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Avian influenza in humans

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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. These range from cowpox, monkeypox, and rabies, which have been known to mankind since ancient times, to HIV and the 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 because of 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 envelopes surrounding viruses. To date, 15 HA and nine NA types are recognised, and individual viral strains may have any combination of HA and NA types. Influenza viruses are well known for their ability to undergo antigenic changes (mainly of the HA and NA antigens) at fairly rapid rates. 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 may result in pandemics of influenza.

HUMAN INFLUENZA OUTBREAKS

Human influenza A nowadays is most commonly caused by H3N2 and H1N1, with H1N2 and H3N1 being encountered very rarely. Other serotypes of influenza A viruses can be found in a variety of animals, but the largest natural reservoir is that of aquatic birds which contains all the HA and NA types of influenza A viruses. These are known collectively 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 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 decimated poultry stocks and 18 human cases were documented (six of whom died). The epidemic was halted after 1·5 million poultry were killed 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. This outbreak was caused mainly by the H5N1 serotype and, in contrast to the 1997 outbreak in Hong Kong, was characterised by a high mortality rate. As of 28 January 2005, 55 human cases of H5N1 infection had been documented in the affected areas with 42 fatalities, giving an overall crude case-fatality rate of 76·4% (WHO, accessed on 1 March 2005). Most of these human infections occurred in Thailand and Vietnam, and one fatal case was recently reported in Cambodia. A clear history of contact with infected poultry was present in most patients. The fulminant nature of the infection could be attributed to a marked inflammatory response to the infection, the so-called 'cytokine storm'. Whether co-administration of an effective antiviral agent with immunomodulators would result in better treatment 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 region to date.

Another major outbreak of human infection due to avian influenza occurred in the Netherlands in 2003. The causative virus was influenza A H7N7, and 89 virologically

documented cases were found, with one death in a veterinarian. A recent study, using a modified haemagglutination-inhibition test, however, has suggested that the actual number of people infected may have been much higher, as the seroprevalence of H7 antibodies to an infected poultry worker among household contacts approximated 59%. Unlike the H5N1 outbreak in Asia, the H7N7 outbreak was characterised by a much lower mortality rate (0·01%) and many of the cases 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.

IDENTIFICATION OF DISEASE

The two most common clinical manifestations in humans due to 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 an uncomplicated ILI, while both H7N7 and H5N1 infections have resulted in severe disease, especially with the latter. Mortality associated with Reye's syndrome was described in H5N1 infections following the use of aspirin in the 1997 Hong Kong outbreak. Gastrointestinal manifestations including diarrhoea were also noted in the 1997 Hong Kong outbreak and the 2004 Vietnam outbreak. Unusual manifestations including 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, 6–17) in the recent Vietnam outbreak.

Since there are no specific signs and symptoms of human avian influenza, apart from contact history with infected birds, early diagnosis and commencement of antiviral therapy remain the cornerstones 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 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 pulmonary consolidation and/or chest radiograph. Those with positive signs are managed as cases of acute community-acquired pneumonia. They are also screened for epidemiological risk factors 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

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 not be avoided to minimise risk of nosocomial spread.
- High flow oxygen mask, non-invasive ventilation should only be used with strict infection precautions.

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 and ducks) 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 amatadine through a mutation in the M2 protein. This worrying finding implied that, for practical purposes, the neuraminidase inhibitors 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 awaits further studies. In human influenza, these antivirals are most active if given within 48 hours of onset of disease. If this is true for avian influenza infections, then in practice the antivirals may have no significant impact on the disease in endemic areas, since most patients in developing countries are unlikely to receive this relatively expensive antiviral agent at the outset of the disease. Although resistance to neuraminidase inhibitors has not been described in avian influenza viruses, the emergence of such resistance in human influenza viruses (e.g. in Japan) means that it is probably only a matter of time before we encounter such resistance in the avian viruses. Aspirin should be avoided as this may cause Reye syndrome in the paediatric patients.

FUTURE CONTROL

Despite intensive research, there are 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 poultry: proper biosecurity measures in animal husbandry, surveillance of the disease, segregation of humans and animals, and culling of flocks in case of outbreaks. These measures, unfortunately, are not always practicable in all parts of the world where the disease is endemic, especially if there is a lack of political commitment and if this entails major economic repercussions to the community. A coordinated international and regional effort is necessary to prevent, or at least delay, avian influenza as the next influenza pandemic.

KEYPOINTS

- Avian influenza and SARS are two zoonotic (spread directly from animals to humans) viral infections capable of causing epidemics or pandemics with serious mortality.
- The influenza viruses (A,B,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 changes 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.
- 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.

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