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Viral lung infections and the potential for a human pandemic

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Abstract

Some newly emerging viral lung infections have the potential to cause large outbreaks of severe respiratory disease amongst humans. In this contribution we discuss infections by influenza A (H5N1), SARS and Hanta virus. The H5N1 subtype of avian influenza (bird flu) has crossed the species barrier and causes severe illness in humans. So far, 328 humans in twelve countries have contracted the disease and 200 have died. The young are particularly affected. Oseltamivir is the antiviral drug of choice and should be given as early as possible. Patients require supportive care, often including invasive ventilation. If H5N1 develops the ability to transmit efficiently between humans, an influenza pandemic is likely. Severe acute respiratory syndrome (SARS) was first seen in China in 2002. The outbreak was finally contained in 2003, by which time 8098 probable SARS cases had been identified with at least 774 deaths. The virus was identified in 2003 as belonging to the coronaviridae family. SARS is transmitted between humans and clusters have been seen. The mainstay of treatment is supportive. Various antiviral agents and adjunctive therapies were tried but none were conclusively effective. Hanta virus is an emerging cause of viral lung disease. In 1993, a new species of Hanta virus was recognized, after an outbreak of a new rapidly progressive pulmonary syndrome in the US, 465 cases of ‘Sin Nombre’ virus have now been seen in the US with a mortality rate of 35%. Many of the confirmed cases had contact with rodents (the major host of hanta viruses). Treatment is supportive, as there is no specific therapy.

Keywords avian influenza; Hanta virus; human pandemic; H5N1; outbreak; SARS – CoV; severe acute respiratory syndrome; Sin Nombre virus; viral lung infections

Avian influenza

Avian influenza infection in birds

Avian influenza (bird flu) is caused by influenza A viruses and is a notifiable disease. It is highly contagious, with mortality rates dependent on the virus subtype and the host bird immunity. The influenza virus was first identified in Italy in the late 19th century. It is spread between birds by either ingestion or inhalation.

Wild birds are the natural host/reservoir for influenza viruses. However, other species can be susceptible. For example, domestic poultry are often subject to rapidly progressive disease with high mortality rates. Migratory birds, by contrast, can be relatively resistant to infection, despite carrying the virus.1

The subtypes of influenza which cause disease in birds are named according to the haemagglutinin and neuraminidase proteins carried by the virus; 16 haemagglutinins and 9 neuraminidases are recognized. Viruses causing mild disease are referred to as low pathogenic avian influenza viruses (LPAI). Symptoms include ruffled feathers and decreased egg production. Those causing serious illness are referred to as highly pathogenic avian influenza (HPAI) viruses. Mortality rates may be up to 100% at 48 hours.2 Features of the severe disease are oedema of the head, cyanosis of the comb and wattles (neck and throat), diarrhoea, loss of appetite and respiratory distress.1 There may be massive internal haemorrhage which leads to the term ‘chicken ebola’. So far the HPAI viruses have been H5 or H7 subtypes.2

H5N1 can lead to highly virulent disease. In 2003/4, outbreaks of H5N1 in Europe and South East Asia led to the destruction of millions of birds either from disease or due to mass culling (in attempts to eradicate the virus from poultry stocks). The H5N1 subtype of avian influenza has also been seen in the UK, recently in Suffolk in February 2007. The outbreak in Dereham, Norfolk, in April 2006 involved the less virulent subtype H7N3.1

Avian influenza causing human infection

Influenza viruses rarely cross the species barrier and those that do usually cause mild disease. Four strains of avian influenza virus have now been shown to cause infection in humans: H5N1, H7N3, H7N7 and H9N2. Of these, H5N1 is unusual in that it has not only crossed the species barrier, but also causes severe disease.

Epidemiology of human H5N1 disease

Hong Kong saw the first outbreak of human infection with H5N1 avian influenza in 1997. Since then (up to September 2007), 328 humans in 12 countries have been infected and of these 200 (61%) have died.3 Of these, 106 cases were in Indonesia and 100 cases in Vietnam.3 The other cases have been in Thailand, Cambodia, China, Turkey, Iraq, Azerbaijan, Egypt, Djibouti, Nigeria and, more recently, Laos.3

Based on data until June 2006, half the patients were aged below 20 years and 90% were aged below 40 years. Cases were seen throughout the year, but incidence peaked during periods correlating with winter and spring in the Northern Hemisphere.5

Clinical presentation and clinical course of human H5N1 disease

Typically, the initial features comprise a high fever (>38 °C) associated with an influenza-like illness. The frequency of other symptoms is listed in Table 1.6 There have been case reports of patients presenting with diarrhoea or encephalopathy ahead of respiratory symptoms.2 The disease is difficult to distinguish from other acute febrile respiratory infections in the absence of epidemiological linkage. A travel, occupational and contact history is therefore very important.7

Patients may deteriorate rapidly, typically developing signs and symptoms of pneumonia 5 to 7 days from symptom onset.
Radiological changes include extensive interstitial infiltration, focal consolidation with air bronchograms and lobar collapse. Progression to respiratory failure has been associated with radiographic changes of adult respiratory distress syndrome (ARDS). The development of multi-organ failure portends a high risk of death despite intensive care support.

**Treatment of human infection with H5N1 avian influenza**

Supportive care, including invasive ventilation, is the mainstay of treatment. Mild cases are best managed in the community. Figure 1 shows a basic treatment algorithm. Oseltamivir is the antiviral of choice and should be given as early as possible. There are no trial data to guide dosage requirements. Standard doses used for human influenza A virus infections (75 mg twice daily for 5 days in adults) have been advocated. Higher doses of up to 150 mg twice daily for 7 to 10 days may be required in severe infections.

In patients presenting with pneumonia, antibiotics to cover the usual pathogens implicated in community-acquired pneumonia are also indicated, especially when the diagnosis may not yet be secure. The use of corticosteroids in the event of respiratory failure or ARDS is currently not evidence-based and therefore is not routinely recommended.

**The threat of pandemic H5N1**

The prerequisites for the development of a human influenza pandemic are:

- emergence of a new influenza A subtype to which there is little or no human immunity
- the ability of the new virus strain to cause significant illness in humans and
- efficient human-to-human transmission of the virus.

In the case of H5N1, only the final prerequisite remains unfulfilled. Direct exposure to diseased poultry within one week before illness onset has been associated with H5N1 disease in humans. There has also possibly been some environmental-to-human transmission, such as the contamination of hands from infected fomites and subsequent self-inoculation. Limited, unsustained human-to-human transmission has also been described within family clusters in northern Vietnam.

Should H5N1 acquire the ability to be transmitted from human-to-human efficiently, a pandemic is likely. It could acquire this ability in two ways. Firstly, genetic material could be exchanged between human virus and avian virus (genetic reassortment). Secondly, there could be a more gradual adaptive process whereby the ability of the virus to replicate and be released from human cells increases through small mutations. It is generally thought that these mutations are more likely to occur when there is close approximation of avian and human influenza viruses.

The World Health Organization (WHO) is coordinating the epidemic and pandemic alert response to H5N1 disease. This is the first time that we may be forewarned of a pandemic. Anti-viral drugs, antibiotics, vaccines and adequate planning may yet help to avoid the high toll of human suffering of past pandemics.
Severe acute respiratory syndrome

The first cases of severe acute respiratory syndrome (SARS) were seen in Guangdong province, South China in November 2002. By February 2003, there had been 305 cases and 5 deaths in the province. The disease spread rapidly to Hong Kong and then to 24 other countries. The outbreak was finally contained in July 2003 when 8098 probable SARS cases had been identified with at least 774 (9.5%) deaths. Since 2003, 4 small outbreaks of SARS have been reported, all of which were rapidly contained.

Identifying the virus

The SARS outbreak was initially thought to be caused by a newly emerging influenza virus. Paramyxoviridae viruses and Chlamydia were also suspected and ruled out. In March 2003, the WHO Multicentre Collaborative Network for SARS diagnosis had been formed. By April 2003, the cause had been identified as a new virus belonging to the coronaviridae family, later called SARS-CoV.

Virus transmission

SARS-CoV is transmitted between humans but the pattern of spread has been unpredictable. In some outbreaks, selected cases appeared to affect large numbers of people. It is not known whether these ‘superspreaders’ secreted an unusually large amount of infectious material or whether another unknown factor amplified transmission. In Hong Kong, an unusually large cluster was noted in an estate of high rise flats. The vast majority of cases were seen in one block, in vertically-linked apartments, raising the intriguing possibility of transmission via sewerage or ventilation systems.

Clinical disease

The incubation period is thought to be between 2 and 10 days. Fever was evident at disease onset in 93% of patients with SARS in Hong Kong. Chills, malaise, myalgia and headache were also common in patients with SARS (see Table 2). A productive cough and sore throat were very uncommon.

The symptoms of SARS overlap with other acute febrile respiratory illnesses. Therefore, the key to making a clinical diagnosis of SARS is the establishment of an epidemiological link with a patient with SARS in conjunction with both of the following:

- the presence of pneumonia ‘resistant’ to usual treatment
- the presence of clinical features of SARS (Table 2).

Confirmation of SARS relies on positive serological or reverse transcriptase-polymerase chain reaction (RT-PCR) identification of SARS-CoV.

The disease may progress rapidly. Pneumonia is the main manifestation. Around 20 to 25% of patients developed severe respiratory failure and ARDS. Mortality in those admitted to intensive care is around 25%.

There are no antimicrobial agents of proven value in SARS. Various antiviral agents were tried but none were conclusively effective. The evidence for adjunctive therapies (e.g. interferons, steroids) was similarly equivocal. The mainstay of treatment is therefore supportive.

Infection control

Infection control was of paramount importance in controlling the SARS outbreak. Virus replication is highest at the end of the first week of illness. Early isolation of the patient is therefore effective at reducing transmission. Nosocomial transmission accounted for around 50% of cases of SARS, emphasizing the risk to healthcare workers and the need for appropriate precautions (e.g. gloves, masks, gowns, handwashing). Aerosol generating procedures (e.g. nebulizer use, bronchoscopy, non-invasive ventilation) should be avoided whenever possible.

Hanta virus

Hanta virus, a single-stranded RNA virus of the bunyavirus family, is named after the Hantan River in Korea, where a form of Hanta virus was first isolated in the 1950s. Different Hanta viruses are each carried by different rodent species. Hanta viruses found in Asia predominantly cause haemorrhagic disease with renal syndromes.

In 1993, an outbreak of new rapidly progressive pulmonary syndrome in the South Western US led to a new species of Hanta virus being recognized. Named ‘Sin Nombre’ virus, its major host is the deer mouse. This virus causes a predominantly respiratory illness (HPS – hantavirus pulmonary syndrome), generally without the haemorrhagic and renal syndromes. Since the first outbreak, cases have been reported throughout the US and Western Europe. Between 1993 and March 2007, 465 cases were confirmed in 30 states in the US, 75% of which were from rural areas. The mean age was 38 years (range 10–83 years); 64% of cases were male and the mortality rate was 35%.

In confirmed cases where exposure information was known, 70% had had exposure to rodents via domestic activities, e.g. cleaning in homes showing signs of rodent infestation. Occupational exposure was less common but HPS has been seen in, for example, grain farmers and field biologists. Cases in the UK have also been seen, particularly in returning travellers.

### Table 2

| Symptom of SARS | Number of initial confirmed cases of SARS reporting the symptom (%) |
|-----------------|---------------------------------------------------------------------|
| Fever           | 751/752 (99.9)                                                      |
| Cough           | 460/702 (65.5)                                                      |
| Malaise         | 317/539 (58.8)                                                      |
| Rigors          | 377/732 (51.5)                                                      |
| Myalgia         | 365/752 (48.5)                                                      |
| Shortness of breath | 282/614 (45.9)                                             |
| Headache        | 292/752 (38.8)                                                      |
| Dizziness       | 163/597 (27.3)                                                      |
| Nausea/vomiting | 8/30 (26.7)                                                          |
| Chest pain      | 47/210 (22.4)                                                       |
| Diarrhoea       | 130/647 (20.1)                                                      |
| Anorexia        | 37/188 (19.7)                                                       |

China, Hong Kong, Canada and Singapore

### Table 3

| Symptom of SARS | Number of initial confirmed cases of SARS reporting the symptom (%) |
|-----------------|---------------------------------------------------------------------|
| Fever           | 751/752 (99.9)                                                      |
| Cough           | 460/702 (65.5)                                                      |
| Malaise         | 317/539 (58.8)                                                      |
| Rigors          | 377/732 (51.5)                                                      |
| Myalgia         | 365/752 (48.5)                                                      |
| Shortness of breath | 282/614 (45.9)                                             |
| Headache        | 292/752 (38.8)                                                      |
| Dizziness       | 163/597 (27.3)                                                      |
| Nausea/vomiting | 8/30 (26.7)                                                          |
| Chest pain      | 47/210 (22.4)                                                       |
| Diarrhoea       | 130/647 (20.1)                                                      |
| Anorexia        | 37/188 (19.7)                                                       |
Clinical presentation

HPS presents with an influenza-like illness lasting 3–5 days. Symptoms include high fever, myalgia, headache and tachycardia, often associated with gastrointestinal disturbance. In some patients, after about seven days, the cardiopulmonary phase may abruptly begin. Hypotension develops with progressive non-cardiogenic pulmonary oedema and severe hypoxia (an ARDS-like picture). Patients often need mechanical ventilation and intensive care support. Chest imaging shows rapid progression from minimal pulmonary oedema to severe bilateral interstitial oedema.

Distinguishing HPS from other viral illnesses is difficult. The presence of rashes, conjunctival haemorrhage, peripheral oedema and multi-organ failure make HPS unlikely.

Typical laboratory findings include atypical lymphocytosis and thrombocytopenia. An echocardiogram may show profound ventricular dysfunction. Serological tests for hanta virus (ELISA or PCR) are the definitive tests but may not be widely available.

There is no specific treatment other than supportive care.

Conclusion

Avian influenza, SARS-CoV and Hanta virus (especially Sin Nombre virus) represent newly emerging viral infections capable of causing outbreaks of severe respiratory disease. Avian influenza in particular has the potential to evolve and result in a human pandemic. Epidemiological clues may enable earlier diagnosis of individual cases.

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