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Severe acute respiratory syndrome (SARS) in children: epidemiology, presentation and management

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This article is dedicated to all front-line health-care workers who have risked their lives to care for patients with SARS all over the world. Eight health-care workers contracted SARS and died during the outbreak in Hong Kong.

KEYWORDS
SARS;
respiratory infection;
coronavirus;
respiratory distress

Summary Severe acute respiratory syndrome (SARS) is a newly recognised and highly contagious respiratory infection caused by a new strain of coronavirus. The disease can result in progressive respiratory failure in adults and the mortality rate has been reported to be 8–15%. This infection spreads by droplet transmission and children appear to acquire SARS through close household contact exposure to infected adults. Disease severity is, however, much milder in the paediatric age group. The common laboratory findings in infected children and adolescents include lymphopaenia and elevated levels of lactate dehydrogenase and creatinine phosphokinase. Air space consolidation is commonly seen during the course of the illness although chest radiographs are normal on presentation in half of the cases. The pathophysiology of SARS appears to be related to immunological dysregulation in response to the coronavirus infection. The optimal treatment of SARS in children remains to be determined. No case fatality in infected children has been reported. The early and proper isolation of infected adults, meticulous infection control measures in the hospital setting, exhaustive contact tracing and quarantine measures are important steps in preventing the spread of the disease among health care workers and into the community. The development of a sensitive and rapid test for early diagnosis is underway. Further controlled trials are necessary to define the optimal treatment of this infection in children.

INTRODUCTION

Since late 2002, outbreaks of atypical pneumonia of unknown aetiology primarily affecting close family contacts and health care workers have occurred in the Guangdong Province in Southern China. The World Health Organization (WHO) was first informed in February 2003 by the Chinese Ministry of Health of an outbreak of acute respiratory syndrome involving 305 cases and five deaths that occurred in Southern China.[1] A number of major outbreaks were then reported in Mainland China, Hong Kong, Vietnam, Toronto, Singapore and Taiwan. With an increasing number of reports of this unusual infection across Asia, the US Centers for Disease Control and Prevention termed this condition severe acute respiratory syndrome (SARS).[2] The case definition of SARS is periodically updated. Based on clinical features, radiological and virological findings and a positive contact history, patients can be categorised into "suspect" and "probable" SARS cases.[3]

The epidemic of SARS in Hong Kong started in March 2003. Of the total of nearly 1800 cases, approximately 110 were children and adolescents. SARS has shown its potential to spread rapidly across the globe. This new respiratory infection has been noted to be highly contagious. Household contacts and health care workers who cared for patients with this type of atypical pneumonia were particularly prone

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to acquiring it. The clinical presentation and progression are very different in children from those in adults. In this paper, we summarise current knowledge on the epidemiology, aetiology, clinical features, laboratory features and the experience in the treatment of SARS in children.

EMERGENCE OF A GLOBAL EPIDEMIC

SARS is believed to have originated in Southern China. Two major case clusters in Hong Kong occurred in a hospital and an apartment complex. It began when an infected doctor who had been treating patients with SARS in Mainland China came from Zhongshan county to Hong Kong in February 2003.[4] He had stayed in the hotel in Hong Kong for just 2 days but many visitors and guests had by then already contracted the disease. These infected individuals from the index hotel returned to their home countries and initiated the SARS outbreaks in the hospital systems of Hong Kong, Toronto, Singapore and Hanoi.[5–8] The clinical features of the infection and the route of spread were not well understood at the beginning of the outbreaks in early March. Health care workers become infected because they did not wear proper personal protective equipment while caring for the infected patients. The infection was subsequently brought outside the health care setting by hospital workers and visitors.

A 26-year-old gentleman who was admitted because of pneumonia to the Prince of Wales Hospital in Hong Kong in early March was among the infected visitors from the index hotel. Within 2 weeks, over 150 health care workers, medical students and the other patients as well as visitors to the index ward were infected.[5] The use of a jet nebuliser in the index case is believed to have generated a large volume of infectious droplets. Following this case cluster, a major community outbreak occurred in a large apartment complex called Amoy Gardens. A patient on renal dialysis who contracted SARS when staying in the index ward visited his relatives at Amoy Gardens; over 300 people were subsequently infected.[9] This outbreak was likely to have been caused by leaky sewage pipes that generated an aerosol that was contaminated with infectious faecal material. The floor drains of the bathrooms and kitchens were connected to the sewage pipes and a backflow of the infectious aerosol probably contributed to the spread of the infection within the apartment building. During this community outbreak, contacts and residents at the Amoy Gardens were put into quarantine to prevent the possible spread of SARS within the community.

Overall, the paediatric burden of the disease is rather limited in all regions with a SARS outbreak. Nearly one-quarter of the infected cases in Hong Kong were health care workers, only 6% of all SARS cases being children or adolescents under 18 years of age. There has not been any spread of SARS in the school setting in Hong Kong despite the fact that many infected children were attending school until they developed symptoms of the infection. Massive public education and campaigns have, however, occurred via different channels of the mass media since late March 2003. Children were advised to stay at home if they had any fever or a respiratory tract infection. Schools were suspended in an attempt to limit the outbreak. Similar quarantine measures were also carried out in Mainland China. The experience in Guangzhou and Beijing was similar to that of Hong Kong, paediatric cases accounting for less than 5% of the total patient number.

NEW SARS-ASSOCIATED CORONAVIRUS

The global collaboration in trying to identify the causative agent for SARS resulted in an unprecedented speed of progress. The WHO has established a laboratory network with 13 laboratories around the world to facilitate the search for the possible infectious agent.[10] SARS was then found to be caused by a new strain of coronavirus called SARS-associated coronavirus.[11,12] Coronaviruses are classified under the order Nidovirales that are a group of enveloped RNA viruses.[13] They are known to cause common respiratory and enteric diseases in humans and animals.[14,15]

Despite the identification of the SARS-associated coronavirus, a reliable laboratory test for early diagnosis is still not widely available. Although the virus can be detected in respiratory secretions, stools and urine using the reverse transcription polymerase chain reaction (RT-PCR), many (>50%) of our SARS patients with coronavirus infection confirmed by serology were initially negative on RT-PCR testing. The sensitivity of this rapid test depends on the types of specimen collected, the quality of the specimens and the timing of their collection.[10,16] Virus isolation can also be performed by co-culturing clinical specimens (stool, urine and respiratory secretions) with Vero cells. These procedures are, however, technically demanding and can only be carried out in specialised laboratories. Serum antibody testing using enzyme immunoassay and indirect fluorescence antibody assay have also been developed but SARS patients will not receive a positive result until the third week of their illness. These tests can therefore only be used to confirm the diagnosis later in the course of the illness.[9,12] A history of close contact with a known SARS patient remains the most important clue to alert paediatricians to a possible diagnosis of this infection. The identification of the genome sequence of this new coronavirus will facilitate the development of accurate rapid diagnostic tests, specific vaccines and other specific anti-viral agents.[17,18]

CLINICAL, RADIOGRAPHIC AND LABORATORY FINDINGS

The clinical presentation and course of illness in adults have been well characterised from several large cohorts in Hong Kong, Singapore and Toronto.[5–9,11,12] The incubation

period of SARS is 5–10 days. Most patients present with fever, a dry cough and shortness of breath. Coryza is relatively uncommon in infected adults. Other common symptoms include myalgia, chills, headache and dizziness. The presentation in children is different. After a similar incubation period, children with this infection usually present with fever, dry cough and a runny nose. These symptoms are clinically indistinguishable from those of other mild upper respiratory tract infections.[19,20] The other typical symptoms of myalgia, dizziness, chills and rigors found in adults are not common in young children. The initial chest examination will be normal in most young children, whereas inspiratory crackles, predominantly in the lung base, are usually found in adolescent and adult patients.

With increasing experience of this disease in adults, there have been many atypical cases that have not had the usual constitutional symptoms.[5,21,22] Many infected elderly people may not have fever and the typical respiratory symptoms. These "silent" patients have caused several small outbreaks in other hospitals in Hong Kong. Because of the generally mild symptoms, a history of household exposure of children to infected adults is the most important clue to the diagnosis of SARS. There has not been any documented spread of this infection from children to children or children to adults. Nevertheless, such potential cannot be ruled out as, in Hong Kong, all infected children were isolated from the onset of their illness. Prompt, early isolation is still mandatory until more information about the infectivity and viral shedding in children is available.

Up to half of the infected children had normal chest radiographs on presentation.[19] The finding of unilateral or perihilar air space consolidation is more common in adolescent patients. Pleural effusion and hilar lymphadenopathy are absent. The radiographic findings are no different from those seen in pneumonia due to other aetiologies. If the initial chest radiographs are normal, thoracic computed tomography may reveal poorly defined, ground glass opacifications of the lungs in approximately 20% (Fig. 1). Lymphopaenia and neutrophilia were the most common haematological findings in adult SARS patients. The counts of CD4-positive and CD8-positive T lymphocytes fell early in the course of illness and these changes were associated with an adverse outcome.[23] Lymphopaenia was also found in almost all paediatric cases but it can also occur in other common viral infections in children. Thrombocytopaenia and mild elevations of lactate dehydrogenase, creatinine phosphokinase and D-dimer were also found in about 10% of paediatric SARS patients.[19,20]

CLINICAL COURSE OF ILLNESS

Typically, the course of illness in adults can be divided into three stages.[24] In the first week, patients have fever and mild respiratory symptoms. This stage is characterised by active viral replication. In the second week, many will develop progressive pneumonic changes with increasing oxygen dependency. One-quarter of adult patients will develop acute respiratory distress syndrome requiring admission to an intensive care unit. The third stage (week 3 onward) is characterised by gradual recovery in most (>80%) patients. In a review of the first 1425 cases in Hong Kong, the estimated case fatality rate was 13.2% for patients younger than 60 years old and 43.3% for patients aged 60 years or older.[25]

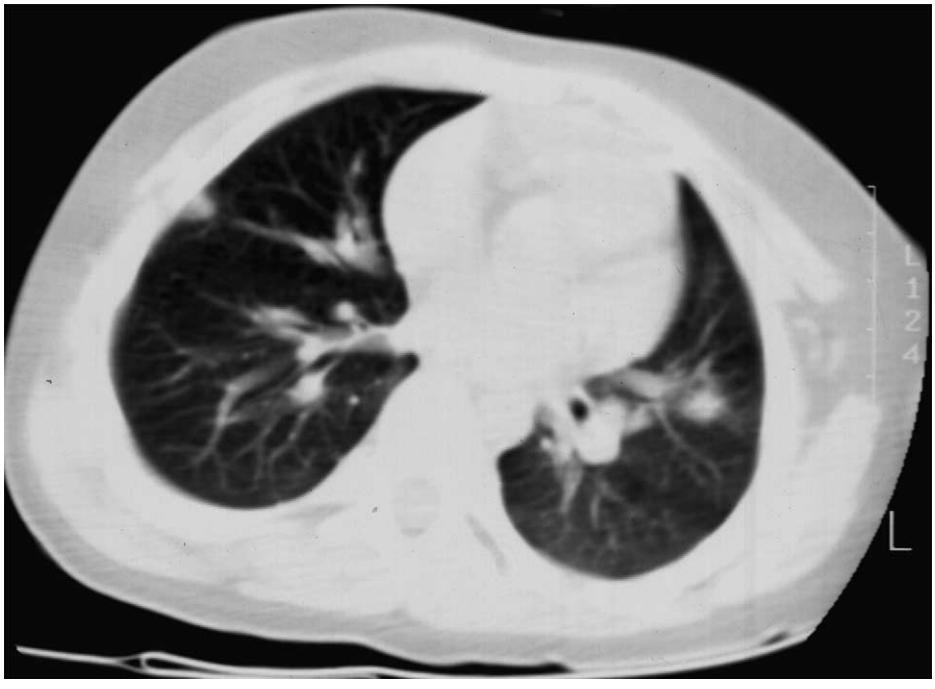

Fig. 1 Computer tomography of the thorax showing ground glass consolidation in the peripheral lung regions in a 3-year-old boy.

The clinical course of the infection in young children is, however, much less severe. Many will just have a mild upper respiratory infection. Most children will become afebrile within 7 days and they do not usually progress to respiratory distress. Young children will not even require supplemental oxygen. Pneumonic changes in the chest radiograph usually disappear within 2 weeks. There have also been paediatric patients who were asymptomatic but in whom subsequent serological screening confirmed the diagnosis of coronavirus infection.

Some adolescent patients may have a slightly more aggressive course with progressive deterioration in the first week or two.[19,20] There has been no fatality among more than 100 paediatric SARS cases in Hong Kong. Only one adolescent patient required intubation and mechanical ventilation. Another adolescent patient was treated with non-invasive positive-pressure ventilation. The term SARS may therefore not be appropriate in describing the infection in children.

TREATMENT OF SARS IN CHILDREN

The optimal medical treatment of SARS remains to be determined. In contrast to the aggressive regimens used for adults,[24] only simple supportive care is needed in children with SARS as a majority of them do not become very ill. For more severely affected adolescents, treatment is largely based on the adult experience. Since there is no known specific anti-viral agent for the SARS-associated coronavirus, ribavirin has been widely used in treating adult cases in Hong Kong. As revealed by the autopsy results of fatal adult cases, the main pathological features in the lungs have been diffuse alveolar damage, hyaline membrane formation and scanty interstitial inflammatory cell infiltrates.[4,5] Epithelial cell proliferation and macrophage infiltration are other characteristic findings.[26] It is believed that the lung damage is caused by immunopathological responses to the viral infection. Anecdotal early experience in adult patients suggested that the combination of systemic corticosteroid and ribavirin appeared to be effective in controlling the disease. Recent experimental data have, however, suggested that ribavirin might be ineffective against SARS-associated coronavirus.[27] The use of corticosteroid with this possibly ineffective anti-viral agent in patients with coronavirus pneumonia can be detrimental. On the other hand, glycyrrhizin extracted from liquorice roots was found to be efficacious in vitro in inhibiting the replication of SARS-associated coronavirus.[27]

In the absence of data on the infectivity of paediatric patients, we usually keep our infected children in hospital for a total of 3 weeks. By that time, all patients will be clinically well and their chest radiographs will have become normal. Preliminary studies in adults suggested that over 50% of patients continued to excrete the virus in stool and urine 3 weeks after the onset of the illness.[9] Because of this finding, we instruct patients and their parents on how to handle patients' excretions upon discharge, on the assumption that their urine and stool may still be infectious. More research is, however, needed to determine the potential infectivity and duration of excretion of the virus from infected children.

INFECTION CONTROL FOR SARS

Meticulous infection control is the cornerstone in preventing the spread of this disease in the community and the hospital setting. The most important route of spread is by close contact droplet transmission. In Hong Kong, over 20% of SARS patients have been health-care workers. In the hospital setting, the use of face masks and gowns and handwashing has been effective in preventing the nosocomial spread of SARS among health-care workers.[28] Infected health-care workers must be properly isolated early in the course of illness or they will spread the infection to their family and into the community.

SARS patients should ideally be managed in hospital on a ward designated solely for the treatment of patients with this infection. If single rooms are available, these patients should be placed in them with negative-pressure ventilation to prevent cross-infection among patients and health-care workers.[29] Health-care workers should also receive proper training on infection control before they start to take care of SARS patients. Proper isolation facilities, droplet precautions (hand hygiene, protective and disposable gown, gloves, N95 masks and eye and face shields) and contact precaution are necessary to protect health-care workers while managing patients with SARS. Visitors should not be allowed in the wards designated for SARS patients. To avoid contamination and subsequent cross-infection, hospital charts and paperwork should not be placed near the patients. Resuscitation and endotracheal intubation have been found to carry a very high risk of spreading SARS as large amount of infectious aerosol may be generated during these procedures. Any procedure that generates infectious aerosol, such as jet nebulisation and non-invasive positive-pressure ventilation, should be avoided.[2]

The exact duration of survival of SARS-associated coronavirus in the environment remains unclear but early results from the WHO laboratory network showed that this virus could survive for at least 1 day in the environment. It remained stable in the urine and faeces for up to 4 days.[30] Since a large amount of viral particles can be recovered from stools and urine, these clinical samples should be handled as potentially infectious materials.

CONCLUSION

Within only 8 weeks, SARS spread to all continents of the globe. Nearly 8500 cases and over 800 deaths have been reported worldwide. This infection results in significant morbidity and a high mortality rate in adults. For reasons

that remain unclear, this disease appears to run a much milder clinical course in children, although some adolescent patients may develop a slightly more severe illness. No fatality among paediatric cases has been reported in Hong Kong or elsewhere. Strict infection control is mandatory to prevent nosocomial infection among health-care workers. If infected adults are promptly isolated, very few children will be affected. Early case detection, the proper isolation of infected patients, meticulous infection control in the hospital setting and exhaustive contact-tracing are all important steps in containing this infection. Although the medical treatment for more severely affected cases remains controversial, the majority of children and adolescents will recover with simple supportive measures. Intensive research is currently underway to develop a rapid and reliable point-of-care diagnostic test. Until such a test is widely available, a history of possible contact with adult SARS cases remains the most important clue for paediatricians in making an early presumptive diagnosis in children. Proper clinical trials are required clearly to define the optimal treatment for SARS in both children and adults.

PRACTICE POINTS

- A history of close contact with known SARS patients is the most important clue to alert paediatricians of the possible diagnosis of SARS in children.
- The presenting symptoms of young children infected with SARS associated coronavirus are clinically indistinguishable from those of other mild viral upper respiratory tract infections.
- Simple supportive care is needed in children with SARS as a majority of them do not become very ill.
- Early case detection, proper isolation of infected patients, meticulous infection control in the hospital setting, and exhaustive contact tracing are the important steps in containing this infection.

RESEARCH DIRECTIONS

- Proper clinical trials clearly to define the optimal treatment for SARS in children and adults.
- More longitudinal follow up data to determine the potential infectivity and the duration of excretion of the virus from infected children.
- Further studies to determine the reasons why infected children have relatively mild disease when compared with infected adults.
- The development of a rapid and reliable point-of-care diagnostic test.

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