Contemporary Issue

Avian Flu – A Bird’s Eye View

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Abstract
Influenza A (H5N1) virus infects a variety of animals, birds and humans. Present ongoing epidemic of this deadly virus in poultry livestock and humans has had major economic and health repercussions. It causes a wide spectrum of clinical features in human beings ranging from mild respiratory tract infection to a fatal pneumonia leading to multi organ system failure. Diagnosis is mainly clinical, aided by lab features like lymphopaenia and non-specific chest X-ray findings. Diagnostic tests are being evolved for rapid and specific diagnosis. Management is mainly symptomatic. Newer and effective antivirals, i.e. amantadine, zanamivir etc are also being tried.

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Introduction
The year 2004 opened on the sinister note of widespread occurrence of ‘Bird Flu’, which if not curtailed and contained has the propensity to emerge as a major pandemic, which would endanger millions of poultry live-stock and humans effecting South Asian economy adversely. Recent outbreaks of avian influenza A (H5N1) in poultry throughout Asia have had major economic and health repercussions. First documented human infection with avian influenza virus was in 1997 in Hong Kong where 18 people were affected out of which 4 died. First case was a three year old child who presented with predominant gastrointestinal symptoms and subsequently died five days after admission due to multi organ dysfunction [1].

Present epidemic
By 30 Jan 2004, 10 Asian countries had reported highly pathogenic avian influenza (HPAI), in an unprecedented spread of the disease in the poultry population. These countries were Cambodia, China, Hong Kong, Indonesia, Japan, Laos, South Korea, Thailand, Vietnam and Pakistan [1]. The occurrence of this disease in humans and reports of death awakened the health authorities globally to the impending disaster. Not only this virus is deadly to human beings, it can also have a devastating impact on booming economies. In a rough estimate severe acute respiratory syndrome(SARS) epidemic costed South East Asian countries 59 billion dollars in 2003 while it is feared that bird flu is going to have even more devastating financial impact [2].

‘Bird Flu’ is an infectious disease of birds caused by type A strains of influenza virus. It was first identified in Italy more than 100 years ago and occurs worldwide [2].

Microbiology
Influenza viruses are members of Orthomyxoviridiae family having genus ‘A’, ‘B’ and ‘C’, which are based on antigenic character of nucleoprotein (NP) and matrix protein (M) antigens. Influenza ‘A’ is further subdivided into strains depending on surface haemagglutinin (H) and Neuraminidase (N) antigens. In human infections usually H1, H2, H3 and N1, N2 are implicated. More than 15 subtypes of H and 9 subtypes of N are recognized [3]. Many of these affect birds, the common lethal ones being H5 and H7. Different strains are denoted as H1N1, H2N2, H3N1, H5N1, H5N2 etc depending on the combinations of these two antigenic variants. The influenza viruses are irregularly shaped spherical particles and have a lipid envelop from the surface of which the ‘H’ and ‘N’ glycoproteins project. ‘H’ is the site by which viruses bind to cell entry. ‘N’ helps in shedding of Progeny virions from the infected cells [3]. The structure of Influenza virus is depicted in Fig. 1.

All influenza viruses are genetically labile. This helps them in eluding the host defences. The viruses lack the ability to proof read and repair the errors which occur
during cell division. These uncorrected errors change the genetic composition of viruses leading to new antigenic variants. These constant, permanent and usually small changes in antigenic composition constitute the phenomenon of “drift”. However, a second and a more dangerous phenomenon occurs in which influenza viruses, including subtypes from different species can swap or re assort genetic material and merge. This is known as “shift” and can result in a subtype different from both parent viruses. These variants can cause highly lethal pandemic as the population would have no immunity against them and available vaccines would be ineffective [4]. Such antigenic shifts can occur when humans live close to domestic poultry and pigs. Pigs, being capable of harbouring both mammalian and avian strains of influenza virus, can serve as “mixing vessels” in which scrambling of genetic material can occur. Evidence is also emerging that even humans can serve as mixing vessels for almost 15 avian influenza virus subtypes. Once this mixing occurs, the virus acquires the capacity of human-to-human transmission [2].

**Clinical Features**

Avian influenza is an infectious disease of birds caused by the influenza A virus, causing wide spectrum of symptoms ranging from mild illness to a highly contagious rapidly fatal illness known as highly pathogenic avian influenza. Migratory waterfowl, most notably wild ducks, are the natural reservoir of avian influenza viruses and are also resistant to the infection. Through them transmission occurs to domestic poultry which are very susceptible. From here on, the virus can either jump the species and infect close handlers or be transmitted after mutation in “mixing vessels” as already described. In the humans, the disease manifests like influenza and the course depends on the immune status of the host [5]. The disease cycle is as illustrated in Fig. 2.

Hong Kong, in 1997, became the first country where avian flu was reported to have affected humans. During that epidemic, 18 proven cases occurred, of whom 6 died [6]. The detailed clinical profiles of 12 of those patients are given in Table 1. In a recently published article on clinical presentations of 10 proven patients with Influenza A (H5N1) infection from Vietnam, authors concluded that Influenza A (H5N1) infection, characterized by fever, respiratory symptoms, and lymphopenia, carries a high risk of death [7]. Although in all these 10 cases, the infection appears to have been acquired directly from infected poultry, the potential exists for genetic reassortment with human influenza viruses and the evolution of human-to-human transmission.

The presentation in humans is with flu like symptoms, however viral pneumonia, acute respiratory distress and other complications occur more frequently. Since the symptoms are non-specific the occurrence of flu like symptoms in the setting of exposure to poultry livestock should raise suspicion and investigations should be carried out for diagnosis. Transmission occurs either through direct handling of these birds, coming in contact with excreta or through live poultry markets, and consuming raw infected eggs. Proper cooking of meat and boiling of eggs kills the virus very rapidly.

**Diagnosis**

Diagnosis is accomplished by isolation of the virus from throat swabs, nasopharyngeal washes or sputum. Chick embryo inoculation can demonstrate the virus in
48 to 72 hrs. Rapid diagnostic tests are available which can test the virus within 30 minutes [5]. Serological methods require comparison of antibody titres in samples obtained during acute illness and those obtained 10-14 days later. Fourfold or greater rise is diagnostic of acute infection. Rapid antigen testing, RT-PCR and immunofluorescence studies can also be used.

Management

Management is basically symptomatic and supportive. Acetaminophen for relief of headache, myalgia and fever may be considered. Use of salicylates, especially in children should be avoided because of fear of Reye’s syndrome. Cough suppressants like codeine preparation might be required. Specific antiviral therapy, if indicated, should be started as early as possible, for any beneficial effect. M2 ion-channel inhibitors, like amantidine and rimantidine, are the usual antiviral drugs used for treating these patients. They work by interfering with the replication of influenza viruses. Either can be used in the dosage of 200 mg/d for 3-7 days. The dose, however, has to be reduced in patients with renal dysfunction.

The other group of drugs which are being increasingly utilized are the neuraminidase inhibitors e.g. zanamivir and oseltamivir. These drugs exert their action by interfering with the release of viruses from infected cells. Zanamivir is used as an inhalation in the dose of 10 mg twice a day for 5 days. Oseltamivir is used orally 75 mg twice a day for 5 days. A nucleoside analogue, ribavirin, has also been reported to show some benefit when used as an aerosol. The role of vaccines is well established in groups exposed to poultry live-stalk or those who have a predisposition to acquiring the traditional influenza infection. It can also be helpful in lowering the availability of these viruses in the host and thereby lowering the possibility of mixing with other strains. Vaccine against a new strain would take more than 6 months for development and clinical use.

Factors associated with severe disease are (a) older age group (b) delay in hospitalization (c) lower respiratory tract infections (d) low total leucocyte counts and lymphopenia during presentation [6].

An immediate priority in any outbreak is to halt the
spread of disease in poultry population by culling and proper disposal of the carcass, and vaccination of poultry and persons at high risk of exposure. Workers involved in handling and slaughtering live stalk must be protected by proper clothing. These workers will need antiviral drugs as prophylactic measure [2].

Conclusions

The avian influenza virus clearly has the ability to jump species barrier and cause devastating illness in humans. Widespread efforts to control the poultry outbreak and increased surveillance among poultry and humans should therefore be our highest priority. The clinical findings (fever, shortness of breath, cough, diarrhoea, lymphopenia) and a history of close contact with poultry may be more helpful in identifying patients with influenza A (H5N1) infection than the results on rapid diagnostic tests for influenza.

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