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Newly emerged respiratory infections – SARS and H5N1

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ABSTRACT Two newly emerged respiratory viruses, SARS-CoV and the highly pathogenic avian influenza A H5N1 virus, have arisen in Asia at the turn of the millennium. They both have the potential to cause global pandemics, facilitated by modern high-speed international transportation. Molecular studies suggest that SARS-CoV could be transmitted to humans from civet cats and other game animals consumed as a culinary delicacy. The H5N1 virus appears to be endemic in bird and poultry populations in Asia, with sporadic transmission to humans. Both SARS-CoV and H5N1 begin with a non-specific influenza-like illness, progressing rapidly to severe pneumonia and ARDS. Although various antiviral and immunomodulatory agents have been tried, or postulated to be useful, none has been proven effective by RCTs. Treatment remains supportive and the mortalities are high for both conditions. No vaccine has yet been approved for either infection, although infection control measures have been found to be effective in hospital settings. While all known chains of person-to-person transmission of SARS were broken in July 2003, a few small pockets of outbreak have occurred since, related to laboratory accidents and contact with game animals. The World Health Organisation has consistently warned of a H5N1 pandemic, and the medical community needs to stay vigilant. Minimising human contact with potentially infected animals, sound infection control measures in hospitals, farms, and markets, and prompt isolation of suspected cases are the mainstays in preventing large-scale outbreaks for SARS and H5N1.

KEYWORDS Avian influenza, coronavirus, H5N1, SARS, viral pneumonia.

LIST OF ABBREVIATIONS Acute respiratory distress syndrome (ARDS), bronchiolitis obliterans organising pneumonia (BOOP), haemagglutinin (HA), high resolution computed tomography (HRCT), immunoglobulin G (IgG), neuraminidase (NA), randomised controlled trial (RCT), reverse-transcriptase polymerase chain reaction (RT-PCR), ribonucleic acid (RNA), severe acute respiratory syndrome (SARS), severe acute respiratory syndrome-associated coronavirus (SARS-CoV), World Health Organisation (WHO)

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SEVERE ACUTE RESPIRATORY SYNDROME

Epidemiology

The 2002–03 SARS epidemics began in Guangdong Province, China, and spread to Hong Kong, Vietnam, Singapore, Canada, and other parts of the world. Between November 2002 and July 2003, 8,096 persons were infected altogether. Of these, 774 died from SARS.

SARS-CoV and its transmission

Severe acute respiratory syndrome is caused by the SARS-associated coronavirus, which is an RNA virus that has fulfilled the Koch's postulates for causation. Coronaviruses isolated from civet cats and other game animals in China have remarkable sequence homology with SARS-CoV, suggesting that humans might have acquired the infection from these animals. Severe acute respiratory syndrome-associated coronavirus appears to spread from human-to-human mainly by droplet transmission. Viral RNA is also detectable in stool for prolonged periods. Fomites and faeces are possible contributors to its spread. Airborne transmission might also have contributed to a large-scale outbreak in Amoy Gardens, a residential complex in Hong Kong. Prolonged viral shedding from the nasopharynx and stool, particularly during pyrexia, may explain the risk of nosocomial transmission.

Clinical and laboratory features

The incubation period for SARS appears to range from 2–10 days. It begins as an influenza-like illness with fever (>38°C), rigor, myalgia, malaise, and headache. Mild respiratory symptoms including a dry cough may also be present, and diarrhoea may occur. Chest radiography could

be normal initially, but a HRCT scan of the thorax usually shows ground glass infiltrates or frank consolidation in the lungs. Diagnosis can be difficult at this stage because the clinical features are non-specific. Epidemiological clues may prompt the clinician to suspect the diagnosis, e.g. travel to epidemic areas, contact with known patients, contact with suspect animals, laboratory accident, clustering of cases. Peripheral lymphopenia is common on presentation. Other common laboratory features include thrombocytopenia, raised aminotransferases, creatine kinase, and lactate dehydrogenase.

The majority of patients will progress, in the second week, with persistence or recurrence of fever, onset of respiratory distress, worsening of radiological findings, and desaturation. Some patients, probably 30–40% of cases, progress relentlessly to ARDS. Viral load peaks at around 7–10 days, which may explain the high risk of nosocomial transmission. Clinical deterioration occurs despite a substantial drop in viral load after ten days. Spontaneous pneumomediastinum and pneumothorax, unrelated to mechanical ventilation, may complicate the course of illness. A significant proportion of patients will require intubation and mechanical ventilation for ARDS, although success has been reported with non-invasive ventilation under strict personal and environmental protection. The case fatality rates in severely affected countries range from 7 to 17%. Old age, presence of co-morbid diseases, and high viral load are poor prognostic factors.

Lung specimens, obtained by biopsy or autopsy, generally show diffuse alveolar damage with hyaline membrane formation, with varying degree of organisation. Bronchiolitis obliterans organising pneumonia-like changes have also been reported and this may explain the anecdotal response of SARS to corticosteroids.

Diagnosis

Owing to the non-specific nature of the disease, initial diagnosis, particularly in the absence of epidemiological linkage, could be difficult and requires careful exclusion of other viral and bacterial infections. Epidemiological clues and the lack of response to treatment targeted at common respiratory pathogens are helpful in making the correct diagnosis. Viral RNA can often be detected by RT-PCR in nasopharyngeal aspirate, stool, and urine, but the sensitivity is variable and multiple, repeated testing might be necessary. Viral culture is of lower yield than RT-PCR. Seroconversion is regarded as the gold standard to diagnose SARS-CoV infection, but a significant fourfold rise in IgG might take more than 60 days, and therefore is not useful for acute management. The presence of an epidemiological link, radiographic deterioration within 48 hours of admission, myalgia, lymphopenia, and elevated alanine transferase classifies a patient as high risk for SARS. Obviously, RT-PCR and seroconversion cannot be relied upon solely for the initial isolation of suspect cases and acute management.

Treatment

The mainstay of treatment is provision of supportive care. Many patients develop ARDS and will require intensive care and mechanical ventilation. The latter should be of the pressure-controlled mode to minimise barotrauma, particularly in light of the presence of spontaneous pneumomediastinum in SARS. Antiviral agents, including ribavirin and lopinavir/ritonavir, have been used during the SARS epidemics, but no RCTs were conducted to prove their efficacy. Corticosteroids were included in many regimens published in the literature with some dramatic responses although RCT data are lacking. Other modes of therapy that have been tried, or postulated to be useful, include: interferons, convalescent plasma, pentaglobulin, nelfinavir, glycyrrhizin, and small interfering RNAs. Animal studies and randomised double-blind placebo-controlled trials are required to examine their therapeutic potentials. A vaccine available in the mainland of China has begun phase I clinical trials although safety data and other results remain unpublished.

HIGHLY PATHOGENIC AVIAN INFLUENZA A (H5N1) VIRUS

Epidemiology

Influenza virus subtype H5N1 has caused outbreaks of disease in poultry in Hong Kong, southern China, Japan, Southeast Asia (Cambodia, Indonesia, Malaysia, Philippines, Laos, Taipei, Thailand, Vietnam), Republic of Korea, Russia, Croatia, Kazakhstan, Romania, Turkey, Iraq, Nigeria, Egypt, India, Niger, and Albania. Of great concern is the increasing number of sporadic avian-to-human transmissions of H5N1. In 1997, an outbreak of H5N1 influenza occurred in poultry in Hong Kong and infected 18 humans, with 6 deaths. The outbreak was probably terminated by massive culling of 1·5 million poultry. Another two cases of H5N1 human infection were described in Hong Kong in 2003, having acquired the disease in mainland China. Since 2003, an increasing number of human cases have been reported from Southeast Asian countries (Indonesia, Vietnam, Thailand, Cambodia and China). At the time of writing, a total of 177 cases with 98 deaths have been described.

H5N1 virus and its transmission

Influenza viruses are RNA viruses with a segmented genome and they display marked antigenic diversity. Influenza A viruses are classified by subtypes of surface glycoproteins, the HA and NA. Aquatic birds are natural reservoirs of influenza A, with 16 HA and 9 NA subtypes. Human infections are commonly associated with three HA subtypes (H1–H3), although avian influenza of other subtypes (H5N1, H9N2, H7N7, and H7N3) have occasionally caused human diseases. Because of the inefficient proof-reading by influenza viral RNA

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polymerase, new influenza viral variants with amino acid substitutions in HA and NA can be produced, and genetic re-assortment between human and avian influenza viruses can produce new strains with pandemic potentials. As influenza virus can be transmitted before the onset of symptoms, it is likely to spread more rapidly and widely than SARS which is less contagious before symptom onset.

So far, most cases of avian influenza infection in humans were acquired through direct contact with sick or dead poultry. Human-to-human transmission of H5N1 has been suggested in several household clusters and in one case of child-to-mother transmission. Intimate unprotected contact was implicated. Serological surveys in Vietnam and Thailand show no evidence of asymptomatic infections among contacts. The risk of nosocomial transmission to healthcare workers remains very low, even under poorly protected conditions. The aforementioned findings suggest that transmission of the virus to human remains very inefficient.

Clinical and laboratory features

Most reported patients have an initial influenza-like illness with high fever (>38°C) and lower respiratory tract symptoms such as dyspnoea. Upper respiratory symptoms are only sometimes present. Diarrhoea, vomiting, abdominal pain, and pleuritic pain have also been reported. Two patients have been reported to present with encephalopathy with readily isolated H5N1 virus from their cerebrospinal fluid. Almost all patients develop pneumonia with respiratory distress, tachypnoea, and radiological consolidation. Rapid progression to ARDS and multi-organ failure with ensuing death occurs in 50–80% of cases. Old age, delayed hospitalisation, presence of pneumonia, and lymphopenia are risk factors for severe disease. Similar to SARS, common laboratory findings include leukopenia, lymphopenia, thrombocytopenia, and elevated aminotransferases. Diffuse alveolar damage is invariably found on autopsy. Reactive haemophagocytosis has been described in the bone marrow and other organs, believed to result from the 'cytokine storm' provoked by the H5N1 virus on macrophages.

Diagnosis

The clinical and laboratory features of H5N1 disease are non-specific. Epidemiological link, such as contact with sick or dead poultry in an area known to be affected by H5N1, is of vital importance.

Rapid presumptive diagnosis of H5N1 can be afforded by immunofluorescence using H5-specific monoclonal antibodies or by RT-PCR of H5-specific RNA on nasopharyngeal aspirates. Viral culture from clinical specimens and H5-specific serological testing allow a definitive, albeit retrospective diagnosis.

Treatment

The first line of defence against H5N1 infection remains infection control measures to reduce its spread among animals, and hospital control measures to avoid nosocomial outbreaks. Recent H5N1 isolates in Southeast Asia are highly resistant to the M2 inhibitors (amantidine and ramitidine) and, therefore, these agents are not recommended for treatment of H5N1 infection. These isolates are susceptible *in vitro* to neuraminidase inhibitors such as oseltamivir and zanamivir. However, the optimal dose and duration of treatment are uncertain. Clinical application of oseltamivir, hailed to be the 'best defence' does not really show significant efficacy from the Vietnamese or Thai experience. Oseltamivir-resistant isolates have been reported in oseltamivir-treated patients with H5N1 infection.

Corticosteroids have been tried in some H5N1 patients but their use did not appear to be beneficial. Interferon-alpha may have antiviral and immunomodulatory properties, but will have to be tested in future RCTs. No licensed vaccine is available for H5N1, although this is an area of active research.

CONCLUSION

Severe acute respiratory syndrome-associated coronavirus and H5N1 are two newly emerged respiratory viruses that could cause severe pneumonia with a rapid downhill course. No specific treatment is proven to be effective. Minimising unprotected contacts with infected animals and human beings, quarantine of contacts, and prompt isolation of infected individuals are the mainstays in preventing outbreaks of these infections.

KEYPOINTS

- Both SARS and avian influenza A (H5N1) virus have pandemic potential.
- Severe acute respiratory syndrome and H5N1 both begin as influenza-like illnesses. Epidemiological information is important for making the diagnosis.
- H5N1 virus appears to be endemic in bird and poultry populations; SARS-CoV-like viruses have been isolated in game animals (e.g. civet cats).
- Severe acute respiratory syndrome and H5N1 infections often progress rapidly to multi-focal pulmonary consolidation and ARDS, with significant mortality.
- Treatment is supportive and no antiviral drug has been shown, by RCT, to reduce the mortality of either infection.
- Minimising unprotected human contact with infected animals and humans, and appropriate quarantine measures are the mainstays in preventing outbreaks of SARS and H5N1 infection.

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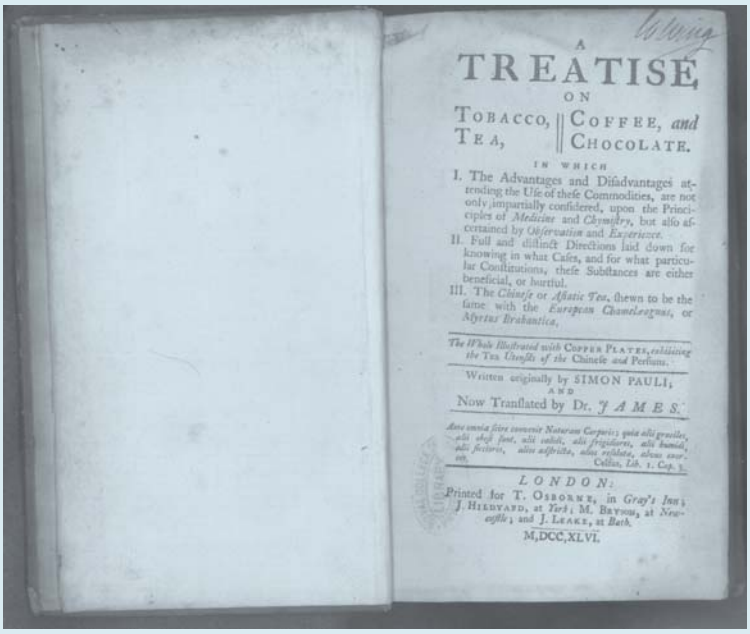

A TREATISE ON TOBACCO, TEA, COFFEE, and CHOCOLATE. IN WHICH

I. The Advantages and Disadvantages attending the Use of these Commodities, are not only impartially considered, upon the Principles of *Medicine* and *Chymistry*, but also ascertained by *Observation* and *Experience*.

II. Full and distinct Directions laid down for knowing in what Cases, and for what particular Constitutions, these Substances are either beneficial, or hurtful.

III. The *Chinese* or *Asiatic Tea*, shewn to be the same with the *European Chamelæagnus*, or *Myrtus Brabantica*.

The Whole Illustrated with COPPER PLATES, *exhibiting the* TEA *Utensils of the* Chinese *and* Persians.

Written originally by SIMON PAULI; AND Now Translated by Dr. JAMES.

Ante omnia scire convenit Naturam Corporis; quia alii graciles, alii obesi sunt, alii calidi, alii frigidiores, alii humidi, alii ficciores, alios adstricta, alios resoluta, alvus exercet. Celsus, Lib. 1. Cap. 3.

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'INJURIOUS TO THE LUNGS'

Warnings against the harmful effects of smoking tobacco are not new. They were being made by physicians over three hundred years ago. Although many during the seventeenth century regarded tobacco to be a remedy for all ills, others argued fiercely against it. Simon Paulli was professor of botany, anatomy and surgery at Copenhagen, and physician to Christian IV of Denmark. In 1665, he published a summary of the arguments for and against tobacco smoking, and 'impartially considered' its use 'upon the principles of medicine and chymistry'.

Paulli was particularly impressed by 'James the Sixth of England' who had 'disputed publickly against the use of tobacco, giving instances of persons who used it who were afflicted with incurable disorders of the breast … after whose death, the lungs were found black and parched, just as if they had been indurated in smoak'. The king had warned his subjects that smoking tobacco 'impaired the body' and was 'injurious to the lungs'.

After presenting the evidence, Paulli regarded those who willingly purchased 'sickness and death' to be 'infatuated and hood-winked'. In conclusion, he stated, 'If any champion for the interests of tobacco should ask me whether I would have the Pope, the Emperor, and all the Kings, Electors, Princes, and Dukes in Europe, prohibit and discharge the use of tobacco? I answer, that such a revolution is really to be wished for'.

Paulli clearly showed his concern for public health; 'what is more frequent than for people of all denominations to spend the whole of the day smoaking tobacco in ale-houses and taverns?' Not any more in Scotland, Dr Paulli! It has taken a long time but some of the 'Princes' are now listening. On Sunday 26 March 2006, Scotland became the first part of the UK to ban smoking in enclosed public places.

John Dallas,
Rare Books Librarian, RCPE

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