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Invited article

Avian Influenza

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Abstract. Avian influenza is due to H5N1 type of influenza virus. It is hosted by birds, but may infect several species of mammals and specially the domestic poultry. The virus is transmitted by infectious droplets and droplet nuclei, by direct contact and, perhaps, by indirect contract. Two features of the current H5N1 outbreaks are striking: the predominance of children and young abults and the high mortality rate. The diagnosis needs a travel and epidemiologic history as well as a close contact with patients or sick poultry. The management of avian flu include treatment and prevention. Oseltamivir is the drug of choice (75 mg twice daily for 5 days). Isolation precautions similar to thoce used for SARS - infected patients are recommended. *Hippokratia 2006; 10 (1):3-6*

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Introduction

Avian influenza (also known as bird flu, avian flu, type A flu) is a flu due to a type of influenza virus that is hosted by birds, but may infect several species of mammals. It was first identified in Serbia Montenegro in the early 1900s and is now known to exist worldwide. A strain of the H5N1-type of avian influenza virus that emerged in 1997 has been identified as the most likely source of a future influenza pandemic and is known to have infected about 152 people in Asia since 2003, killing 83 (data on January 25, 2006)[1,2].

Humans can be infected with influenza types A, B, and C viruses. Subtypes of influenza A that are currently circulating among people worldwide include H1N1, H1N2, and H3N2 viruses. Avian influenza viruses compose the *Influenzavirus A* genus of the Orthomyxoviridae family and are negative sense, single-stranded, segmented RNA viruses. There are 16 different HA antigens (H1 to H16) and nine different NA antigens (N1 to N9) for influenza A. Sixteen HA types had been recognized, each with up to 9 N subtypes, yielding a potential for 144 different H and N combinations[3].

The avian influenza subtypes that have been confirmed in humans, ordered by the number of known human deaths, are: H1N1 caused Spanish flu, H2N2 caused Asian Flu, H3N2 caused Hong Kong Flu, H5N1, H7N7, H9N2, H7N2, H7N3, H10N7[3,4].

Avian influenza A virus strains are classified as low pathogenic (LPAI) or highly pathogenic (HPAI) on the basis of specific molecular genetic and pathogenesis criteria. Most avian influenza A viruses are LPAI viruses that are usually associated with mild disease in poultry. In contrast, HPAI viruses can cause severe illness and high mortality in poultry. More recently, some HPAI viruses (e.g., H5N1) have been found to cause no illness in some poultry, such as ducks. LPAI viruses have the potential to evolve into HPAI viruses and this has been documented in some poultry outbreaks. Avian influenza A viruses of the subtypes H5 and H7, including H5N1, H7N7, and H7N3 viruses, have been associated with HPAI, and human infection with these viruses have ranged from mild (H7N3, H7N7) to severe and fatal disease (H7N7, H5N1). Human illness due to infection with LPAI viruses has been documented, including very mild symptoms (e.g., conjunctivitis) to influenza-like illness. Examples of LPAI viruses that have infected humans include H7N7, H9N2, and H7N[1-3].

Wild birds are the natural host for all known subtypes of influenza A viruses. Typically, wild birds do not become sick when they are infected with avian influenza A viruses. However, domestic poultry, such as turkeys and chickens, can become very sick and die from avian influenza, and some avian influenza A viruses also can cause serious disease and death in wild birds.

Emerging infectious diseases represent a significant threat. Outbreaks of both endemic and pandemic infections have occurred throughout history and will continue to occur well into the future. Pandemics occur when a pathogen rapidly changes (antigenic shift) or continuously evolves (antigenic drift) and develops the ability to: (1) cause human infections, (2) result in severe disease, and (3) spread by sustained human-to-human transmission. The avian influenza A H5N1 virus has already achieved the first 2 characteristics. While sporadic human-to-human transmission has occurred, it is not sustained. If this occurs, this virus may very well result in a severe disease with global impact. It is well known that if a strain of avian influenza virus to which humans have not been previously exposed undergoes antigenic shift to the point where it can cross the species barrier from birds to humans, the new subtype created could be both highly contagious and highly lethal in humans. Such a subtype could cause a global pandemic similar to the

Spanish Flu. There have been 3 previous influenza pandemics in the past century. The Spanish flu of 1918-1919 resulted in 20-40 million deaths worldwide. The Asian flu of 1957-1958 and the Hong Kong flu of 1968-1969 were responsible for 2-5 million deaths. In the 1957 and 1968 pandemics the new viruses contained components of previous human as well as avian influenza viruses. Sporadic transmission of H5N1 to humans during the 2004-2005 Asian epizoonotic have prompted concerns that the next pandemic is imminent[1,6,7].

Incidence: Table 1 shows cases of avian influenza A (H5N1), which reflects data through January 25 2006. Cases in humans reflect outbreaks of avian epidemics in Asia in 2004 and 2005. Two features of the current H5N1 outbreaks are striking: the predominance of children and young adults and the high mortality rate[2,3].

Transmission: Human influenza is transmitted by infectious droplets and droplet nuclei, by direct contact, and perhaps, by indirect (fomite) contact, with self-inoculation to the upper respiratory tract or conjunctival mucosa. For human influenza A (H5N1) infections, evidence is consistent with bird-to-human, possibly environment-to-human, and limited, nonsustained human-to-human transmission to date. With bird-to-human transmission, the defined risks are exposure to ill poultry and butchering of birds or other close contact with birds in at least 80% of cases. The human-to-human transmission has been suggested in only 1 well-verified case report[8]. There are no cases of transmission by small-particle aerosol. Serologic testing of approximately 550 healthcare workers who are responsible for the care of patients with avian influenza and household contacts of these cases showed positive results in 15[1-3].

Avian influenza virus spreads in the air and in manure and survives longer in cold weather. It can also be transmitted by contaminated feed, water, equipment and clothing; however, there is no evidence that the virus can survive in well cooked meat. Of great concern are the increasing numbers of sporadic avian-to-human transmission of different subtypes of avian influenza reported in Asia, the Netherlands and British Columbia during the last few years. Although avian influenza virus generally replicate inefficiently in humans, some subtypes can replicate within the human respiratory tract and cause disease[1-3,7].

Clinical features: The incubation period is 3 to 5 days. Symptoms in animals vary, but virulent strains can cause death within a few days. The typical case in human is a previously healthy child or young adult who has exposure to sick poultry, develops the onset of flulike illness at a median incubation period of 4 days, develops typical symptoms of influenza but with a relatively high frequency of diarrhea and infrequent pharyngitis, quickly develops acute respiratory distress syndrome (ARDS), and dies on illness day 8. In humans, avian flu viruses cause similar symptoms to other types of flu. The features are variable, being determined in part by the strain. Generally, the symptoms varies in severity. The most severe disease occurs in patients older than 12 years old. Main features include fever, cough, sore throat, muscle aches, conjunctivitis and, in severe cases, severe breathing problems and pneumonia that may be fatal (Table 2). Also, elevated aminotransferases, pancytopenia, and sometimes encephalopathy. The severity of the infection will depend to a large part on the state of the infected person's immune system and if the patient has been exposed to the strain before, and is therefore partially immune[1,3,4,9].

Diagnosis: The differential diagnosis of avian flu includes: atypical pneumonia, and typical respiratory infections. The diagnosis needs a travel and epidemiologic history as well as a close contact with patients or sick poultry. The diagnosis is confirmed by viral isolation, detection of H5-specific RNA (RT-PCR) with pharyngeal specimens (throat swabs) or serology. The optimal specimen is a nasopharyngeal aspirate obtained within three days of symptoms onset. Serologic testing, by a combination of methods including virus neutralization, ELISA and Western blotting, for the specific virus strain, is a useful tool for epidemiologic studies and retrospective diagnosis. A positive test is a four-fold or greater increase in antibody titer between a sample obtained as soon as possible after the onset of symptoms and one obtained after at least 14 days. Obviously, serologic testing may not be helpful for acute diagnosis. Patients who should be tested for avian influenza virus are:

a. high risk patients with history of travel within 10 days of symptom onset to a country with documented H5N1 avian influenza in poultry and/or humans, and patients with radiographically confirmed pneumonia, acute respiratory distress syndrome or severe respiratory illness for which an alternate etiology has not been established.

b. low risk patients suspected human case in an H5N1 affected country within 10 days of symptom with a history of contact with domestic poultry or a known or onset and documented fever > 38° C and one or more of the following: cough, sore throat, shortness of breath[1-3].

Management. The management of avian flu includes *treatment* and *prevention*[1,10,11]. Most of the patients require ventilatory support within 48 hours of admission and care in the intensive care unit for multiorgan failure. Routine treatment includes broad-spectrum antibiotics, antiviral agents, and often corticosteroids. Two classes of drugs are effective against influenza: M2 ion channel blockers (amantadine, rimantadine) and neuraminidase inhibitors (oseltamivir, zanamivir). Although no outcome trials have been performed in humans infected with avian influenza, tissue cultures and animal model studies suggest that neuraminidase inhibitors may be of benefit. Today, oseltamivir is the drug of choice and is recommended in a dose of 75 mg twice daily for five days, for treatment of suspected cases since it has proven benefit against human influenza and may decrease viral shedding. Note that it

must be administered early in the course of the disease. Also note that there is a report for a strain resistant to oseltamivir. The mortality rate was 76% among 25 patients who were given oseltamivir and 75% in 12 patients who did not receive this drug. It is noted that the virus could generally not be cultivated within 2-3 days of oseltamivir, but there was clinical progression anyway. There was no evidence of response to corticosteroids.

At present there are no licenced vaccines against avian influenza. Multiple phase I trials are underway in many countries.

When suspecting highly pathogenic avian influenza, specimens must be handled and processed using appropppriate biosafety precautions.

For both hospitalized patients and those managed in the outpatient setting, isolation precautions similar to those used for SARS-infected patients are recommended (Table 3)[1-3,12].

Table 1. *Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO*

25 January 2006

Date of onset	Cambodia		China		Indonesia		Thailand		Turkey		Viet Nam		Total	
	cases	deaths	cases	Deaths	cases	Deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
2003	0	0	0	0	0	0	0	0	0	0	3	3	3	3
2004	0	0	0	0	0	0	17	12	0	0	29	20	46	32
2005	4	4	8	5	16	11	5	2	0	0	61	19	94	41
2006	0	0	2	2	3	3	0	0	4	2	0	0	9	7
Total	4	4	10	7	19	14	22	14	4	2	93	42	152	83

Total number of cases includes number of deaths.
WHO reports only laboratory-confirmed cases.

Table 2. *Clinical Features of Avian Flu*

Feature	Cases (n = 59)*
Age (median)	15 years
Incubation period (median)	4 days
Exposure – ill poultry	80%
Clinical findings (admission)	
Fever > 38°F	54 of 55 (98%)
Cough	52 of 55 (95%)
Dyspnea	34 of 51 (61%)
Diarrhea	19 of 58 (33%)
Outcome – death	38 of 59 (64%)
Time to death from onset of symptoms (median)	8 days

** Incomplete data in most categories.*

Table 3. *Prevention of Influenza A (H5N1)*

Risk Group	Comments
Hospitalized patients	Precautions: standard, contact, droplet, and airborne Negative pressure single-patient room with door closed N95 mask, face shield, gloves for HCW If possible – dedicated HCW (no other patients)
HCW exposures	Monitor temperature twice daily; if fever, remove from patient care; do diagnostic testing; give oseltamivir (5-150 mg twice daily x 5-10 days) Exposure to aerosol, secretions, etc: oseltamivir 75 mg once daily x 7-10 days
Household contacts	Hand hygiene; consider N95 mask and eye cover Contact in hospital/home: prophylactic oseltamivir 75 mg once daily x 7-10 days plus
Travelers	Trivalent influenza vaccine = 2 weeks prior to travel Avoid contact with poultry and undercooked eggs/poultry Consult provider if fever and respiratory symptoms within 10 days of return

HCW = healthcare workers

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