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REVIEW

Bird flu: lessons from SARS

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Summary Severe acute respiratory syndrome (SARS) and avian influenza are two important newly emerged infections with pandemic potential. Both infections have crossed the species barrier to infect humans. SARS originated from southern China and spread to many countries in early 2003. The close collaboration of scientists around the world resulted in a rapid identification of the causative agent, and the early isolation of infected cases and meticulous infection control measures were the key to successfully controlling the outbreak of SARS. The first outbreak of human cases of avian influenza was reported in 1997 in Hong Kong. Since 2003, there have been many small outbreaks of human cases around the world, and the reported mortality is greater than 50%. Current evidence suggests that the human-to-human transmission of avian influenza is rather inefficient, but mutation might occur in the future resulting in improved transmission and possibly a pandemic in humans. As with the outbreak of SARS, the development of sensitive and accurate early diagnostic tests is extremely important for successful control of the outbreak at source. The availability of isolation facilities, the stockpiling of antiviral agents and effective and safe vaccination will be extremely important in minimising the damage of a new influenza pandemic.

Severe acute respiratory syndrome (SARS) and avian influenza are the two newly emerged infections with pandemic potential that have arisen from Asia in the new millennium. With modern and efficient air travel, SARS originated from southern China and rapidly transmitted to more than 30 countries in early 2003. In just 6 months, there were more than 8000 infected individuals, with over 700 deaths worldwide.[1] The other infection resulting in equally deadly consequences was caused by a highly pathogenic avian influenza A (H5N1) virus. It was first described in a mini-outbreak in Hong Kong in late 1997. The outbreak came to an end with the slaughter of all the poultry in farms and markets in Hong Kong. Since early 2003, there have been many reports of outbreaks of this infection in wild birds and domestic poultry in many countries.

Human-to-human transmission has been relatively inefficient such that no major human outbreaks have occurred. However, more than 240 human cases and 140 deaths have been reported since 2003.[2] In adults, SARS usually results in rapidly progressive disease, and approximately 20% of infected adults develop respiratory failure.[3,4] Children infected with SARS usually develop symptoms of mild upper respiratory infection or uncomplicated pneumonia,[5–7] but the reported mortality rate for children infected with avian flu has been close to 50%.[8] In this paper, we will review the lessons we have learnt from the outbreak of SARS to illustrate how we can prepare for the possible major outbreak or even pandemic of avian influenza infection in humans.

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SARS: EPIDEMIOLOGY. CLINICAL PRESENTATION, DIAGNOSIS AND TREATMENT

The outbreak of SARS started in late 2002 in Guangdong Province in southern China, the infection having been brought to Hong Kong by an infected physician from mainland China.[5,7] While staying in a hotel in Hong Kong, the infected physician managed to infect many other guests or visitors. These infected individuals then spread the diseases from Hong Kong to Vietnam, Singapore and Canada when they returned to their home countries. This incident illustrates how a new infection can nowadays spread quickly from one region to another by efficient air travel.

With modern molecular biological techniques and the close collaboration of scientists from different laboratories, the causative agent was quickly identified to be a newly described strain of coronavirus (SARS-CoV).[8–10] Studies of wild animals and animal traders have provided evidence that this virus most likely originated from wild animals including palm civet and raccoon dogs[11] and jumped the species barrier to infect humans.

Pre-pubertal children tend to develop symptoms of mild upper respiratory tract infection, while adolescents may develop severe pneumonia with progressive deterioration leading to respiratory failure.[7] The most important clue to the diagnosis of SARS in children is a history of exposure to infected adults.[12] The incubation period is between 5 and 10 days. For many adult and paediatric patients, their initial chest radiographs may be normal, while early thoracic computer tomography may show poorly defined, ground-glass opacification of the lung in the subpleural areas.[4,7]

The typical course of illness in infected adults has been described as triphasic.[3] The initial phase is characterised by fever, chills, myalgia, cough and other constitutional symptoms. The second phase is associated with progressive clinical and radiological deterioration, and increasing oxygen requirements. The clinical progression is believed to be due to an exaggerated host immune response to the SARS-CoV. About 25% of patients will progress further to respiratory failure in the subsequent 2 weeks. Gradual recovery is expected in over 80% of patients by 3–4 weeks into the illness. Those patients with more severe disease may show the typical laboratory findings such as lymphopenia, thrombocytopenia and an elevation of liver enzymes.[7] A community-wide serological screening of 12,000 people in Hong Kong found an extremely low rate (0.008%) of asymptomatic SARS infection.[13] On the other hand, a recent case-control study in children did not reveal any clinical or initial laboratory results that might reliably differentiate SARS from pneumonia resulting from other viral or bacterial aetiologies.[12]

In the early period of the epidemic, the major difficulty was the lack of a reliable and sensitive test for this infection. Serological testing is only useful for subsequently confirming the diagnosis. With a sequential improvement in microbiological and molecular techniques, early diagnosis can be made by reverse transcription-polymerase chain reaction to detect the virus in respiratory secretions and plasma.[14] Such early diagnosis will enable us to put these patients in the appropriate type of isolation facility, which is likely to be in high demand during outbreaks of similar infections.

Despite the many studies that have been conducted in adults and children, the exact pathophysiology of SARS remains unclear. The most intriguing aspect is the marked discrepancy in clinical severity between infected adults and young children. Approximately 25% of adults will deteriorate progressively to respiratory failure requiring intensive care support,[14] while fewer than 1% of infected children develop respiratory failure requiring mechanical ventilation.[15]

It has been postulated that the SARS-CoV may behave like H5N1 influenza virus and act as a potent inducer of proinflammatory cytokines. There is evidence to show that H5N1 influenza may upregulate the production of various cytokines such as tumour necrosis factor-α.[16] Such a cytokine storm may be partly responsible for such severe multiorgan involvement in adult patients. Longitudinal studies in children infected with SARS-CoV, however, have not revealed any significant elevation of proinflammatory cytokines such as interleukin-6 and tumour necrosis factor-α.

A larger longitudinal study has also been performed in adult patients, the results showing a significant elevation of the neutrophil chemokines interleukin-8, monocyte chemoattractant protein-1 and T-helper cell chemokine interferon-γ-inducible protein-10.[17] This process may lead to a recruitment and accumulation of macrophages and neutrophils, causing inflammatory damage to the lung parenchyma and other tissues or organs. The important implication of these studies is that one may need to use different treatment approaches for SARS infection in adults and children as their immune systems may respond differently to the same infection.

The treatment of SARS in paediatric patients is largely supportive as the majority of patients will recover uneventfully.[3] Currently, there is no proven effective treatment for SARS. Although a variety of antiviral agents along with steroids were used during the outbreak in 2003, there has not been any proper clinical trial to formally evaluate the various forms of treatment.[14] For more severely affected adolescents, treatment was largely based on the adult experience. Since SARS was shortly found to be caused by a coronavirus, ribavirin was widely used in treating adult cases in Hong Kong. Autopsy findings in fatal adult cases revealed diffuse alveolar damage, hyaline membrane formation and interstitial inflammatory cell infiltrates.[4] This led to the suggestion that an exaggerated immune response might be the possible pathophysiological process leading to the severe damage of the lungs and other organs.

Early anecdotal experience in adult patients seemed to suggest that a combination of the systemic corticosteroid and ribavirin might to be useful in controlling the disease. As a result, both adults and severely affected adolescents were treated with steroids and ribavirin. However, subsequent experimental data revealed that ribavirin was most likely ineffective against SARS-associated coronavirus.[18] The use of corticosteroids with this possibly ineffective antiviral agent in patients with coronavirus pneumonia can be detrimental. In fact, many adult patients eventually died of other nosocomial infections,[19] and such infections might be related to the excessive immunosuppression associated with the use of high-dose corticosteroid treatment. Furthermore, 15% of adult patients in one series developed avascular necrosis of the femoral head, and 6% had bilateral involvement.[19] It is important to note that steroids and ribavirin were not used in many other centres during the outbreak in 2003, and the mortality rates of their patients were similar to or better than that of patients treated with such a combination.[20,21]

When we are faced with a new disease, especially one as deadly as SARS, physicians are often tempted to try new treatments based on anecdotal experience. The argument of trying new therapy is that we should not be withholding potentially useful treatment. However, we must remember the principles of evidence-based medicine as we may be protecting our patients by withholding potentially harmful treatment too. Although it may not be easy when we encounter a large number of patients affected by a new infection, one should test any new and potentially useful treatment modality in a systematic way to document its efficacy before recommending it for all patients.

Although the majority of pediatric patients recovered uneventfully, a follow-up study of 47 patients revealed that 34% of them had radiological abnormalities such as ground-glass opacification and air-trapping as detected on high-resolution computed tomography of the lungs.[22] The use of methylprednisolone and a lower lymphocyte count on admission were predictive of abnormal high-resolution computed tomography findings, and these two features may simply be markers of more severe disease in the acute stage. Furthermore, a study of 34 children revealed impaired peak oxygen consumption and lower oxygen uptake efficiency at 15 months' follow-up.[23] The mechanism resulting in such a reduction in aerobic capacity remains unclear, and further follow-up study is necessary to determine whether such impairments might improve with time.

HUMAN INFECTION WITH AVIAN INFLUENZA

Avian influenza in humans has been another major global health threat. Although this infection commonly affects many wild birds and domestic poultry, the virus is species-specific and dose not usually cross the species barrier. There has always been the worry that reassortment of the viral genome might result in severe human infections as in those pandemics which occurred in 1957 and 1968. In Asia, the risk of reassortment is particularly high where large populations of domestic poultry and pigs are living in close proximity to humans. Furthermore, live birds and poultry are sold in the markets, thereby increasing the chance of the spread of infection from sick birds to humans.

One of the most devastating pandemics in human history was the influenza outbreak of 1918, which killed at least 20 million people worldwide. Recent molecular analysis of the complete genome of the 1918 virus revealed that this virus was not a reassortment strain but more likely to be an avian virus that had adapted to infect humans.[24] This is particularly threatening as the recent outbreak of human cases of avian influenza may possibly lead to a new pandemic.

The first outbreak of human disease resulting from avian influenza occurred in 1997 in Hong Kong. There were a total of 18 cases with six deaths.[25] Since late 2003, there have been a series of reports confirming outbreaks of avian influenza (H5N1) in many countries in Asia, Europe and Africa. Up until September 2006, more than 240 human cases and 140 deaths had occurred.[2] In contrast to SARS, the reported morbidity and mortality for human cases of avian influenza are very high in both adults and children.[8] Current evidence suggests that the transmission of avian influenza between humans is rather inefficient, but the recent report of probable person-to-person transmission highlights the importance of preparing ourselves for the potential of new epidemic.[26]

Epidemiology

The first case of H5N1 infection was reported in Hong Kong in May 1997. Shortly before the outbreak of human infection of avian influenza, there were reports of outbreaks of fatal avian influenza in chicken farms in the northwestern part of Hong Kong.[27] Subsequent molecular analyses revealed that the H5N1 virus isolated from humans showed more than 99% sequence homology to the avian isolates.[28] This suggests a direct chicken-to-human cross-species transmission of the virus without involving an intermediate host as a 'mixing vessel'.

Epidemiological investigation of the 1997 outbreak revealed that exposure to live poultry within a week before the onset of illness was associated with disease in humans.[29] There has been a recent report of probable person-to-person transmission to two family members who took care of an infected girl.[26] However, extensive serological studies of health-care workers exposed to infected human cases suggests that human-to-human transmission is relatively inefficient. Furthermore, surveys in Vietnam and Thailand have not revealed any evidence of asymptomatic infections among the contacts of index cases.[30,31] Although these early data may be reassuring, they do not exclude the

possibility of a progressive mutation of the H5N1 strain leading to adaptation in the human host and improved transmission among humans.

Clinical presentation and diagnosis of avian influenza

Our current knowledge of the clinical presentation of human H5N1 infections is primarily based on the reported cases of hospitalised patients and may not truly represent the full spectrum of the illness. The incubation period of avian influenza (H5N1) has been reported to be 2–8 days.[8] Most cases have been previously healthy children or adults. The common presenting features are fever and symptoms of respiratory tract infection, including cough, sore throat and rhinorrhoea. Similar to other influenza infections, headache, myalgia, vomiting and sputum production have also commonly been reported. The disease usually progresses rapidly within the first week to respiratory failure.[8,27]

The initial radiological findings include multifocal or patchy infiltrates and segmental or lobar consolidation. As the patients progress to respiratory failure, the chest radiographs show diffuse, bilateral ground-glass consolidation. Many patients develop multiorgan failure resulting in death in the second week. The median time from the onset of illness to respiratory failure has been reported to be range from 4 to 13 days. Laboratory studies have typically revealed lymphopenia, thrombocytopenia and elevated aminotransferase levels. Increased risk of mortality has been reported to be associated with marked lymphopenia.[32] The laboratory diagnosis can be made by viral isolation or the detection of H5-specific RNA by a molecular method.

The reported mortality is similar in adults and children, ranging from 50% to 100%, which is in marked contrast to the rather benign nature of SARS in affected children and the relatively much more severe disease in adults.[3,4] Similar to the management of SARS, physicians have to maintain a high index of suspicion for cases of unexplained severe pneumonia, particularly when there is possible exposure to wild birds and poultry.

Pathogenesis and management of avian influenza

With other human influenza A diseases, severe cases or fatal cases are usually due to underlying debilitating or co-morbid conditions such as cardiovascular or pulmonary diseases. Human avian influenza infection, however, is a very severe disease in previously healthy adults and children. The exact pathophysiological mechanism responsible for the severity of H5N1 disease in humans remains unclear.

It has been postulated that H5N1 virus can activate multiple pathways of innate immunity resulting in elevated levels of various cytokines and chemokines.[33] With such uncontrolled upregulation of many cytokine pathways, severe pneumonia and multiorgan damage can develop. Reports of post mortem examination have showed diffuse severe alveolar inflammation, interstitial lympho-plasmacytic infiltration, and scattered histiocytes showing reactive haemophagocytic activity. Examination of the bone marrow and spleen has also shown similar reactive haemophagocytic activities. It is still unclear what mechanisms are responsible for this cytokine-driven haemophagocytic syndrome.[33] Further studies are needed to clarify the precise pathophysiolgical mechanism resulting in such severe disease and to shine light on possible effective treatment for this potentially fatal infection.

As the mechanisms leading to severe organ damage in avian influenza are unknown, the optimal treatment for human H5N1 infections is still unclear, and the current treatment is primarily supportive. Proper isolation is of paramount important in order to prevent possible spread of the disease. Since many patients will deteriorate rapidly within the first week of illness, patients suspected or proven to have H5N1 influenza should be hospitalised in facilities with strict isolation.

Current practice is to provide empirical treatment with neuraminidase inhibitor while waiting for confirmatory testing.[8] Both oral oseltamivir and inhaled zanamivir have been documented to be beneficial in human influenza.[34–36] Clinical experience in human avian influenza infection has suggested that early treatment may provide greatest clinical benefits.[32] Although the approved dose of oseltamivir for adults is 75 mg twice daily for 5 days, a higher dosage and longer duration have been used for more severe influenza diseases. The exact dosage and duration of treatment for avian influenza are not known, and proper prospective trials are needed to evaluate the various regimes for the treatment of human avian influenza infections.

Finally, prevention is always the preferable option for any infectious disease. There have been international collaborative efforts to try to manufacture effective vaccines against avian influenza. In fact, two phase I randomised clinical trials have reported the immunogenicity and safety data on inactivated split-virion[37] and adjuvant whole-virion vaccines for avian influenza (H5N1).[37,38] A two-dose regimen with both vaccines resulted in a haemagglutinin-inhibition seroconversion rate of 67% and 78% respectively among the adult volunteers. The availability of avian influenza vaccines will provide the ultimate solution to combat this potentially fatal infectious disease.

CONCLUSION

The SARS outbreak in 2003 shocked the world, but the successful identification and control highlighted the importance of international collaboration and implementation of public health measures in controlling the spread of a newly emerged infection. Early case recognition, the meticulous isolation of infected cases and the prevention of spread were the key to control the infection. The world has learnt

many important lessons in the control of the SARS outbreak. Unlike SARS, the transmission of avian influenza between humans is relatively inefficient. It is highly likely that further mutation of the avian strain will result in more efficient transmission. The control of trading and the human consumption of wild animals appear to be important in preventing the re-emergence of SARS. With modern air travel, containment of the infection within a country or region has become much more difficult.

The control of avian influenza is more challenging than that of SARS, as the natural reservoirs of avian influenza are many species of birds and domestic poultry. Furthermore, many species of birds can carry the virus without any apparent signs of illness. The occurrence of many mini-outbreaks and possible human-to-human transmission gives us forewarnings of a possible pandemic. Eventually, mutation of the avian virus may occur, resulting in a strain that is very efficient in transmission among humans, and a pandemic resulting in significant global morbidity and mortality may become a reality.

To reduce the impact of such a pandemic, we will need to prepare ourselves for the availability of isolation facilities, the stockpiling of antiviral agents and the development of effective and safe vaccination. Clinicians have to be alerted to unusual clusters of severe pneumonia, especially in the presence of epidemiological links such as recent exposure to wild birds and poultry or travel to endemic areas. The development of sensitive and accurate early diagnostic tests is a top priority for the successful control of the outbreak at its source. The outbreak of SARS has taught us that the effective isolation of infected cases and border control will be of paramount importance to minimise the impact of avian influenza when outbreaks of human cases do occur. With all the important lessons learnt during the SARS outbreak, it is hoped that we will be able to minimise the damage of a new influenza pandemic.

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