Review Article

Review of Human Infections with Avian Influenza H5N1 and Proposed Local Clinical Management Guideline

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Abstract

Introduction: The current avian and human H5N1 influenza epidemic has been in resurgence since 2004. We decided to evaluate published evidence in relation to epidemiology, clinical features and course, laboratory diagnosis, treatment and outcome of human H5N1 influenza, and develop institutional clinical management guidelines. Methods: A search of PubMed was conducted for all English language articles with search terms "avian", "influenza" and "H5N1". The bibliography of articles was searched for other references of interest. Results: Published case series from Hong Kong in 1997, and Thailand and Vietnam since 2004 have indicated a rapidly progressive primary viral pneumonia resulting in acute respiratory distress syndrome. The majority of human H5N1 infections can be linked to poultry exposure. Hitherto there has been no evidence of efficient human-to-human transmission. Case fatality rates have varied from 71% in Thailand to 100% in Cambodia. Oseltamivir appears to be the only potentially effective antiviral therapy. H5N1 isolates in Vietnam have become resistant to oseltamivir, resulting in persistent viral replication and death. There is as yet no effective human H5N1 vaccine. Conclusions: National and international preparedness plans are well advised. Clinical trials to evaluate higher dose oseltamivir therapy and immunomodulatory treatment are urgently needed.

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Key words: H5N1 subtype, Influenza A, Influenza in birds, Literature review

Introduction

The current human H5N1 outbreak occurred in Hong Kong for the first time in 1997, with another 2 human cases in the same city in February 2003. Since December 2003, when the resurgent outbreak of avian influenza H5N1 occurred in poultry in Seoul, Korea, it has spread to 12 Asian countries (Japan, China, Laos, Cambodia, Thailand, Vietnam, Malaysia, Indonesia, Taiwan, Hong Kong, Mongolia and India) and 15 countries in western and eastern Europe (France, Germany, Greece, Italy, Romania, Austria, Bulgaria, Russia, Bosnia, Croatia, Slovenia, Azerbaijan, Ukraine, Kazakhstan and Turkey) as of 27 February 2006. In addition, avian H5N1 has also been reported in Africa (Egypt and Nigeria) and the Middle East (Iraq and Iran).[1] The first avian-to-human transmission was reported in Vietnam and Thailand in January 2004,[2] and as of 27 February 2006, 7 countries have confirmed human H5N1 infections (Cambodia, China, Indonesia, Iraq, Thailand, Turkey and Vietnam).[3] The current number of human H5N1 infections totalled 170 cases, with 92 deaths.[3] This has led to frenetic media attention and unprecedented international and national alertness, and preparation for a potential influenza pandemic in the event of increasingly efficient human-to-human transmission.

Excellent reviews of human influenza[4] and avian influenza[5] have been published recently. This review aims to outline the basic virology of influenza, with an emphasis on the differences between human and avian influenza, and detail the current published experience in human cases of avian influenza H5N1 in terms of its epidemiology, clinical features and course, laboratory diagnosis, treatment and outcome. It also discusses the proposed criteria for admission during the pre-pandemic phase with H5N1 outbreaks in poultry and human cases elsewhere in the world, and the clinical management of human H5N1 influenza, including assessment, data collection, laboratory investigations, treatment and discharge criteria.

Virology of Influenza

The influenza virus is an RNA virus of the *Orthomyxoviridae* family and comprises an eight-segment genome, which codes for 10 proteins.[6] It is divided into

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types A, B and C on the basis of differences in its nucleoprotein. Influenza A and B are able to cause seasonal epidemics, while all influenza pandemics of the last century have been caused by influenza type A.[4]

Influenza A is further subtyped based on differences in its surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA). There are 16 haemagglutinins and 9 neuraminidases, all of which are found in avian species but only H1 to H3 and N1 to N2 are found in humans.[6] In contrast, H1, H3, N1, N2 and N7 are found in pigs and H7N7 and H3N8 have been commonly described in horses. The natural reservoir of all avian influenza viruses is waterfowl, in which there is an optimal adaptation with no clinical disease resulting from infection.[5]

Haemagglutinin plays a critical role in allowing influenza virus to gain entry into host cells by attaching to sialic acid receptors, while neuraminidase allows virions that have successfully multiplied in host cells to be released by cleaving glycosidic linkages to sialic acid. Antibody to haemagglutinin is neutralising and protective whereas antibody to neuraminidase is only partially neutralising.[4]

Point mutations in these surface glycoproteins, called antigenic drift, result in new strains of influenza virus annually, necessitating a new seasonal influenza vaccine. In contrast, pandemic influenza results when influenza A virus acquires a new haemagglutinin with or without a new neuraminidase, a process described as antigenic shift.[4] The 1918 influenza pandemic was caused by H1N1, believed to be an avian influenza virus that had undergone adaptive mutation, while the 1957 influenza pandemic was caused by H2N2 with an avian H2 and N2, and the 1968 influenza pandemic was caused by H3N2 with an avian H3, a process described as reassortment.[5]

Human influenza virus preferentially recognises an α2, 6 linkage on sialic acid receptors on human host cells, while avian influenza virus recognises an α2, 3 linkage. This receptor preference partially explains the barrier to inter-species transmission. Sialic acid receptors with α2, 3 receptors are found in human conjunctiva and nasal ciliated columnar epithelium,[6] which explains why many human infections with avian influenza virus in the past tended to manifest as conjunctivitis or upper respiratory infections. The current H5N1 avian influenza virus retains this α2, 3 linkage receptor preference but it has been theorised that only 1 or 2 mutations are needed to change that to a preference for an α2, 6 linkage.[7]

Highly pathogenic avian influenza has a multiple basic amino acid sequence at its haemagglutinin cleavage site that renders it susceptible to cleavage by a wide range of tissue proteases, resulting in disseminated disease in avian species.[8] This same motif has been found in the current H5N1 avian influenza, although viral dissemination is still unusual.[6]

Human Infections by Avian Influenza H5N1

Avian influenza outbreak has occurred intermittently since 1959, incidentally with H5N1 in Scotland.[9] Avirulent avian influenza manifests as mild respiratory signs, depression, diarrhoea or decreased egg production, while highly pathogenic avian influenza results in systemic symptoms (depression, listlessness, ruffled feathers, cessation of egg laying, excessive lacrimation, oedema, cyanosis, diarrhoea and nervous system disorders).[5] Highly pathogenic avian influenza mainly comprises H5 and H7.[5] Human infections with avian influenza have also occurred since 1959 with H7N7 in the United States of America, but severe pneumonia due to avian influenza was not reported till the 1997 H5N1 outbreak in Hong Kong.[9]

Brief Overview of Human Influenza

Human influenza in adults and adolescents classically present with abrupt onset of fever, chills, myalgia, malaise, anorexia, headache, sore throat and a dry cough. Fever peaks within 24 hours and lasts 1 to 5 days.[10] In children, a non-specific febrile illness, croup, bronchiolitis, bronchitis, gastrointestinal complaints, and febrile convulsions may also occur.[10] The incubation period of human influenza is 1 to 4 days.[10] Virus is detectable in respiratory secretions within 24 hours of the onset of illness, peaks for 24 to 72 hours and falls to low values by the fifth day.[4] This asymptomatic viral shedding may contribute to disease transmission, but it is associated with low viral titres. Viral shedding may persist for weeks in young children.[4] Human influenza virus can be recovered from children up to 6 days before and 21 days after the onset of symptoms.[2]

A recent study affirmed a positive predictive value of 85% and specificity of 81% for laboratory-confirmed influenza, with the presence of fever and cough of more than 36 hours duration during community outbreak. Interestingly, contrary to common knowledge, the presence of sore throat is a significant negative clinical predictor of laboratory-confirmed influenza.[11]

Epidemiology of Human Cases of Avian Influenza H5N1

Published experience from the 1997 Hong Kong outbreak and the 2004 Thailand and Vietnam outbreak suggests that 70% to 100% of cases had had exposure to ill poultry.[12] There is some indirect evidence of inefficient human-to-human transmission, with both clinical illness and seroconversion without clinical illness.[7,13,14] Among the 15 patients in the 1997 Hong Kong outbreak, the only significant risk factor was exposure to live poultry in market [odds ratio (OR), 4.5]. Notably, consumption of

poultry, undercooked poultry and poultry organs, as well as exposure to H5N1 cases, were not significant risk factors for H5N1 infections.[15]

An epidemiological investigation in the same outbreak showed a seropositivity of 12% among household contacts and 4% among tour group members exposed to H5N1 human cases.[13] In comparison with non-exposed healthcare workers, healthcare workers exposed to H5N1 human cases had a significantly higher seropositivity rate of 3.7%, which remained significant after adjustment for poultry exposure.[14] Investigation into occupational exposure to avian cases revealed a seropositivity of 10% among poultry workers and 3% among government workers involved in poultry culling. Among poultry workers, activities significantly associated with seropositivity were working in the retail poultry market (OR, 2.7), the presence of more than 10% mortality among poultry (OR, 2.2), butchering poultry (OR, 3.1), feeding poultry (OR, 2.4) and preparing poultry in restaurants (OR, 1.7).[16]

In contrast, while 95% of 83 hospital employees in Hanoi had been exposed to 1 or more H5N1 human cases and 2.4% were possible secondary case patients, none had detectable antibody to H5N1 by the microneutralisation test.[2] Similarly, among 60 of 62 exposed healthcare workers in Ho Chi Minh City who were able to provide clinical samples [nasal swab for reverse transcriptase polymerase chain reaction (RT-PCR) for H5 and paired sera tested with H5-specific microneutralisation assay], there was no evidence of seroconversion.[17] In the Hanoi study,[2] 9.8% of the hospital employees were laboratory workers while 15% of the healthcare workers in Ho Chi Minh City were laboratory and radiology workers.[17] In addition, no healthcare workers developed illness consistent with suspected or confirmed human H5N1 infection in Thailand.[18,19] Likewise, despite the lack of full droplet and respiratory infection control measures, no similar illness was detected among healthcare workers exposed to confirmed H5N1 patients in Vietnam.[20]

Hence, during the pre-pandemic phase, eliciting risk factors of exposure to poultry and known H5N1 cases should be undertaken for diagnosing suspected cases.

Clinical Features, Course and Outcome of Human Cases of Avian Influenza H5N1

In contrast to human influenza, the incubation period of H5N1 infection is a median of 3 to 4 days (range, 2 to 8).[12] This will have an impact on contact tracing and isolation precautions. Cases presented to hospital at a median of 3 to 8 days from the onset of illness (range, 1 to 8).[12] In Vietnam, the incubation period ranged from 2 to 4 days[20] while in Thailand, this was 2 to 8 days.[18] This delayed presentation compromises the efficacy of antiviral therapy, which may

be effective if given within 48 hours of onset of illness.

Fever was present in 98% cases. Headache, myalgia and sore throat were present in 28%, 24% and 32%, respectively. In the 1997 Hong Kong outbreak, cough, coryza and breathlessness were noted in 67%, 58% and 6%. In contrast, the 2004-2005 outbreak documented cough, coryza and breathlessness in 98%, 24% and 89%. Lower respiratory infections were more common in the more recent outbreak. Likewise, gastrointestinal complaints were more common; in 1997, vomiting, abdominal pain and diarrhoea were present in 33%, 17% and 17%, in comparison with 16%, 29% and 52% in the 2004-2005 outbreak.[12]

Chest X-ray was abnormal in 61% in 1997 compared with 100% in 2004-2005. Lymphopaenia was present in 64% and thrombocytopaenia in 54%. Transaminitis was present in 67% and acute renal impairment in 22%. Cardiac failure developed in 26%. Respiratory failure was more common in the 2004-2005 outbreak, occurring in 80%, compared with 44% in 1997. Likewise, more cases died in the more recent outbreak, 78% compared with 33% in 1997.[12]

Diarrhoea may precede respiratory illness by 1 week.[12] Breathlessness occurred at a median of 5 days (range, 1 to 16), chest X-ray became abnormal at a median of 7 days (range, 3 to 17) and acute respiratory distress syndrome developed at a median of 6 days (range, 4 to 13).[18]

Significant predictors of severe disease were older age, more delayed presentation, presence of pneumonia, leukopaenia and lymphopaenia in the 1997 Hong Kong outbreak.[8] In the 2004 Thailand outbreak, acute respiratory distress syndrome (which was in turn significantly associated with leukopaenia, lymphopaenia and thrombocytopaenia) and lymphopaenia on admission were significant prognostic factors for death.[18]

A recent questionnaire-based survey in Vietnam suggested that there might be transmission of mild highly pathogenic avian influenza to human beings exposed to sick or dead poultry. However, there was no serological confirmation.[21] This is not an unusual finding. Two studies in Vietnam which serologically evaluated exposed healthcare workers found no documented cases of seroconversion despite 12% of healthcare workers in Ho Chi Minh city reporting influenza-like illness in the preceding 2 weeks[17] and 72% similarly affected in Hanoi, with 5.4% too ill to work.[2] Hence, hitherto, where laboratory confirmation was available, the majority of symptomatic human H5N1 cases (88%) resulted in pneumonia.[12]

Cytokines in Human H5N1 Infections

In the 1997 Hong Kong outbreak, autopsy was performed on 2 of 6 patients who died. The main finding was one of haemophagocytosis. Retrospective cytokine assay showed

elevation in soluble interleukin (IL)-2 receptor, IL-6 and interferon (IFN)-γ during the first 10 days.[22] During the 2003 Hong Kong outbreak, autopsy performed on a father and his son who died similarly showed haemophagocytosis. Cytokine studies revealed rise in IFN-induced protein 10 (IP-10) and monokine induced by IFN-γ (MIG) that was sustained in the 33-year-old man but decreased by day 5 in his 8-year-old son.[23]

In vitro macrophage study to evaluate cytokine response to the 1997 Hong Kong H5N1 virus showed much greater increase in messenger RNA expression and concentration of various cytokines in a time-dependent manner.[24] At 1 hour post-infection, there was a rise in tumour necrosis factor (TNF)-α, IFN-β, IL-1β and IFN-α, while at 6 hours, monocytes chemotactic protein (MCP)-1, RANTES (regulated on activation, normal T cell expressed and secreted), IL-12 and IL-6 became elevated. The internal genes of H5N1/97 were found to be crucial to the high TNF-α phenotype.[24] Similar findings of raised TNF-α and IP-10 were made in another in vitro macrophage study with the 2003 Hong Kong H5N1 virus. [25]

However, it is far less apparent how therapeutic interventions can ameliorate this cytokine storm that seems central to the pathogenicity of human H5N1 infections. Human volunteer studies have shown the efficacy of intravenous zanamivir in preventing infection by H1N1 influenza and abrogating the local cytokine and chemokine responses.[26] Whether immunomodulatory therapy, such as intravenous immunoglobulins, corticosteroids and interferons, might be beneficial, is beyond the scope of this review.

Laboratory Diagnosis of Human Cases of Avian Influenza H5N1

The laboratory diagnosis of human influenza virus infection has been recently reviewed.[27] Viral culture in Madin-Darby canine kidney cell culture is the gold standard but has a turnaround time of 4 to 5 days. Rapid shell-vial culture decreases the turnaround time but has slightly lower sensitivity. Serology gives a retrospective diagnosis and is not useful in the acute setting.[27] Laboratory diagnosis of avian influenza H5N1 in human cases in Hong Kong has also been reviewed.[6,22]

Published experience from the 1997 Hong Kong outbreak and the 2004 Vietnam and Thailand outbreaks provide some information specific to human H5N1 infections. RT-PCR appears to be the most promising rapid viral diagnostic test. In Hong Kong, it had a sensitivity of 100%.[8] However, its yield varied with the H5 primer used for the amplification. In Vietnam, all 6 nasal or throat swabs were positive by RT-PCR using H5b primer, in comparison with 4 of 6 (67%) when H5-1 and H5-2 primer pairs were used.[20]

Rapid viral antigen testing is far less reliable for the detection of H5N1. It was positive in 33% in Vietnam (Capillia Flu A/B and QuickVue)[20] and 86% in Hong Kong (Directigen Flu A).[8]

Seroconversion typically occurred more than 14 days after the onset of illness.[12,16] Microneutralisation assay appeared to be more sensitive than haemagglutination inhibition assay for the detection of H5N1 antibody;[28] however, it needs 96 hours and a biosafety level 3 laboratory.[6] Combined with H5-specific Western blot test, the microneutralisation assay has a sensitivity of 88% and specificity of 100% in children, and a sensitivity of 80% and specificity of 96% in adults.[28] All serological tests have reduced specificity in patients older than 60 years.[28]

H5N1 influenza virus will produce an easily detectable cytopathic effect after 4 to 5 days of incubation in Madin-Darby canine kidney cell culture, which can be confirmed by H5-specific RT-PCR or H5-specific monoclonal antibodies.[22]

Prolonged viral shedding was common in H5N1 human infections, which has important implications for infection control and discharge policy for hospitalised patients. In the 2004 Vietnam outbreak, 1 patient had positive respiratory sample by antigen detection and RT-PCR on day 12 of illness, while another patient had positive respiratory culture on day 7 of illness.[20] In the 1997 Hong Kong outbreak, nasopharyngeal culture was positive at day 16 after onset of illness. In 2004 in Thailand, similarly culture was positive at day 16, while antigen detection was positive on day 18. In 2004 in Vietnam, RT-PCR was positive for H5N1 in throat swabs on day 15 of illness.[12]

Treatment of Human Cases of Avian Influenza H5N1

Neuraminidase inhibitors are proven effective treatment for human influenza[29,30] and have in vitro and animal data for their use in avian influenza H5N1 infections.[31,32] However, the limited published experience of the use of oseltamivir to treat human H5N1 infections is far less promising. Importantly, the current available experience is limited by small numbers and, frequently, patients were treated more than 48 hours after the onset of illness.

Four of 5 patients treated with oseltamivir in Vietnam died but they were treated between days 5 and 12 of illness.[20] In contrast, 5 of 7 patients treated with oseltamivir survived in Thailand. Earlier treatment (4.5 days of illness compared with 9 days) was associated with survival.[18]

Expert opinions recommend the use of oseltamivir 150 mg twice daily for 7 to 10 days for the treatment of severe human H5N1 infections.[6,12] This is supported by a murine model that demonstrated significant improved protective efficacy of oseltamivir at a higher dose for a longer period.[33]

The role of corticosteroids was even more uncertain.

Sixty per cent of patients in Hong Kong,[12] 86% in Vietnam[20] and 75% in Thailand[18] died despite being treated with corticosteroids.

Intravenous[8] and oral ribavirin[20] have been tried in 1 and 2 patients respectively without success in human H5N1 infections. The World Health Organization (WHO) recommends against the use of ribavirin in the treatment of human H5N1 infections.[34]

Amantadine was used to treat 8 of 12 patients in the 1997 Hong Kong outbreak but in all cases it was given more than 4 days after the onset of illness.[8] H5N1 isolates from Vietnam in 2004 have been shown to be resistant in vitro to amantadine and rimantadine[20] as a result of an asparagine residue at position 31 of the M2 protein.[6]

Hence, it appears that neuraminidase inhibitors are the mainstay of treatment for human H5N1 infections, in addition to intensive care unit support for severe cases. Experience in human influenza showed that 90% of influenza-infected patients defervesced within 36 hours of taking their first dose of oseltamivir.[35] Despite delayed treatment in human H5N1 infections, viral culture initially positive for H5N1 became negative within 2 to 3 days of oseltamivir therapy.[12] However, the worrisome development of oseltamivir resistance in 18% of Japanese children treated with oseltamivir and the detection of drug-resistant H5N1 in a patient treated with oseltamivir in Vietnam[30] may compromise our limited armamentarium in the event of an influenza pandemic arising from the current avian H5N1 outbreaks with limited poultry-to-human transmission. In fact, in a recent report from Vietnam, 3 of 4 patients who died despite treatment with standard dose oseltamivir had detectable H5N1 in respiratory specimens, 2 of which developed H274Y mutation in the neuraminidase gene. In contrast, 3 of 4 patients who survived had no detectable H5N1.[36]

There is no naturally occurring resistance to neuraminidase inhibitors.[37] In clinical trials, resistance to oseltamivir developed in 0.4% to 1.3% of adults[4,30] and 4% to 8.6% of children.[4,30] No zanamivir resistance has been detected in immunocompetent patients[30,37] although it has been detected in a paediatric bone marrow transplant recipient with influenza B infection.[4] While neuraminidase inhibitor-resistant mutant influenza viruses were associated with low infectivity and virulence in animal models,[4] and there has been no documented transmission of oseltamivir-resistant virus between people,[4,30] an oseltamivir-resistant variant has been recently shown to be readily transmitted in a ferret model.[30] Resistance to neuraminidase inhibitors may be due to mutation in haemagglutinin, which often confers resistance to both zanamivir and oseltamivir, while mutation in neuraminidase may render oseltamivir ineffective but retains susceptibility to zanamivir.[38]

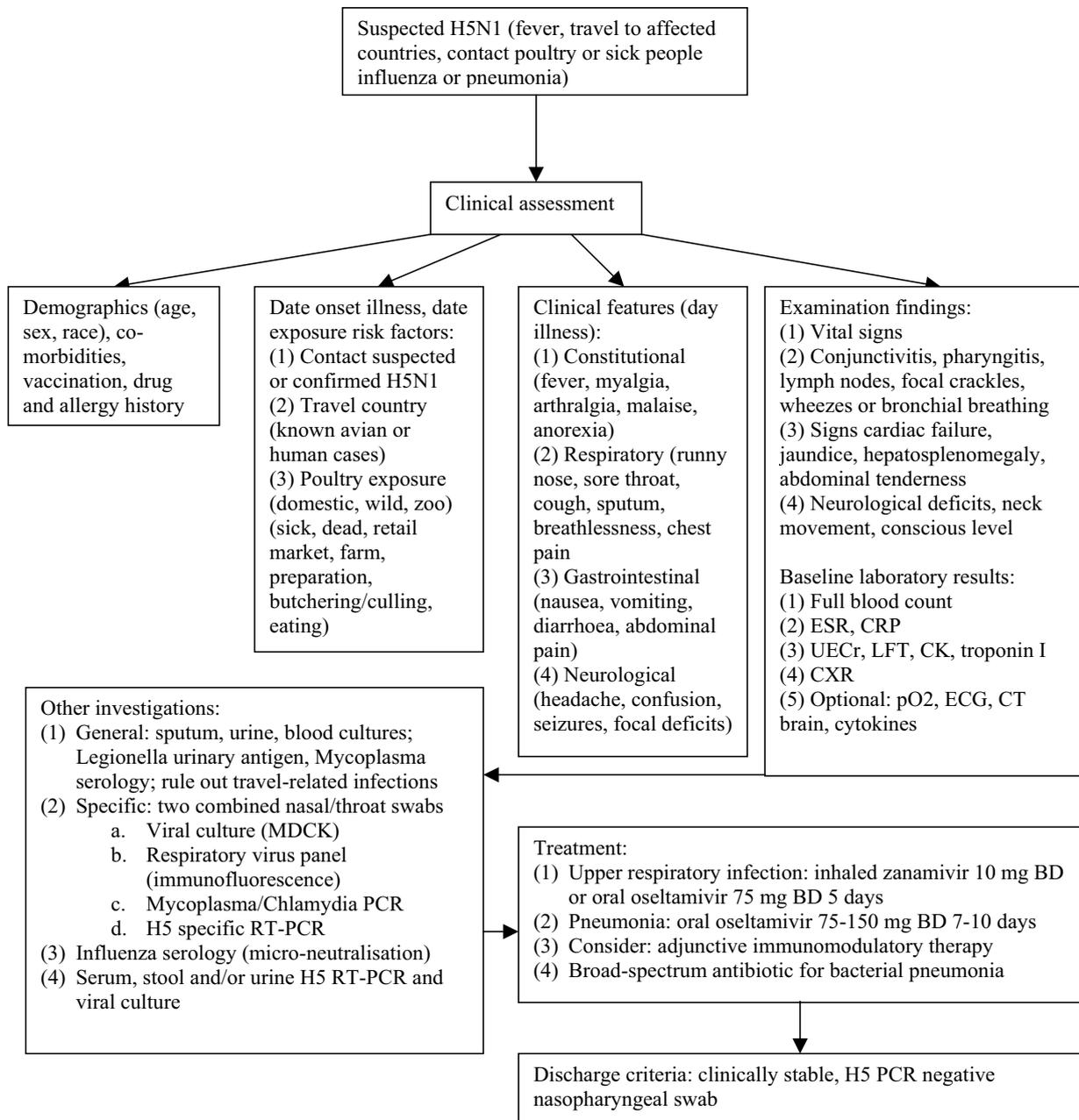## Infection Control Issues in Influenza

Influenza A and B viruses could be cultured from non-porous surface for up to 48 hours, porous surface for up to 12 hours and hands for up to 5 minutes after experimental contamination. Transmission from surface to hand lasts for a much shorter period, from non-porous surface to hands for 24 hours and from tissues to hands for 15 minutes.[39] This evidence suggests the potential for contact transmission involving fomites. Notably, 95% alcohol is viricidal to influenza virus on hands.[39] Influenza virus can be inactivated by povidone iodine, sodium hypochlorite and alcohol. The WHO recommends the use of 70% alcohol.

There are animal models suggesting that influenza virus can be spread by airborne transmission. An outbreak of influenza on an unventilated aircraft with 91% attack rate provided observational human data to support airborne transmission. However, a hospital ward outbreak in the 1958 influenza pandemic revealed an epidemic curve that suggested more an initial point source outbreak with subsequent person-to-person spread.[39] The paucity of nosocomial cases despite the infrequent use of negative-pressure room for patients with influenza at the University of Virginia, Charlottesville provided another piece of indirect evidence against efficient airborne transmission.[40]

Despite this low likelihood of airborne transmission, in view of the high mortality, it is advisable to observe strict contact and airborne precautions with good compliance with hand hygiene in managing a patient suspected of H5N1 infection during the pre-pandemic phase.

Healthcare worker prophylaxis after unprotected exposure to a patient with laboratory-confirmed H5N1 infection is controversial in the pre-pandemic phase. As previously discussed, there was no clinical illness consistent with human H5N1 among exposed healthcare workers in Thailand,[18,19] and no serology-proven clinical illness among exposed healthcare workers in Vietnam.[2,17] However, exposed healthcare workers in Hong Kong in 1997 were more likely to be seropositive for H5 even after adjustment for exposure to poultry outside of work.[14] At this stage, there is some evidence of inefficient human-to-human transmission. The consequence of human H5N1 infection is severe. As such, at our institution, we recommend neuraminidase inhibitor for prophylaxis after unprotected exposure to a laboratory-confirmed H5N1 patient. While there is no published data for healthcare worker prophylaxis in human H5N1 infections, zanamivir is known to reduce clinical influenza in healthy adults after household exposure by 81% while oseltamivir has been reported to reduce laboratory-confirmed influenza by 85% to 89% after household exposure, and by 92% as seasonal prophylaxis in an institutional setting.[30]

Fig. 1. Flow chart management of suspected avian influenza H5N1 patients at Tan Tock Seng Hospital and Communicable Disease Centre, Singapore (WHO phases 3-4).

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┌─────────────────────────────────────┐
│ Suspected H5N1 (fever, travel to     │
│ affected countries, contact poultry  │
│ or sick people influenza or          │
│ pneumonia)                           │
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                  │
                  ▼
        ┌──────────────────────┐
        │ Clinical assessment  │
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Demographics (age, sex, race), co-morbidities, vaccination, drug and allergy history

Date onset illness, date exposure risk factors:
(1) Contact suspected or confirmed H5N1
(2) Travel country (known avian or human cases)
(3) Poultry exposure (domestic, wild, zoo) (sick, dead, retail market, farm, preparation, butchering/culling, eating)

Clinical features (day illness):
(1) Constitutional (fever, myalgia, arthralgia, malaise, anorexia)
(2) Respiratory (runny nose, sore throat, cough, sputum, breathlessness, chest pain
(3) Gastrointestinal (nausea, vomiting, diarrhoea, abdominal pain)
(4) Neurological (headache, confusion, seizures, focal deficits)

Examination findings:
(1) Vital signs
(2) Conjunctivitis, pharyngitis, lymph nodes, focal crackles, wheezes or bronchial breathing
(3) Signs cardiac failure, jaundice, hepatosplenomegaly, abdominal tenderness
(4) Neurological deficits, neck movement, conscious level

Baseline laboratory results:
(1) Full blood count
(2) ESR, CRP
(3) UECr, LFT, CK, troponin I
(4) CXR
(5) Optional: pO2, ECG, CT brain, cytokines

Other investigations:
(1) General: sputum, urine, blood cultures; Legionella urinary antigen, Mycoplasma serology; rule out travel-related infections
(2) Specific: two combined nasal/throat swabs
    a. Viral culture (MDCK)
    b. Respiratory virus panel (immunofluorescence)
    c. Mycoplasma/Chlamydia PCR
    d. H5 specific RT-PCR
(3) Influenza serology (micro-neutralisation)
(4) Serum, stool and/or urine H5 RT-PCR and viral culture

Treatment:
(1) Upper respiratory infection: inhaled zanamivir 10 mg BD or oral oseltamivir 75 mg BD 5 days
(2) Pneumonia: oral oseltamivir 75-150 mg BD 7-10 days
(3) Consider: adjunctive immunomodulatory therapy
(4) Broad-spectrum antibiotic for bacterial pneumonia

Discharge criteria: clinically stable, H5 PCR negative nasopharyngeal swab

Criteria for Admission to Hospital during Pre-pandemic Phase (WHO Phases 3 and 4)

Possible cases in Singapore may comprise travellers (who may be Singaporeans or foreigners) exposed to avian influenza H5N1 in countries with avian outbreaks. As previously discussed, the main risk factors are exposure to poultry. However, although current evidence suggests inefficient and limited human-to-human transmission, exposure to patients with suspected or confirmed human H5N1 infections in countries with avian outbreaks should also be considered a risk factor in order to detect early cases of increasing human-to-human transmission. In addition, if avian H5N1 influenza is detected in Singapore, people exposed to sick poultry locally should be considered possible cases.

All such cases should be admitted to hospital for investigation and isolation until H5N1 infection is excluded. This serves the purpose of containing an early local outbreak

from an imported case of human H5N1 infection and detecting a change in circulating influenza virus from human influenza H1N1 and H3N2 to a H5N1 variant. All efforts should be made to obtain appropriate respiratory specimens for viral culture and RT-PCR.

Clinical Management for Suspected Human Cases of Avian Influenza H5N1

The proposed management is outlined in Figure 1. In the initial stages, it is critical to characterise the new influenza strain to guide further management in terms of contact tracing, isolation and discharge criteria. While the 1997 Hong Kong outbreak and the 2004-2005 Vietnam and Thailand outbreaks provide information on avian influenza H5N1, the clinical illness may be quite different if it becomes adapted to human transmission. In addition, while the current genotype Z of avian influenza H5N1 appears the most likely candidate to evolve into a pandemic influenza strain, we cannot be complacent and assume that a pandemic influenza virus will necessarily be H5N1. Hence, attack rate, asymptomatic viral shedding, incubation period, clinical illness and outcome, and response to antiviral drugs (both amantadanes and neuraminidase inhibitors) will need to be characterised early in the course of an influenza pandemic.

Information will be collected to determine epidemiological risk factors and incubation period. Clinical features to determine clinical predictors of laboratory confirmed influenza (to help guide subsequent triaging for antiviral therapy) and severity of illness (to modify criteria for admission), and atypical presentations will be documented. Microbiologic studies aim to exclude an alternative diagnosis (e.g., bacterial causes of community-acquired pneumonia and travel-related infections), to determine the new influenza strain, and to characterise viral shedding, systemic dissemination and cytokine response.

The current treatment recommendations are based on limited experience in human H5N1 infections and expert opinions. For upper respiratory infections with H5N1, it will be reasonable to use either inhaled zanamivir or oral oseltamivir. However, for pneumonia secondary to H5N1, given the risk of viral dissemination beyond the respiratory tract and the limited systemic level of inhaled zanamivir[4,30] it will be more prudent to use oral oseltamivir. Clinical trials to investigate other adjunctive therapy of severe human influenza, such as corticosteroids, intravenous immunoglobulins and interferons, need to be considered.

Criteria for Discharge from Hospital

Currently, the WHO recommends isolation for adult patients for 7 days after resolution of fever and 21 days for children.[34] As discussed in the previous section, it is important to determine the duration of viral shedding early in the course of pandemic influenza to help guide discharge policy. In WHO phases 3 and 4, this can still be observed. However, such prolonged duration of isolation will quickly overwhelm the capacity of acute healthcare facilities to care for new cases of pandemic influenza needing admission as well as patients who need hospitalisation for surgical and medical emergencies, and may not be pragmatic for paediatric patients.

Antigen detection is not sensitive for H5N1 while RT-PCR may detect non-infectious viral material after effective antiviral therapy. With the current limited experience, viral culture is said to become negative after 2 to 3 days of treatment with oseltamivir.[12] At this stage, a prudent approach will be to discharge a suspected H5N1 case only after RT-PCR is negative during the pre-pandemic phase. During a pandemic, discharge policy for convalescent patients will depend on clinical needs, actual viral shedding and public health priorities.

Conclusions

Human infections with avian influenza H5N1 are associated with high mortality and its persistence in causing avian outbreaks in Asia and Europe raises concern about evolution to pandemic influenza. However, such concern should be tempered with the observation that as of 27 February 2006 only 170 human cases have occurred so far. Nevertheless, it is prudent for us to prepare for an influenza pandemic given the ample forewarning since 2004.

Early case detection via clinical case definition and rapid laboratory confirmation may identify patients who can be treated early with a neuraminidase inhibitor, which may prevent progression to more severe disease. The efficacy of neuraminidase inhibitors in treating influenza pneumonia has never been proven even in human influenza but given the high mortality associated with H5N1 infections, it would be unethical not to treat with the only antiviral drugs with demonstrated activity in vitro and in animal models against H5N1. In addition, in severe H5N1 infection with multi-organ failure, intensive care support is critical. Other adjunctive treatment modalities such as ribavirin, corticosteroids, intravenous immunoglobulins and interferon should only be undertaken in a properly designed clinical trial as clinical data on their use and efficacy are lacking.

Disclaimer: All authors have no conflict of interest

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