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Avian influenza in humans – an update

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ABSTRACT Despite control of the poultry outbreak by culling and sometimes vaccination, poultry outbreaks and sporadic cases in humans continue to occur in South East Asia and is spreading to Europe. The human disease is characterised by a rapidly progressive community-acquired pneumonia and frequently diarrhoea with leukopenia, lymphopenia and impaired liver functions. Virus can be detected in the intestine, spleen, serum, cerebrospinal fluid, in addition to the respiratory secretions. Acute encephalitis or acute gastroenteritis were occasionally reported as early manifestations. Most of the cases are caused by poultry-to-human transmission. Human-to-human transmission is still inefficient but has occurred in health care workers and family contact. In endemic areas, patients presenting as community-acquired pneumonia with a history of contact with sick or dead birds should be isolated, investigated and empirically treated for H5N1 infection. Infection control measures should include contact, droplet and airborne precautions. The globalisation of this avian epidemic by migratory birds and the crude fatality rate of 50% in humans have triggered a global response of preparedness for a coming influenza pandemic which may occur with genetic reassortment or mutations conferring the virus the capability of efficient human to human transmission.

KEYWORDS Avian influenza, infection control, neuraminidase inhibitors.

LIST OF ABBREVIATIONS community-acquired pneumonia (CAP), cerebrospinal fluid (CSF), haemagglutinin (HA), human immunodeficiency virus (HIV), influenza-like illness (ILI), neuraminidase (NA), severe acute respiratory syndrome (SARS), World Health Organization (WHO)

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Direct transmission of viral infections from animals to humans (without the need for an arthropod vector) has been known for centuries (zoonotic infection). These range from cowpox, monkeypox, and rabies which have been known to mankind since ancient times, to HIV and filoviruses of more recent memory. In the past eight years, two emerging zoonotic viral infections – avian influenza and SARS – have become major concerns throughout the world, both medically and for their economic impacts. Unlike most other zoonotic viral diseases (with the possible exception of HIV), these two infections have a high propensity to cause epidemics, and perhaps pandemics, carrying significant morbidity and mortality.

THE VIRUSES

The family *Orthomyxoviridae* includes the Isavirus (infectious salmon anaemia virus), the tick-borne Thogotovirus, and three genera of influenza viruses, Influenza virus A, B, and C. The single-stranded negative sense RNA genome of the influenza viruses is divided into eight segments (except influenza C which has seven segments). Two of the gene products are important in the classification of influenza A viruses, these are the HA and NA which are surface proteins found on the envelope of the viruses. To date, 16 HA and nine NA types are recognized, and individual viral strains may have any combinations of HA and NA types. Influenza viruses are well known for their ability to undergo antigenic changes (mainly at the HA and NA antigens) at fairly rapid paces. Such changes may involve antigenic drift (relatively minor changes as a result of genetic mutations) or antigenic shift (major changes as a result of reassortment of the RNA fragments), the latter of which may result in pandemics of influenza.

HUMAN INFLUENZA OUTBREAKS

Human influenza A nowadays is most commonly caused by H3N2 and H1N1 viruses, with H1N2 and H2N2 viruses being encountered less frequently. Other serotypes of influenza viruses can be found in a variety of animals, but the largest natural reservoir is the aquatic birds which contains all the HA and NA types of influenza A viruses. These are collectively known as the avian influenza viruses. Prior to 1997, human infections due to avian influenza had been reported only rarely – either as a result of natural transmission or laboratory-acquired – often presenting as

TABLE 1 Management of patients with ILI or CAP.

Patient characteristics	ILI with no signs of pneumonia	Mild CAP not requiring hospital admission	Moderate to severe CAP requiring hospital admission+
1. History of touching dead or sick bird including poultry	1. Outpatient follow-up for deterioration (admit if there is a positive contact history)	1. Amoxicillin-clavulanate	1. Amoxicillin-clavulanate and azithromycin (levofloxacin in adult if the patient is allergic to beta-lactams)
2. Family members with suspected or confirmed H5N1 influenza	2. Oseltamivir	2. Outpatient follow-up and chest radiograph for deterioration (admit if there is a positive contact history)	2. Oseltamivir
3. Health care workers caring for suspected or confirmed H5N1 influenza patients	3. Personal hygiene	3. Oseltamivir	3. Contact isolation with droplet precaution
4. Laboratory workers handling specimens or viral cultures from such patients	4. Microbiological work up for influenza A H5N1 in those with positive exposure	4. Personal hygiene	4. Microbiological work up for influenza A H5N1 virus
		5. Microbiological work-up for influenza A H5N1 is indicated if exposure or travel history is positive	5. Intensive care support and mechanical ventilation if clinically indicated

- Wear standard surgical mask at home with frequent handwashing especially after handling respiratory secretion.
- Avoid aspirin in children <16 years of age.
- Oxygen therapy by nasal cannula.
- High-flow oxygen mask or nebulizers should be avoided to minimise risk of nosocomial spread.
- High flow oxygen mask, non-invasive ventilation should only be used with strict infection precautions.

conjunctivitis and caused by influenza A H7N7. The first major outbreak of human infections due to avian influenza occurred in Hong Kong in 1997 when the influenza A H5N1 virus caused massive deaths in the poultry with 18 documented human cases, six of whom died. The epidemic was halted after 1·5 million poultry were slaughtered in the farms and markets throughout Hong Kong.

Since 1997, sporadic cases of H5N1 infection have occurred in humans and poultry in Hong Kong and southern China. From late 2003 to early 2004, the largest epidemic of avian influenza in history occurred in a number of southeast Asian countries, extending as far north as South Korea and Japan and as far south as Indonesia. In 2005, this avian virus genotype Z has extended its geographical range to Russia, Romania and Turkey. This outbreak was caused mainly by the H5N1 Z genotype and was characterised by a high mortality rate. As of 15 October 2005, 117 human cases of H5N1 infection had been documented in the affected areas with 60 fatalities, giving a crude overall case-fatality rate of 50% (WHO, accessed on 11 January 2005; www.who.int/csr/disease/avian_influenza/country/cases_table_2005_01_07/en/). Most of these human infections occurred in Thailand, Indonesia and Vietnam as three different waves. A clear contact history with infected poultry was present in most of the patients. The fulminant nature of the infection could be related to extrapulmonary systemic dissemination to blood, CSF, spleen and intestine and a highly pro-inflammatory response to the infection, the so-called 'cytokine storm'. Whether co-administration of an effective antiviral agent with immunomodulators will result in a better treatment outcome might warrant further studies. Despite extensive slaughtering of tens of millions of poultry in the affected areas, cases of animal and human infections due to H5N1 are still reported in the Eurasian region to date.

Another major outbreak of human infections due to avian influenza occurred in the Netherlands in 2003. The causative virus was influenza A H7N7, and 87 virologically documented cases were found, with one death in a veterinarian. A recent study using a modified haemagglutination-inhibition test, however, suggested that the actual number of people infected could be much higher, with seroprevalence of H7 antibodies among household contacts of an infected poultry worker approximating 59%. Unlike the H5N1 outbreak in Asia, the H7N7 outbreak was characterised by a lower mortality and many of the case presented with conjunctivitis and/or an ILI. Similarly, influenza A H9N2 is the third avian influenza virus which has been shown to be transmissible to humans in Hong Kong.

CLINICAL IDENTIFICATION OF DISEASE

The two most common clinical manifestations of avian influenza infections are conjunctivitis (mainly seen with H7N7) and respiratory symptoms (H7N7 and H5N1). Respiratory symptoms range from an uncomplicated ILI to severe and fatal pneumonia. To date, all human H9N2 infections have presented as uncomplicated ILI while both H7N7 and H5N1 infections may result in severe disease, especially with the latter. Mortality associated with Reye syndrome has also been described in H5N1 infections following the use of aspirin and other nonsteroidal anti-inflammatory drugs in the 1997 Hong Kong outbreak. Gastrointestinal manifestations including diarrhoea has also been noted in the 1997 Hong Kong outbreak and 2004 Vietnam outbreak. Unusual manifestations including encephalitis, hepatic impairment, renal failure unrelated to rhabdomyolysis, and pancytopenia were also described. Factors associated with severe disease included older age, delay in hospitalisation, lower respiratory tract involvement, and a low total peripheral white blood cell count or lymphopenia at admission. The median time to death from the onset of illness was nine days (range, six to 17) in the recent Vietnam outbreak.

Since there are no pathognomonic signs and symptoms of human avian influenza apart from contact history with infected birds, early diagnosis and commencement of antiviral therapy remains the cornerstone of therapy if severe complications are to be avoided. Patients are defined as having ILI if they have a clinically unexplained elevated temperature of 37·8°C or higher, and systemic symptoms such as myalgia and fatigue (with or without chills, headache), or respiratory symptoms such as cough (with or without rhinorrhoea, sore throat). During the peak flu season, the combination of fever, cough, fatigue, and myalgia has a sensitivity of around 30% and specificity of around 80%. Patients with ILI are then screened by physical examination of the chest for signs of consolidation (crepitations, decreased air entry, bronchial breathing, or increased dullness) and/or chest radiograph. Those with positive signs are managed as cases of acute community-acquired pneumonia. They are also screened for the epidemiological risk factor of exposure to possibly infected chickens and risk factors of poor prognosis. Subsequent investigations and management are summarised in Table 1.

CONTROL OF SPREAD

Though avian influenza appears to be less infectious than human influenza or SARS, infection control measures must be strictly adhered to in all confirmed or suspected cases. Droplet and contact precautions are the basis for preventing hospital cross-infection in patients admitted with undiagnosed ILIs. Although there is no evidence to suggest that avian influenza virus could spread by the airborne route, current WHO guidelines do recommend airborne precautions for patients with documented avian influenza infections.

SPREAD AND DRUG RESISTANCE

To date, there is at least serological evidence that avian influenza viruses (H5N1 and H7N7) are capable of human-to-human transmission. Unlike human influenza viruses, interpersonal transmission does not appear to be very efficient. Nevertheless, the possibility of genetic reassortment between human and avian viruses in humans or other permissive animals (e.g. swine) is a constant threat to the genesis of a highly pathogenic virus that is readily transmissible from person to person. The readiness of influenza viruses to undergo genetic changes is also evidenced by the evolution of a highly pathogenic H5N1 genotype Z that has become the predominant genotype in Asia, which accounts for the major Asian outbreak of avian influenza in 2003–2004. The current epidemic strain of H5N1 also acquired resistance to the antiviral agent amantadine through a mutation in the M2 protein. This worrying finding implied that for practical purposes, the neuraminidase inhibitors (e.g. oseltamivir) are the only viable antiviral alternative for treatment and chemoprophylaxis of human infections. Though the avian influenza viruses are susceptible to neuraminidase inhibitors, their role in clinical management still awaits further studies. In human influenza, these antivirals are most active if given within 48 hours of onset of disease. If this is also true for avian influenza infections, then in practice the antivirals may not have significant impact on the diseases course in endemic areas, since most patients in developing countries are unlikely to receive this relatively expensive antiviral agent at the outset of the disease. Resistance to the neuramindase inhibitor oseltamvir due to the mutation H274Y is beginning to emerge in patients on prophylaxis or treatment for H5N1 infection. This is expected because 18 per cent of the H3N2 infection in Japanese children on treatment with oseltamivir has developed resistance. A higher dose of oseltamivir up to 500mg bid and/or combination with inhaled zanamivir are being considered to improve clinical outcome and minimise resistance. High doses of oseltamivir are well tolerated in adult volunteers but the systemic absorption or lung distribution of inhaled zanamivir could be highly variable. As the H5N1 virus is found in blood, cerebrospinal fluid, spleen and intestine, a very low level of zanamvir may help to promote resistance at these sites and at consolidated lung where the inhaled zanamvir may not reach. At the moment oral oseltamivir at an increased dose should be the treatment of choice. An extended duration of therapy to two weeks should be given till neutralising antibody has developed.

FUTURE CONTROL

Despite intensive research and some phase one clinical trials, there is still no commercially available vaccines against avian influenza viruses for human use. The efficacy of such vaccines, if they were eventually available, may be hampered by the rapid antigenic changes which are common to all influenza viruses. Prevention of human infections due to avian influenza ultimately depends on control of the disease among the poultry. Proper biosecurity measures in animal husbandry, surveillance of the disease, segregation of humans and animals, and slaughtering of flocks in cases of outbreaks. These measures, unfortunately, are largely not practised in parts of the world where the disease is endemic. A coordinated international and regional effort is necessary to prevent, or at least delay, avian influenza as the next influenza pandemic. All countries should have their plan for pandemic preparedness. Stockpiles of antiviral, diagnostic tests and vaccine stored under WHO should be sent to the site where first cases of human to human transmission are detected in order to halt a pandemic.

Disease control in poultry is central to the control of human disease. No vaccines are available currently, and rapid viral genetic change may limit the value of any developed.

KEYPOINTS

- Avian influenza and SARS are two zoonotic (spread directly from animal to humans) viral infections capable of causing epidemics or pandemics with serious mortality.
- The influenza viruses (A, B and C) have an RNA genome and belong to the *Orthomyxoviridae* family of viruses. The largest natural reservoir of influenza A virus is in aquatic birds and these viruses are the avian influenza viruses.
- Influenza viruses readily undergo antigenic change making the effectiveness of vaccines short-lived.
- Most outbreaks of human infection have occurred in South East Asia, but an outbreak has also occurred in the Netherlands.
- Early recognition of avian influenza is important, but there are no specific features of the illness other than a history of contact with infected birds. Anyone with an unexplained temperature above 37·5°C, respiratory symptoms, or systemic symptoms such as aching muscles, should be regarded as having an ILI.
- Avian influenza viruses do not yet pass readily from one human to another, but this may not always be the case and WHO recommendations should be followed.

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