

Severe Acute Respiratory Syndrome in Children

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Summary. Severe acute respiratory syndrome (SARS) is a newly described and highly contagious respiratory infection. Many adult patients will develop progressive hypoxia, and a large proportion will develop respiratory distress syndrome (RDS), possibly related to massive and uncontrolled activation of the immune system. The mortality has been reported to be quite high, especially in the elderly with comorbid conditions. The causative agent has been identified as a novel coronavirus, and children appear to acquire the infection by close-contact household exposure to an infected adult. However, the severity is much milder and the clinical progression much less aggressive in young children. The exact pathophysiology of SARS is still unclear, and the medical treatment of SARS remains controversial. The main treatment regime used in Hong Kong is a combination of ribavirin and steroid. To date, there have been no reported case fatalities in children with this disease. The success of reducing the burden of this infection in children will depend on proper isolation of infected adults early in the course of illness. Strict public health policy and quarantine measures are the key in controlling the infection in the community. **Pediatr Pulmonol.** 2003; 36:261–266. © 2003 Wiley-Liss, Inc.

Key words: severe acute respiratory syndrome; respiratory infection; coronavirus.

INTRODUCTION

Severe acute respiratory syndrome (SARS) is a highly contagious respiratory infection, and many reports document that a significant proportion of adult patients will deteriorate rapidly into respiratory failure requiring mechanical ventilatory support. The global epidemic of this infection apparently started in southern China, where there have been unofficial reports of outbreaks of atypical pneumonia of unknown etiology since late 2002. The outbreak in Hong Kong started in early March 2003, and children acquired the infection almost exclusively from household contact with an infected adult. With increasing recognition of this unusual infection, the US Centers for Disease Control and Prevention (CDC) termed this condition *severe acute respiratory syndrome* (SARS).¹ The available literature related to SARS is primarily about adults. The disease spectrum and progression of this infection are very different in children. In this review, we summarize the current understanding of the epidemiology, presentation, and management of this disease in children.

EPIDEMIOLOGY

The global epidemic apparently started in the Guangdong Province in southern China. In the initial stage of the outbreak, the disease was confined to household contacts and healthcare workers who looked after patients with an

unusual type of atypical pneumonia of unknown etiology that was subsequently termed severe acute respiratory syndrome. The epidemic of SARS in Hong Kong began when an infected physician from southern China came to Hong Kong in late February 2003.² He passed the infection to many other visitors and guests at a hotel where he stayed. The infected individuals from this hotel started the outbreaks in their home countries when they returned home to Canada, Singapore and Vietnam.^{3,4} One of the infected visitors was admitted to the Prince of Wales Hospital (Hong Kong) in early March with pneumonia, and spread the infection to over 150 healthcare workers, medical students, and other patients, as well as to visitors to the index ward. The use of the jet nebulizer in the index patient is believed to be the possible cause of such an extensive outbreak, since it might have generated a large

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amount of infective droplets from him. The first pediatric cases were household contacts of the initial cohort of adult patients from this hospital outbreak.

Unfortunately, a chronic renal patient contracted the infection while staying in the index ward, and in turn spread the infection to over 320 residents at an apartment complex where he had visited his relatives a few times. His main symptom initially was diarrhea. Preliminary public health and environmental investigations suggested that the likely route of spread was via leaky sewage pipes, resulting in an aerosol contaminated with infectious fecal material which escaped into the narrow light well between the buildings. In addition, the building is designed such that the floor drains of the bathrooms are connected to the sewage pipes: a backflow of infectious aerosol may also have played a role in this outbreak. More than 40 children living in the apartment complex contracted the disease in this outbreak. The other infected residents in turn spread the disease at work or via other social contacts, resulting in a territory-wide outbreak in Hong Kong.

Although many children were attending schools up until they were admitted with respiratory symptoms or fever, there has not been any case of spread in the school setting in Hong Kong. However, it should be noted that public awareness of this infection was very high in the community. Parents were instructed not to allow their children to go to schools if they had any fever or respiratory tract symptoms. Furthermore, all residents of a section of the apartment complex were subsequently put under quarantine in an attempt to limit the spread of the infection, and schools were suspended for almost 4 weeks. All these measures probably helped to minimize the spread of infection to more children in the territory. Of the initial cohort of infected adults admitted to our hospital, only 5% of close family contacts were infected. This suggests that patients are noncontagious during the incubation period. Overall, only 6% of all SARS cases in Hong Kong were children or adolescents under 18 years of age. The majority of them were a consequence of the outbreaks at the Prince of Wales Hospital or the apartment complex.

ETIOLOGY OF SARS

Due to the urgency of identifying the causative agent for SARS, the World Health Organization (WHO) established a laboratory network around the world to facilitate the collaboration in search of the possible infectious agent.⁵ It is now known that SARS is due to a newly described strain of coronavirus.^{6,7} Several laboratories also reported that human metapneumovirus could be recovered from some patients with SARS, but the exact role of this virus in SARS remains to be explored.^{2,3} Coronaviruses are classified as members of the order Nidovirales, a group of enveloped, positive-sense RNA viruses.⁸ They are known to cause common respiratory and enteric diseases

of humans.^{9,10} Human aminopeptidase N is the receptor for coronavirus, and this receptor is expressed on the apical surfaces of respiratory and intestinal epithelium as well as on kidney tubular epithelium.¹¹ In the early stages of illness, the virus can be detected by a reverse-transcription PCR test of respiratory secretions, stools, and urine.¹² However, this test is still not sensitive enough to confirm the diagnosis early in the course of the illness. Although SARS was confirmed as a coronavirus infection by serology, up to 70% of cases were negative in their initial PCR testing. The other diagnostic tests currently being used include viral isolation and serum antibody tests; however, these tests are only useful for retrospective confirmation of the diagnosis.¹² It should be noted that many infected patients will not become seroconverted until 3 weeks into the illness. Until a reliable and rapid diagnostic test is widely available, contact of known SARS patients will remain the most important clue to alert pediatricians to the possible diagnosis of this infection in an early stage.

CLINICAL PRESENTATION AND COURSE OF ILLNESS

After an incubation period of about 3–11 days, children and adolescents will usually present with fever (>90%). The other most common presenting symptoms are dry cough (50%) and a runny nose (60%), especially in young children. Symptoms of malaise, loss of appetite, chills, and dizziness are present in some patients, but these symptoms are nonspecific. Clinically, these children may not be different from children suffering from mild upper respiratory tract infections.¹³ The typical symptoms of myalgia, headache, chills, and rigors found in adults are notably absent in infected young children. These symptoms, however, are more common in adolescent patients.¹⁴ Initial examination of the chest in infected young children is usually normal, while adolescent patients may reveal inspiratory crackles predominantly in the lung base.

Since the presentation and severity of illness of young children are quite different from those of adults, the most important clue to the diagnosis is household exposure to an infected adult. Pediatricians should be aware of the differences in the spectrum of the disease in children and adults. When there is community outbreak of this infection, a detailed contact history of any adult with severe respiratory infection should be sought when children present with respiratory infections. There have been no documented cases of spread from children to children or children to adults in the community. However, the potential for this cannot be ruled out, because all our infected children were strictly isolated from the onset of their illness. A high index of suspicion and proper early isolation are still mandatory until we learn more about the infectivity of children with this infection.



Fig. 1. Chest radiograph of 3-year-old boy with no obvious consolidation at presentation.

Initially, about 20% of adult patients with SARS have normal chest radiographs.² Indeed, 50% of children may also have normal chest radiographs at presentation (Fig. 1), and the findings of unilateral or perihilar air-space consolidations are more common in adolescent patients. Pleural effusion and hilar lymphadenopathy are absent. For suspicious cases of documented household contact with normal initial chest radiographs, we suggest performing thoracic computed tomography. In about 20% of the cases, it will show a poorly defined, ground-glass opacification of the lungs (Fig. 2). The initially laboratory findings are rather nonspecific. Lymphopenia occurs in 90% of pediatric cases, but it can also occur in other viral infections. Leukopenia (20%), mild thrombocytopenia (24%), and mild elevation of D-dimers (15%) are occasionally found.¹⁴

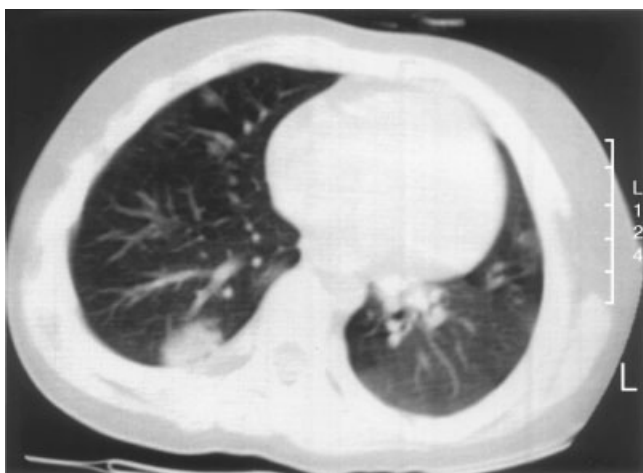


Fig. 2. Computer tomography of thorax of same patient as in Figure 1, showing ground-glass consolidations in peripheral regions.

The course of illness in adults has been described as triphasic.¹⁵ In the first week, patients are relatively stable, and this stage is characterized by active viral replication. In the second week, about 80% will develop progressive pneumonic changes with an increasing oxygen requirement (“immune response phase”). Approximately 25% of adult patients will develop acute respiratory distress syndrome (ARDS), requiring admission to the intensive care unit (ICU). The reported mortality in adults ranged from 8–15%.¹⁴ The clinical progression of this infection in young children is drastically different from that of adults. Most children will become afebrile within 7 days, and they usually do not progress to respiratory distress (Fig. 3). In fact, most young children will not even require supplemental oxygenation. The minor pneumonic changes seen in their chest radiographs usually disappear within 2 weeks after the onset of illness.¹⁴

In contrast, some adolescent patients may have a more aggressive course, with progressive deterioration within the first week or two with an increasing oxygen requirement.¹³ However, their illness is still less aggressive than that of infected adults, because approximately 15% of infected adults will require mechanical ventilatory support.² Among approximately 100 pediatric cases in Hong Kong, there have been no fatalities, and only one adolescent patient required intubation for mechanical ventilation. Thus the term SARS may not be appropriate for describing this infection in children. As regards children, we suggest calling it *mild acute respiratory syndrome* (MARS). In Hong Kong, there have also been pediatric cases who were asymptomatic, but subsequent serological screening confirmed the diagnosis of coronavirus infection. The case definition, clinical, epidemiological, and laboratory criteria for diagnosis of SARS provided by the CDC is updated periodically. In the latest update, published on June 5, 2003, we note that asymptomatic or mild respiratory infection does not rule out the diagnosis of SARS-associated coronavirus infection.¹⁶

TREATMENT OF SARS-ASSOCIATED CORONAVIRUS INFECTION

As the pathophysiology of this infection is still unclear, the optimal medical treatment of SARS remains to be determined. The treatment of SARS in children is largely based on the adult experience. Since there are no known specific antiviral agents for SARS-associated coronavirus, we have been using ribavirin in the treatment of both pediatric and adult cases in Hong Kong. As revealed by the autopsy results of fatal adult cases, the main pathological features of the lungs were diffused alveolar damage, hyaline membrane formation, and scanty interstitial inflammatory-cell infiltrates.² It is believed that the lung damage is due to immunopathological dysregulation and

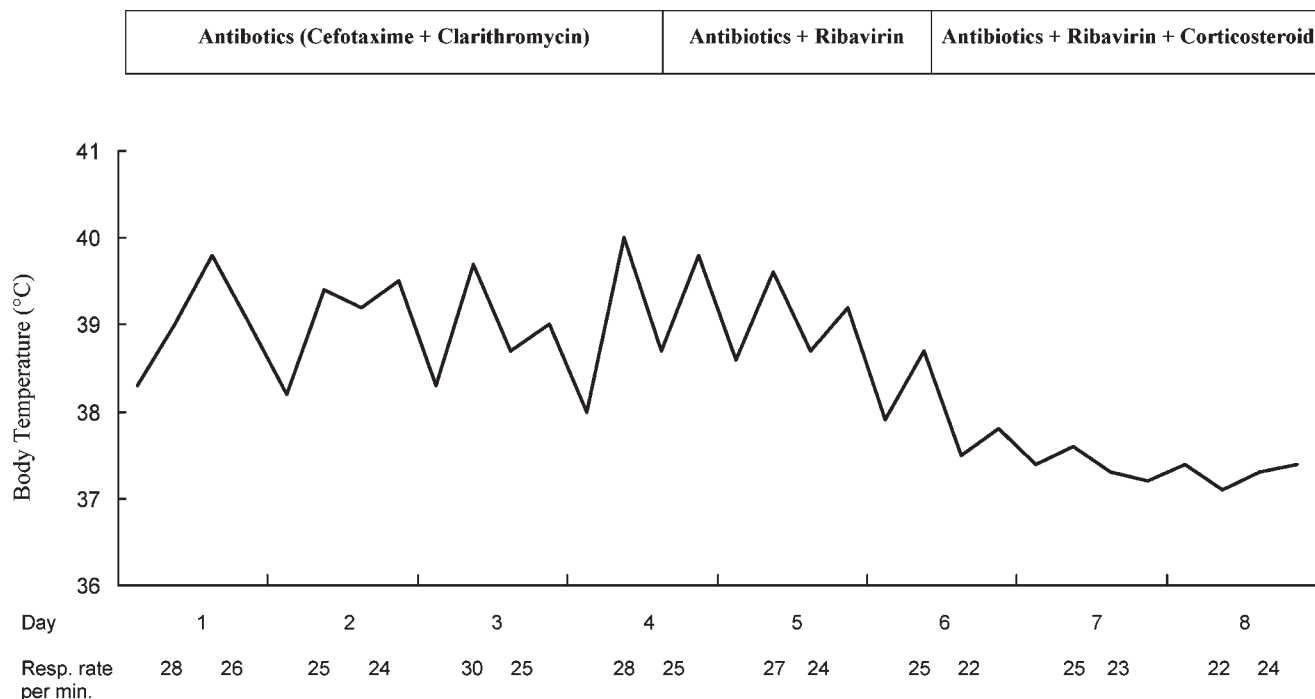


Fig. 3. Fever pattern of 3-year-old child in response to combination of ribavirin and corticosteroid treatment.

activation of a “cytokine storm” in response to the viral infection. Some of the radiological features are similar to bronchiolitis obliterans organizing pneumonia, which is sensitive to steroid therapy.¹⁷ Adult patients appear to respond well to a combination of ribavirin and steroid.^{2,4} Experience in adult patients also suggests that the deterioration in the second week of illness may respond to high-dose pulse steroid therapy.² Therefore, we have adopted such a regime as our standard treatment protocol for children.

When children present with respiratory tract infection, they are started on ribavirin 40–60 mg/kg/day orally in three divided doses if the contact history with an adult case of SARS is definite. If fever persists after 2–3 days, prednisolone at 0.5–1.0 mg/kg/day or hydrocortisone 1–2 mg/kg/dose i.v. given every 6 hr will be added. For patients who continue to deteriorate or have progressive radiographic changes, pulses of methylprednisolone 10 mg/kg/day for up to three doses will be given. These patients are usually switched over to i.v. ribavirin 40–60 mg/kg/day in three divided doses. Such deterioration is more common in adolescent patients. Ribavirin is usually given for a total of 10 days, while steroid is usually tapered off within 2 weeks. Our patients are hospitalized for a total of 3 weeks. Preliminary studies in adults suggest that over 50% of patients continued to excrete the virus in their stool and urine 3 weeks after onset of illness.¹⁸ We therefore instruct parents on how to handle the excretions of these recovered patients on the assumption that their urine and fecal material may still be infectious for some

time. Further studies are necessary to determine their infectivity and the duration of excretion of the virus from these children recovering from the disease.

Some adult patients continued to deteriorate despite ribavirin and pulse methylprednisolone, and they were treated with convalescent serum obtained from patients who recovered from SARS.¹⁴ However, proper clinical trials are necessary to determine the effectiveness of this form of treatment. We have not used this form of therapy in any of our pediatric patients. Furthermore, the use of other forms of anti-inflammatory agents or of anticytokine treatment remains to be explored.

INFECTION CONTROL MEASURES

The outbreaks of SARS in Singapore, Toronto, and Hong Kong clearly show that infection control in the hospital setting is of paramount importance in preventing spread of the disease. SARS is a very contagious infection, and it appears to spread mainly by close-contact droplet transmission.¹⁹ Children acquire the disease by close contact with an infected adult. Exactly how long this new coronavirus can survive in the environment remains unknown, although early studies by the WHO collaborative network revealed that the virus remained stable in urine and feces up to 4 days.²⁰ Feces and urine should be considered and handled as infectious material. Healthcare workers should have proper training in terms of infection control before they start to care for SARS patients. Sadly, more than 20% of all SARS patients in Hong Kong were

healthcare workers. However, very few were healthcare workers looking after children with SARS. It may possibly be related to a lower viral load shed by infected pediatric patients. The adult experience suggests that resuscitation and intubation are very high-risk procedures for healthcare workers, probably related to generation of large amounts of infectious droplets from patients during such procedures. Therefore, one should have adequate personal protective equipment before carrying out these procedures.¹

When there is a community outbreak, it is preferable that SARS patients be managed in hospitals with wards designated for treating patients with this infection. In Hong Kong, frequent sessions of infection control training are conducted at various hospitals before the staff is deployed to work in wards designated for SARS patients. Because of the highly contagious nature of this infection, we do not allow visitors to wards designated for SARS patients. Until further data are available, we will refrain from using jet nebulizers, as they may generate more infective droplets from patients, and put healthcare workers at higher risk of contracting the disease. Ideally, SARS patients should be treated in individual rooms with negative pressure ventilation to prevent cross-infection among patients. The details of isolation procedures and the use of personal protection equipment for the healthcare workers are available in the WHO and related websites.²¹

CONCLUSIONS

Severe acute respiratory syndrome is a serious respiratory illness that frequently leads to respiratory failure in adult patients. However, this disease appears to run a much milder course in children, although a proportion of adolescent patients may behave similarly to infected adults. Therefore, the term SARS may not be appropriate in describing children with this infection. There have been no reported fatalities among pediatric cases seen in Hong Kong or elsewhere. Although the fecal-oral route is a possible mode of transmission, the most important route of transmission appears to be by respiratory droplets. Strict adherence to all steps of infection control is necessary in order to minimize the rate of infection among healthcare workers. The burden of this disease will depend on the control of this infection in adults. The control of spread of this infection relies on early case detection, proper isolation of infected patients, meticulous infection control in the hospital setting, and exhaustive contact tracing to stop the chain of spread. Furthermore, strict public health policies and quarantine measures are mandatory to prevent spread of the infection in the community. Development of a sensitive and specific rapid diagnostic test will greatly facilitate the early confirmation of the disease. Further clinical trials are required to clearly define the optimal treatment for this infection in children and adults.

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