

Practical management of avian influenza in humans

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ABSTRACT

There has been much alarm about avian influenza and its potential for a global pandemic ever since the current epidemic of avian influenza infections in humans began in 2003. While there have been a number of published reports on the clinical features of avian influenza, there are few guidelines on the practical management of patients with avian influenza. A symposium organised by the Society of Infectious Disease (Singapore), Society of Intensive Care Medicine and the Singapore General Hospital was held in Singapore to gather the views of experts from Turkey, Thailand, Vietnam and Indonesia who collectively had first-hand experience of the management of the majority (more than 100 of 192) of cases of avian influenza worldwide. The experts emphasised the importance of adapting international guidelines to the practicalities of situations on the ground. There was stress on wide screening using clinical criteria primarily, molecular diagnostic techniques (with reference laboratory confirmation) for diagnosis, and rational use of antiviral prophylaxis as well as infection control using at least surgical masks, gowns and gloves. A detailed analysis of data from a pooled database from these and other affected countries is critical to building up the evidence base for practical internationally applicable guidelines.

Keywords: avian influenza, infection control, infectious disease, influenza, viral infection

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INTRODUCTION

On February 11, 2006, the Society of Intensive Care Medicine, together with the Society of Infectious Disease (Singapore) and the Singapore General Hospital, organised a symposium on avian influenza, with the support of the Ministry of Health,

Singapore and the sponsorship of Drager Medical. Clinical experts from Turkey, Thailand, Vietnam and Indonesia who collectively had first-hand experience of the management of the majority of patients with avian influenza worldwide, shared their experiences in the management of these patients. This paper summarises the proceedings of the afternoon symposium in which each expert shared the practices in their own settings.

METHODS

A series of questions were posed to each of the panelists and their answers were projected onto the main screen as they were provided. The experts present were: Professor Nguyen Duc Hien, Director of the Institute for Clinical Research in Tropical Medicine, Hanoi, Vietnam; Professor Sardikin Giriputro, Deputy Director of RSPI Sulianti Saroso, Infectious Disease Hospital, Jakarta, Indonesia; Dr Thanomsak Anekthananon, Department of Preventive and Social Medicine, Siriraj Hospital, Bangkok, Thailand; and Professor Haluk Eraksoy, Head of the Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Istanbul University, Turkey, and President of the Turkish Society of Clinical Microbiology and Infectious Diseases. Singaporean participants were encouraged to raise questions and discuss responses from the different specialists. Two Singaporean moderators (DCBL and PAT) helped to guide the discussions.

RESULTS

Screening

Participants were asked what criteria they used to select patients for screening for avian influenza, given the non-specific initial presenting signs and symptoms. All four centres mandated a contact history in determining who to screen. For the centre from Turkey, the emphasis was on unprotected high-risk contacts within the previous ten days which included close contact with sick or dead birds, defeathering, contact with bird excreta, slaughtering of birds or

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prolonged unprotected contact with human cases of H5N1, including body fluids and potentially infected materials or equipment. For the Indonesian, Thai and Vietnamese centres, any contact history was considered relevant, not just unprotected contact. In Vietnam, this included residence in an area where avian outbreaks were documented, and in Indonesia, it included contact with fertilisers (because of the use of poultry excreta). All centres were also alert for clusters of febrile respiratory illnesses.

Clinical features used to screen patients for avian influenza in all four countries included fever or history of fever, which was in all cases defined as a temperature of $>38^{\circ}\text{C}$, and one other symptom. All four included respiratory symptoms, although the Turkish centre included myalgia as an alternative to the common symptoms of cough, shortness of breath and other upper respiratory symptoms. In Vietnam, chest pain with fever in a patient with contact history would prompt screening for H5N1. In addition, Indonesia screened individuals with no definite contact history but with rapidly-progressive community-acquired pneumonia. The Thais screened individuals with a family history of community-acquired pneumonia or suspected H5N1 infection. Clusters (especially families) were noted in Indonesia and Thailand, thus clusters were also used as a screening tool.

Although diarrhoea has been reported as a presenting symptom of H5N1 influenza in children, none of the centres did screening of individuals with fever and diarrhoea without respiratory symptoms, as the numbers would be prohibitive. Three of the four centres did not use laboratory features in addition to clinical features to determine who to screen. The exception was the Indonesian centre which used leucopaenia or lymphocytopenia, in addition to clinical criteria, for screening. Overall, these strategies resulted in screening thousands of individuals in the countries with the longer outbreaks (Thailand and Vietnam) and hundreds in the countries with more recent outbreaks (Turkey and Indonesia). In the current scenario where H5N1 influenza was not efficiently transmitted from human to human, even in a setting where H5N1 avian influenza is endemic in birds, the yield from this screening strategy was less than 10%.

Testing

All four centres used nasopharyngeal, throat or nasal swabs. In Turkey, only throat swabs were used, while in Indonesia and Vietnam, nasal swabs were used with throat swabs. In Thailand, they were used together with nasopharyngeal aspirates obtained

by specially-trained respiratory technicians. Nasal swabs as well as endotracheal aspirates were used. The Asian centres required at least two swabs before excluding bird flu. In Turkey, one negative swab before declaring an individual free from H5N1 could be satisfactory to exclude a diagnosis of bird flu. However, if a high clinical suspicion was still present, second and third samples were obtained, as required. Viral transport medium was used in one of the centres and all four centres made use of a cold chain before transfer to a reference laboratory which was either onsite or at a national reference facility. In addition, our experts from Vietnam, Indonesia and Turkey all used World Health Organisation (WHO) collaborating centre reference laboratories in Hong Kong and London for confirmation of the results from their national laboratories. The WHO collaborating laboratory in the UK confirmed at least 12 (including four fatalities) of the 21 Turkish cases of H5N1 avian influenza at the time of the symposium. The other countries also reported good concordance between local results and results from WHO reference laboratories.

All four centres relied heavily on molecular diagnostic techniques using polymerase chain reaction (PCR). Real-time PCR was performed in most centres as the primary diagnostic tool, with good results. This had the advantage of a turnaround time of within a day at all centres. Thailand had the innovation of mobile laboratories with the capability for PCR detection of H5N1. All four centres used different primer sets including US CDC primers, and primers from WHO, the Institute Pasteur and Thailand. It was noted that the US CDC had recently issued a set of primers through their laboratory response network and this is perhaps something that can be considered on an international level. Only the Thai centre did routine viral cultures for H5N1 and this is probably related to the biosafety requirements for the culture of this highly pathogenic virus. Rapid antigen tests were used in all the centres but the results were almost uniformly unhelpful, with the possible exception of one assay which is not widely available commercially. In terms of serology, immunofluorescence (IFA) was used in one centre and in another, haemagglutination inhibition was used. This was primarily used in most centres for epidemiological surveillance rather than clinical diagnosis because, as with most viral infections, the seroconversion tends to lag behind clinical disease and is less useful in the acute stage. All four centres reported good sensitivity and specificity with molecular diagnostic tests with very small numbers

of false positives and false negatives. In summary, the main emphasis was on molecular diagnosis, and as clinicians, we would prefer standardisation of molecular diagnostic methods so that reliable, rapid diagnosis can be made available for cases that we strongly suspect to be H5N1 avian influenza.

Management

In Indonesia and Vietnam, there were designated hospitals for the management of avian influenza patients, with reserve hospitals if these are overwhelmed. Jakarta had two designated hospitals and the major cities in Vietnam (Hanoi, Hue and Ho Chi Minh City) each had a designated hospital. In contrast, for Thailand and Turkey, all the tertiary hospitals in the country were prepared to manage patients with avian influenza; patients were transferred from primary and secondary facilities to any tertiary hospital. In Thailand and Turkey, there were no designated "bird flu hospitals". All centres preferred single rooms for all patients with suspected or confirmed avian influenza but occasionally, cohorting was necessary. In general, negative pressure facilities, if available, were used for patients with confirmed avian influenza. Patients suspected of H5N1 infections were isolated in single rooms. In settings where there were designated hospitals for H5N1, this was often not possible and thus, suspected patients needed to be cohorted. Intensive care resources ranged from cohorted intensive care with three beds in a negative pressure area to a "mobile intensive care" system. This is an innovation where some general ward rooms in some hospitals in Thailand were equipped for ventilatory support so that patients do not need to be moved to reduce the risk of transmission of respiratory pathogens to staff.

All four centres provided N95 masks for healthcare workers managing patients with suspected or confirmed avian influenza; these were kept for eight to 24 hours in the different centres. Patients were given surgical masks in two centres and N95 masks as tolerated in one centre. Family members and visitors were provided with surgical masks in two centres. The other centres did not allow visitors or family members near suspect or confirmed patients. Eye protection was only used for procedures in all centres. Powered air purifying respirators were not used in any centres. None of the centres reported the use of re-useable cloth masks. Disposable gloves were used in all centres. Washable gowns were used in two centres and disposable gowns in the other two. Thus, the minimum level of personal protective equipment used was disposable surgical masks (N95 masks for

healthcare workers), gloves and washable gowns.

All four centres used oseltamivir exclusively for antiviral prophylaxis. No other antiviral agents were used. All centres used oseltamivir for clinical cases on the basis of high clinical suspicion or in one centre, a positive rapid test. In the two centres with more recent outbreaks, all suspect cases were prescribed oseltamivir once they were classified as suspect. The standard dose of 75 mg twice daily in adults with the appropriate paediatric dose adjustment was used in all the centres, although a clinical trial of a higher dose is planned and should begin by the middle of this year. Among the adverse reactions noted by the experts, gastrointestinal side effects were the most prominent. Dizziness was reported in two centres, interestingly primarily among healthcare workers receiving prophylaxis. Prophylactic oseltamivir was offered to healthcare workers and family members of confirmed patients and in one centre, to symptomatic contacts of suspect patients. Distribution of prophylaxis in all centres was primarily by public health officials rather than infectious disease clinicians.

In two centres, prophylaxis was reserved for those with unprotected contact while in one of the centres, healthcare workers were offered prophylaxis for all contacts. This resulted in almost continuous use of antiviral prophylaxis which led to rotation of staff from other areas of the hospital to the H5N1 isolation wards. The duration of antiviral prophylaxis varied considerably for staff in the other centres, with a minimum of a week. In general, it was impossible to assess the efficacy of oseltamivir treatment as the numbers were small in each of the centres. The most well-documented oseltamivir treatment failures were reported from Vietnam in which two individuals who received oseltamivir developed oseltamivir-resistant virus on treatment, with a rise in viral load and rapid progression to death. These reports have been published⁽¹⁾.

Three of the four centres used steroids routinely for severe cases of H5N1 avian influenza, generally in high doses, up to 2 mg/kg/day of prednisolone or the equivalent in dexamethasone. The results were in general disappointing, although the numbers are too small for any definitive conclusions to be drawn. In the remaining centre, the use of adjunctive steroid therapy was left to the discretion of the individual treating physicians. Other adjunctive therapies such as interferon were not used at any of these centres, although intravenous immunoglobulin had been used in fatal cases in Turkey.

A summary of these recommendations is listed in Table I.

Table I. Summary of recommendations by panel from four centres with clinical experience in the treatment of human cases of avian influenza H5N1.

	Practices at the four centres
Screening	
a. Contact history	All 4 centres: unprotected high risk contact with sick/dead birds. All 4 centres: clusters of febrile respiratory illness. 3 of 4 centres: any contact, 1 of 4 residence in endemic area.
b. Clinical features	All 4, fever plus one other symptom (mainly respiratory)
c. Laboratory features	Only 1 of 4 used leucopaenia/lymphopaenia as additional criteria
Testing	
a. Sample source	1 - 3 swabs from throat, nose or nasopharynx.
b. Transport	Viral transport media and cold chain necessary for all 4 centres.
c. Diagnosis	RT-PCR in all 4 centres, confirmed by WHO reference labs. All primers different. Viral cultures used in 1 of 4 centres, serology not helpful acutely.
Management	
a. Designated hospital	Used in 2 of 4 countries.
b. Isolation	For confirmed cases, negative pressure where available. Cohorting if necessary
c. PPE	Minimum of surgical mask, gloves and washable gown, N95 for staff.
d. Antiviral prophylaxis	For unprotected contact in most settings, duration varied from at least 7 days to many more.
e. Treatment	Oseltamivir used routinely. Adjunctive steroids in 3 of 4 centres.

DISCUSSION

At the time of writing (April 2006), the resurgent H5N1 avian influenza in birds that started in East Asia in 2004 has spread across Europe, Eurasia, Asia and Africa⁽²⁾. Human infections with H5N1 have been reported from Hong Kong, Cambodia, Vietnam, Thailand, Indonesia, Turkey, Azerbaijan, Egypt and Iraq, with 109 deaths out of 192 confirmed cases⁽³⁾. Despite treatment with oseltamivir, pneumonia occurred in the vast majority of human cases with many developing fatal respiratory failure⁽⁴⁾.

Singaporeans travel frequently to the countries affected by avian influenza in humans and even more so to the ever-growing list of countries with avian influenza in birds. Febrile respiratory illness is the second commonest travel-related infection for travellers to Southeast Asia⁽⁵⁾. It will be difficult to screen all travellers with febrile respiratory illnesses. In settings with human cases of H5N1 influenza,

clinicians have also looked beyond contact with poultry to family clusters, or in some cases, unexplained severe respiratory illness in the setting of a poultry outbreak, to screen for H5N1 and this strategy might be necessary. While febrile respiratory illness is still the cardinal feature of human H5N1 influenza, case reports^(6,7) of atypical presentations with diarrhoea should raise the index of suspicion in the appropriate epidemiological setting.

It is possible that published cases might suffer from a reporting bias, with the more severe viral pneumonias reaching medical attention. Recently, a questionnaire survey in Vietnam has raised the possibility of mild human H5N1 infections⁽⁸⁾. Unfortunately, none of the cases in that survey had serological confirmation. It is thus very helpful to know that most cases seen in Indonesia, Thailand, Vietnam and Turkey still manifested mainly as primary viral pneumonia. For infection control and therapeutic efficacy, rapid diagnosis is critical as neuraminidase inhibitors are believed to work best within 48 hours of illness onset⁽⁹⁾. It is noteworthy that collectively, reverse transcriptase PCR detection of H5 is the most useful test when done on a variety of respiratory specimens. In contrast to human influenza, there are some reports that throat swabs may be more useful than nasal swabs in H5N1⁽⁴⁾. As all these tests are new and evolving, it is thus important to make sure a good specimen is taken so that the laboratory has enough good material to work with. When doubt exists about a negative H5 PCR result, it is prudent to repeat the test as is practised in all these four countries.

The transmission of influenza is a combination of airborne and droplet borne⁽¹⁰⁾. Importantly, at University of Virginia Hospital in Charlottesville, which is the one of the world's most important centres for research on nosocomial influenza, patients with influenza are managed in single rooms without negative pressure. Staff are vaccinated, screened and sent home when ill. This strategy has not resulted in a single case of nosocomial influenza in recent years⁽¹¹⁾. This is especially helpful in resource-poor countries where hand hygiene, face mask and universal precautions may well be all that are practicable as infection control measures. In an influenza pandemic, even developed countries are unlikely to have enough negative pressure isolation rooms to care for all influenza-infected patients.

With regard to the treatment of human H5N1 infections, oseltamivir still seems to be our best option although the most recent strains of H5N1 influenza circulating in China and Turkey are susceptible to the older agents amantidine and rimantidine⁽¹²⁾.

However, recent reports of oseltamivir-resistant H5N1 from Vietnam⁽¹⁾ and increasing oseltamivir resistance in human influenza in Japanese children⁽⁹⁾ raise grave concerns. Fortunately, zanamivir remains effective in these oseltamivir-resistant infections⁽¹²⁾.

In addition, mortality from human H5N1 infection seems to be related to a cytokine storm and haemophagocytosis in autopsy, in-vitro and animal studies⁽¹³⁻¹⁵⁾. Antiviral therapy thus has to be initiated early enough to reduce the damage before the cytokine storm or possibly immunomodulatory therapy might need to be considered. Salvage therapy is unlikely to help as corticosteroids have been shown not to improve mortality in acute respiratory distress syndrome⁽¹⁶⁾. Studies are urgently needed to address the role of adjunctive therapies in H5N1 human infections.

The symposium was an important first step in the process of establishing a practical database to better understand the experiences of clinicians who have actually managed cases of avian influenza in humans. We hope that the World Health Organisation or some other international body will establish a pooled database for rigorous scientific analysis. This will help generate an evidence base so that we can be prepared for a possible pandemic of avian influenza on the basis of science rather than speculation.

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REFERENCES

1. de Jong MD, Tran TT, Truong HK, et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N Engl J Med* 2005; 353:2667-72.
2. World Organisation for Animal Health. Update on Avian Influenza in Animals. Available at: www.oie.int/download/AVIAN%20INFLUENZA/A_AI-Asia.htm. Accessed April 11, 2006.
3. World Health Organisation. Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO. Available at: www.who.int/csr/disease/avian_influenza/en/. Accessed April 11, 2006.
4. The Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. Avian influenza A (H5N1) infection in humans. *New Engl J Med* 2005; 353:1374-85. Erratum in: *N Engl J Med* 2006; 354:884.
5. Freedman DO, Weld LH, Kozarsky PE, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. *N Engl J Med* 2006; 354:119-30.
6. Apisarnthanarak A, Kitphati R, Thongphubeth K, et al. Atypical avian influenza (H5N1). *Emerg Infect Dis* 2004; 10:1321-4.
7. de Jong MD, Bach VC, Phan TQ, et al. Fatal avian influenza A (H5N1) in a child presenting with diarrhoea followed by coma. *N Engl J Med* 2005; 352:686-91.
8. Thorson A, Petzold M, Nguyen TK, Ekdahl K. Is exposure to sick or dead poultry associated with flu like illness? : a population-based study from a rural area in Vietnam with outbreaks of highly pathogenic avian influenza. *Arch Intern Med* 2006; 166:119-23.
9. Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med* 2005; 353: 1363-73.
10. Bridges CB, Kuehnert MJ, Hall CB. Transmission of influenza: implications for control in health care settings. *Clin Infect Dis* 2003; 37:1094-101.
11. Salgado CD, Farr BM, Hall KK, Hayden FG. Influenza in the acute hospital setting. *Lancet Infect Dis* 2002; 2:145-55. Erratum in: *Lancet Infect Dis* 2002; 2:383.
12. Hayden F. Antiviral resistance in influenza viruses – implications for management and pandemic response. *N Engl J Med* 2006; 354:785-8.
13. Chan PKS. Outbreak of avian influenza A (H5N1) virus infection in Hong Kong in 1997. *Clin Infect Dis* 2002; 34(Suppl 2): S58-64.
14. Peiris JSM, Yu WC, Leung CW, et al. Re-emergence of fatal human influenza A subtype H5N1 disease. *Lancet* 2004; 363:617-9.
15. Guan Y, Poon LL, Cheung CY, et al. H5N1 influenza: a protean pandemic threat. *Proc Natl Acad Sci USA* 2004; 101: 8156-61.
16. Siegel MD. Novel therapies for the acute respiratory distress syndrome. In: *UpToDate Critical Care Medicine* [online]. Available at: www.uptodate.com/index.asp. Accessed February 24, 2006.