposure to poultry or wild birds or their remains or to environments contaminated by their faeces.
c. Consumption of raw or undercooked poultry products
d. Close contact with a confirmed H5N1 infected animal other than poultry or wild birds (e.g. cats or pigs).
e. Handling samples (animal or human) suspected of containing H5N1 virus in a laboratory or other setting.

Probable H5N1 case is a person meeting the criteria for a suspected case AND One of the:

a. infiltrates or evidence of an acute pneumonia on chest radiograph plus evidence of respiratory failure, or
b. positive laboratory confirmation of an influenza A infection but insufficient laboratory evidence for H5N1 infection.

Confirmed H5N1 case is a person meeting the criteria for a suspected/probable case AND One of the following positive results conducted in a laboratory whose H5N1 test results are accepted by WHO as confirmatory:

a. Isolation of an H5N1 virus
b. Positive H5 PCR results from tests using two different PCR targets
c. A fourfold or greater rise in neutralization antibody titer for H5N1 based on an acute and a convalescent serum specimen. The convalescent neutralizing antibody titer must also be > 1:80
d. A microneutralization antibody titer for H5N1 of 1:80 or greater in a single serum specimen collected at day 14 or later after symptom onset and a positive result using a different serological assay.

There were 27 confirm H5N1 case from 296 suspected cases managed in Sulianti Saroso Infectious Disease Hospital in Jakarta. Twenty one cases had a fatal outcome with 6 cases survivors. While in Dr. Soeotomo General Hospital Surabaya, there are 5 confirm H5N1 case and 3 cases had fatal outcome and 2 cases survivors.

The mean age of patient with H5N1 AI infection was 16,9 ± 11,6 years old in Jakarta and 24 ± 8,51 years old in Surabaya. Whereas the youngest age of patient with H5N1 AI infection was 1 year. There was no difference beetwen male and female in H5N1 AI infection and mortality in both of Jakarta and Surabaya.[7,10]

Vital Signs

Most patients have initial symptoms of high fever (typically a temperature of more than 38° C) and an influenza-like illness with lower respiratory tract symptoms. At presentasion the patiens had fever with temperature was more than 38° C in Surabaya But in Jakarta they were found 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).

Laboratory Findings

Common laboratory findings have been leucopenia, particularly lymphopenia; mild-to-moderate thrombocytopenia; and slightly or moderately elevated aminotransferase levels.

In Surabaya, all of cases were leucopenia. Platelets had declining trend in most H5N1 AI infection cases. Particularly patient showed a elevated aminotranferase levels.

Radiological Findings

Radiologic findings of H5N1 HPAI can show as a mild pneumonia until severe pneumonia or Acute Respiratory Distress Syndrome (ARDS). In Jakarta, 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. While in Surabaya, all of cases show a bilateral pneumonia.

Management

Based on information collected from publications as well as reports on A(H5N1) cases in affected countries, WHO gives a recommended guideline to H5N1 HPAI infection

1. Diagnosis
2. Site of care
3. Antiviral treatment
   a. Oseltamivir
   b. Other antiviral agent
   c. Virological monitoring
4. Other pharmacological intervention
   a. Antibiotics
   b. Immunomodulator
   c. Haemophagocytosis and intravenous immunoglobulin
5. Supportive therapy for critical ill care
6. Special consideration
7. Infection control condiseration

Oseltamivir remains the primary recommended antiviral treatment. Treatment with oseltamivir is also warranted when the patient presents to clinical care at a later stage of illness (viral replication was more prolonged than with seasonal influenza, to last up to 15–17 days after illness onset. Oseltamivir should be given 75 mg, twice a day dor 5 days for adult and 2 mg/kgBW (max 75 mg), twice a day for 5 days for children (age > 1 of age).

When pneumonia was present, antibiotic treatment was appropriate initially for community-acquired pneumonia according to published evidence-based guidelines. When available, the results of microbiologic studies should be used to guide antibiotic usage for suspected bacterial co-infection.[11,12]

Monitoring of oxygen saturation should be performed: at presentation and routinely during subsequent care(pulse oximetry, arterial blood gases). Supplemental oxygen should be provided to correct hypoxemia. Oxygen therapy Monitor oxygen saturation and maintain SaO_2 over 90% with nasal cannulae or face mask.[11,13]

Non invasive Ventilatory is not recommended to support oxygen therapy for H5N1 HPAI infection patient in ARDS state, instability hemodynamics and multiorgan failure, despite NIV could increase risk for infectious aerosol to other patient. The recommended mode for mechanical ventilatory was inspiratory positive pressure ventilator.[11,13]

SUMMARY

H5N1 HPAI infection in human was not different between endemic and non-endemic region include route of transmission, clinical severity, pathogenesis and respon to therapy. Case detection was confounded by the nonspecificity of initial manifestations of illness, so that detailed contact and travel histories and knowledge of viral activity in poultry were essential. There was an urgent need for more coordination in clinical and epidemiologic research among institutions in countries with cases of influenza A (H5N1).

REFERENCE

1. Webster RG, Govorkova EA. H5N1 Influenza— continuing evolution and spread. N Engl J Med 2006; 355: 2174–7.
2. The Writing Committee of WHO consultation on human influenza A/H5, Avian Influenza A (H5N1) Infection in Humans. N Engl JMed 2005; 353: 1874–85.
3. The Writing Committee of WHO consultation on human influenza A/H5, Update on Avian Influenza A (H5N1) Infection in Humans. N Engl JMed 2008; 358: 261–73.
4. Schultsz C, Dong VC, Chau NVV, *et al*. Avian influenza H5N1 and healthcare workers. Emerg Infect Dis 2005; 11: 1158–9.
5. World Health Organization. Avian influenza — situation in Indonesia — update 16. 2010. (Accessed August 20, 2010, at http://www.who.int/csr/don/2010_08_04/en/print.html.)
6. Sumiarto B, Arifin B, Overview on Poultry Sector and HPAI Situation for Indonesia with Special Emphasis on the Island of Java, 2007 available access on http://www.hpai-research.net/index.html.
7. Sardikin *et al*, Clinical and Epidemiological Features of Patients With Confirmed Avian Influenza Presenting to Sulianti Saroso Infectious Diseases Hospital, Indonesia, 2005–2007, Ann Acad Med Singapore 2008; 37: 454–7.
8. de Jong MD, Cam BV, Qui PT, *et al*. Fatal Avian influenza A (H5N1) in a child presenting with diarrhea followed by coma. N Engl J Med 2005; 352: 686–91.
9. To KF, Chan PK, Chan KF, *et al*. Pathology of fatal human infection associated with avian influenza A H5N1 virus. J Med Virol 2001; 63: 242–6.
10. Annual report database patient H5N1 AI Infection in Dr. Soeotomo Hospital.
11. World Health Organization. WHO interim guidelines on clinical management of humans infected by influenza A(H5N1). February 20, 2004.
12. Yen HL, Monto AS, Webster RG, Govorkova EA. Virulence may determine the necessary duration and dosage of oseltamivir treatment for highly pathogenic A/Vietnam/1203/04 influenza virus in mice. J Infect Dis 2005; 192: 665–72.
13. Frederick G, Hayden, Antiviral Resistance in Influenza Viruses – Implications for Management nad Pandemic Response. N Engl J Med 2006; 354: 785–8.
14. World Health Organization. Summary of the second WHO consultation on clinical aspects of human infection with avian influenza A (H5N1) virus. (Accessed August 20, 2010, at http://www.who.int/csr/ disease/avian_influenza/meeting19_03_ 2007/en/index.html.)