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33 Pediatric Severe Acute Respiratory Syndrome

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Although severe acute respiratory syndrome (SARS) has wreaked havoc in Southeast Asia and other parts of the world, it appears to be a disease that predominantly affects adults. Less than 10% of the infected population were children. Among these infected children, only 5% required intensive care unit admission, and less than 1% required mechanical ventilation. In contrast to its adult counterpart, the clinical course of affected children is usually milder, the time to resolution is shorter, and the potential of children to infect others is low.

These very different features in children have led some to create the acronym "MARS" (mild acute respiratory syndrome). This chapter will discuss the clinical features, radiologic presentation, management, and outcome of children suffering from SARS based on our institutional experience.

■ EPIDEMIOLOGY

Severe acute respiratory syndrome was brought to Hong Kong on 21 February 2003 by an infected medical doctor from Guangdong, China, who stayed in a local hotel. It has been estimated that at least 12 guests and visitors to this hotel became infected through contact with this medical doctor directly or indirectly. The disease then spread from Hong Kong rapidly to Hanoi, Singapore, and Toronto when infected visitors and guests returned to their home countries. One of the infected visitors, the index case of Hong Kong's first outbreak, was admitted to the Prince of Wales Hospital in early March with pneumonia, and he subsequently infected 138 hospital staff, patients, and visitors.[1] The use of nebulized medications in the index case is believed to have caused this very extensive hospital outbreak, since nebulization could have generated a large amount of infective droplets. The first few pediatric cases were household contacts of the initial cohort of adult patients from the hospital outbreak. At that time, SARS had not yet been recognized as a highly infectious disease. The disease involving health care workers spread rapidly to the community by visitors to the hospital wards.

Most, if not all, children with SARS have either been in close contact with infected adults, as a household contact or in a health care setting. These are believed to be the important routes of transmission that put children at a particular risk. Surprisingly, in Hong Kong there has been no major spread of the disease among classmates in schools. This may partly be explained by the early strict hygiene precautions undertaken by schools following a large-scale educational program conducted by the local government.

■ VIROLOGY

Severe acute respiratory syndrome is now known to be caused by a novel coronavirus (SARS-CoV), and over 95% of well-characterized cohorts of SARS patients have evidence of recent SARS-CoV infection.[2–6] Coinfection with human metapneumovirus or other pathogens was also documented in a proportion of patients. Whether such coinfections contribute to enhancing the pathogenesis or transmission of the disease is still unclear.[7–9]

The genome of SARS-CoV indicates that it is a novel virus within the family of Coronaviridae, a group of enveloped positive-sense RNA viruses.[10] It is not related to any of the human or animal coronaviruses known to date. Viruses closely related to SARS-CoV have recently been isolated from animals such as civet cats.[11] It is postulated that SARS-CoV was an animal virus that had overcome the species barrier and adapted to human-to-human transmission. The presence of this animal reservoir may imply possible future animal-to-human transmission and the initiation of further disease outbreaks.

■ CLINICAL AND LABORATORY FEATURES

The incubation period of SARS is between 2 and 10 days, and the mean has been estimated to be 6.4 days (95% confidence interval, 5.2–7.7), with the mean time from onset of clinical symptoms to hospital admission between 3 and 5 days.[12] The frequency of common presenting symptoms from several pediatric series is summarized in Table 33-1.[13–15] The predominant and most consistent symptom is fever, which is present in most of the patients (>90%) so far diagnosed to have SARS. Other symptoms include coryza and cough. Chills, rigor, myalgia, and malaise, which are common in adult patients, may also be present in older children and adolescents, but are rare in young children. Some patients, adults and children alike, may present with diarrhea. Young children appear to have milder disease with shorter time period to resolution, while the course of disease in older children is more similar to that of the adults. It is unclear why children, especially those under the age of 12 years, would be less severely affected, but it might be because they have been exposed to many other respiratory viruses, which could make their immune systems more resilient. Others have proposed that young children are not able to mount a "heightened" mature immune response as seen in adult patients during the immune dysregulation phase of SARS and thus suffer less organ damage with its associated morbidity and mortality. Besides, children in general present with fewer comorbidities than adults. Physical examination is normal in most if not all young children, whereas inspiratory crackles over the lung bases are present in some adolescent and adult patients.

Laboratory features from the three published pediatric series of SARS are summarized in Table 33-2.[13–15] Lymphopenia is quite consistently present in children affected with SARS. There may also be thrombocytopenia, a moderately deranged clotting profile, as well as elevated concentrations of liver enzymes, lactate dehydrogenase, and creatinine kinase. These laboratory parameters, together with the presenting clinical features, may help in the clinical diagnosis of the disease. We have also studied

■ **TABLE 33-1.** Presenting clinical features (%) among pediatric series of severe acute respiratory syndrome

	Hon and Co-workers[13] (*N* = 10)	Chiu and Co-workers[15] (*N* = 21)	Bitnun and Co-workers[14] (*N* = 10)
Fever	100	91	100
Malaise	20	62	10
Chills or rigor	50	48	10
Myalgia	40	10	NR
Cough	80	43	60
Dyspnea	NR	14	10
Headache	40	14	10
Dizziness	10	38	NR
Sputum production	NR	14	NR
Sore throat	30	5	10
Coryza	60	33	40
Anorexia	NR	57	NR
Nausea and vomiting	20	NR	20
Diarrhea	NR	10	10
Chest pain	NR	NR	NR
Abdominal pain	10	NR	NR
Febrile convulsion	10	NR	NR
Rash	NR	5	NR

NR, not recorded.

■ **TABLE 33-2.** Abnormal laboratory findings (%) among pediatric series of severe acute respiratory syndrome

	Hon and Co-workers[13] (*N* = 10)	Chiu and Co-workers[15] (*N* = 21)	Bitnun and Co-workers[14] (*N* = 10)
Lymphopenia	100	91	40
Neutropenia	NR	NR	30
Thrombocytopenia	50	48	10
Leukopenia	70	24	20
High lactate dehydrogenase	NR	71	20
High creatinine kinase	10	43	10
High alanine transminases	50	24	20
High D-dimer	NR	14	NR
Prolonged activated partial thromboplastin time	NR	29	NR

NR, not recorded.

the inflammatory cytokine profile in SARS patients. They have markedly raised concentrations of circulating interleukin-1β, which may suggest the selective activation of the caspase-1-dependent pathway. Other key proinflammatory cytokines (interleukin-6 and tumor necrosis factor-α) were only mildly elevated; this is in sharp contrast to H5N1 influenza infection, in which these cytokines are significantly elevated.[16]

■ RADIOLOGIC FEATURES

The radiologic appearances of SARS are nonspecific, and differentiation from other commonly encountered childhood respiratory illnesses causing airspace disease is difficult. Similarly to adults, children with early SARS may have a normal chest radiograph but changes of typical airspace consolidation in their computed tomography (CT) thorax. However, routine CT thorax should not be carried out because of the significant radiation; more importantly, this might lead to overdiagnosis, since other viral infections could give rise to similar radiologic changes.

Based on our institutional experience, (1) the primary radiographic finding in pediatric patients with SARS is airspace opacification, which can be unilateral focal (two thirds of cases) or unilateral multiple/bilateral (one third of cases), (2) younger children and those with mild disease usually present with unilateral focal consolidation, while multifocal and bilateral involvement tend to occur in older patients and those with more severe disease, and (3) there is a higher prevalence of involvement of the lower lung zone.

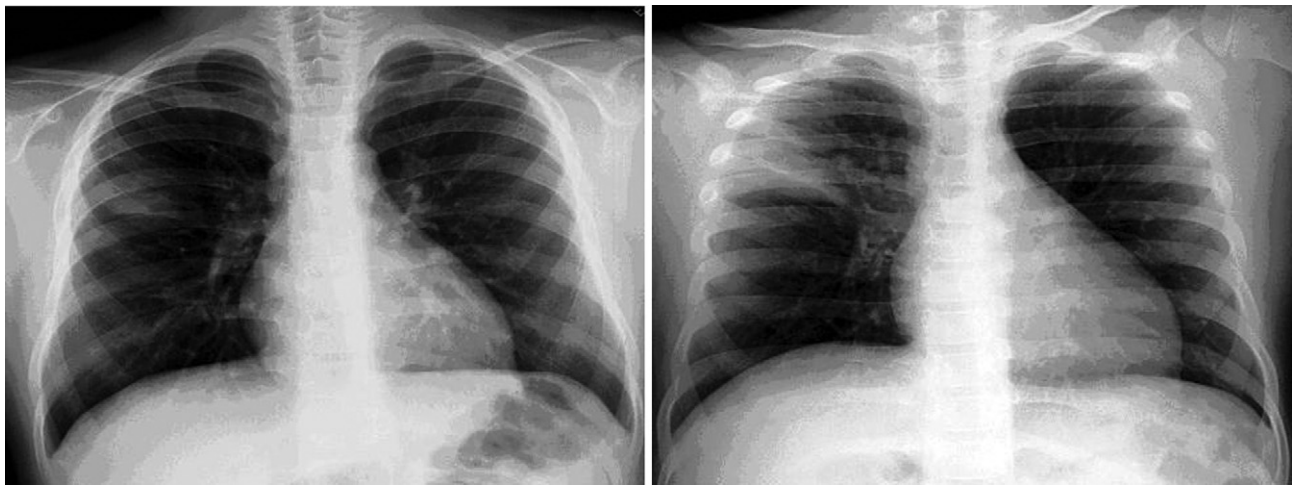
In our patients with SARS, the airspace opacification is the worst on day 5 to day 7 after the onset of fever. Unlike adults whose radiographic findings usually progress to multiple areas of involvement, the majority of our children only showed an increase in extent of airspace opacification in the same lung zone (Figs. 33-1 and 33-2). The mean duration of time taken for complete radiographic resolution is 16 days (range, 8–30 days). No definite scarring, volume loss, bronchial thickening, or bronchiectasis has been identified in the follow-up radiographs of our pediatric patients who have recovered from the illness. Again, the initial report from adults that pulmonary complications in the form of pulmonary fibrosis and bronchiectasis may be as high as 20% stands in contrast to this.[5]

Similar to the findings on plain radiography, most patients presenting with a milder form of the disease show focal segmental airspace disease on high-resolution CT. Ground-glass opacification and consolidation are the two predominant features on high-resolution CT. It is common to find a combination of both findings. There is, however, no specific preference of distribution of the disease in children; approximately equal involvement of subpleural and peribronchial regions has been observed. In patients with multifocal disease, a mosaic pattern of lung attenuation with ground-glass and airspace infiltrates is observed, simulating the appearance of bronchiolitis obliterans organizing pneumonia. Again, the aforementioned radiologic appearances are nonspecific. Both ground-glass opacity and consolidation attenuation are common findings in children suffering from pneumonia of any etiology.[17] Pulmonary nodules, septal thickening, and lymphadenopathy are not features of SARS.

Babyn and colleagues[18] reviewed chest radiographs and thoracic CTs of 62 pediatric cases of SARS (25 suspect and 37 probable) and found that 35.5% of the patients had a normal chest radiograph. The most prominent radiologic findings observed were areas of consolidation (45.2%), often peripheral with multifocal lesions present in only 22.6% of the cases. Peribronchial thickening was noted on chest radiographs of 14.5% of patients. Pleural effusion was seen in one case, aged 17 years and 11.5 months. Interstitial disease was not observed in any patient.

■ DIAGNOSIS

Since the presentation is nonspecific and often indistinguishable from other childhood infections, the diagnosis is often difficult unless there is clear contact history with an infected patient. The U.S. Centers for Disease Control and World Health



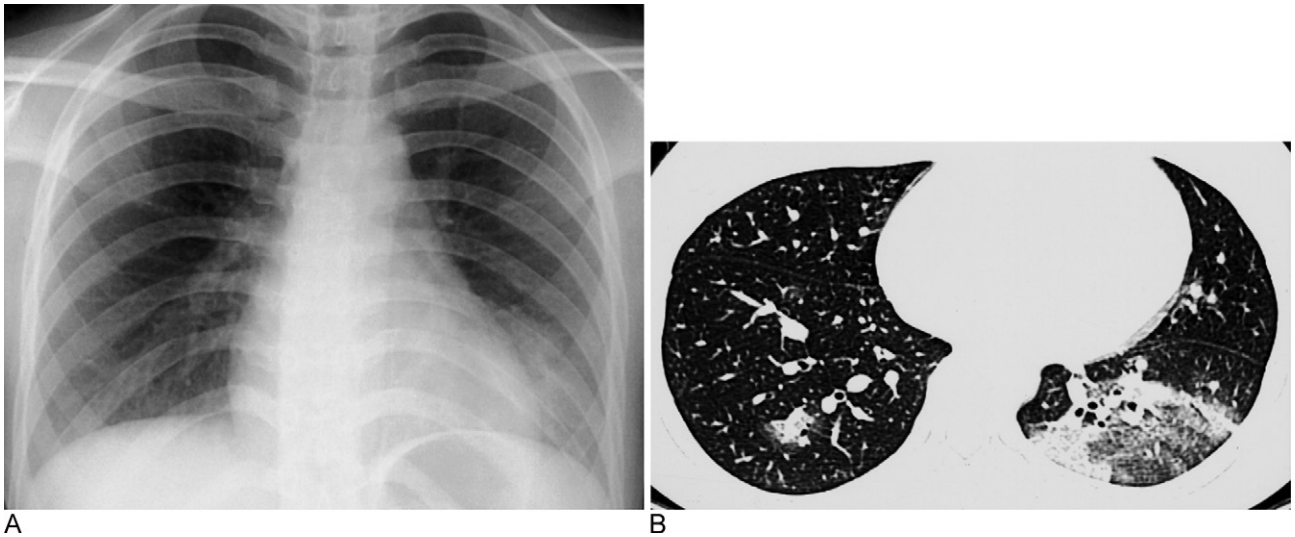
■ **FIGURE 33-1.** Radiologic progression over 3 days of focal consolidation affecting the right upper zone in a 13-year-old girl with SARS.

Organization have promulgated a case definition for SARS (Box 33-1). These definitions and criteria, while being applicable to both adults and children, are based mainly on adult experience.[19]

This case definition is useful in guiding clinicians in decision making regarding treatment. However, since the early symptoms of children affected with SARS are very much similar to those of other forms of upper or lower respiratory tract infections, the decision on admission, as to whether to isolate, and how to treat children presenting with fever but without a definite contact history remains difficult. Sometimes even the contact history might be misleading. In our hospital, we came across two children whose initial symptoms were suggestive of SARS and who had a definite history of contact with an affected individual, but who were later diagnosed to have bacterial septicemia.[20] The World Health Organization has subsequently revised the definition of a probable case to include a suspected case of SARS that is positive for SARS-CoV.

All suspected cases will be subjected to a battery of investigations: (1) Microbiologic studies to rule out common pathogens, including blood culture, nasopharyngeal aspirate for immunofluorescence and viral culture, and viral serology; (2) serial complete blood count and differential count; (3) serial liver and renal function tests, creatinine kinase and lactate dehydrogenase concentrations; (4) serial clotting profile including partial thromboplastin time, and D-dimer; and (5) serial chest radiograph. It is important to note that obtaining nasopharyngeal aspirate is an aerosol-generating procedure that may spread the virus. Staff performing the procedure should use adequate protection: mask, gloves, gown, and face shield.

The detection rates for SARS-CoV using reverse transcriptase–polymerase chain reaction are generally low in the first week of illness. The positivity rates on urine, nasopharyngeal aspirate, and stool samples have been reported to be 42%, 68%, and 97%, respectively, on day 14 of illness, and serology for confirmation may take up to 28 days for seroconversion.[5] Quantitative measurement of blood SARS-CoV RNA with real-time polymerase chain reaction technique has been developed with a detection rate of 87.5% to 100% within the first week



A B

■ **FIGURE 33-2.** **A,** Chest radiograph of a 14-year-old girl presenting with fever and cough. There is ground-glass opacification in the left lower zone on admission. **B,** High-resolution CT of thorax on day 4 after onset of fever shows a combination of ground-glass opacification and consolidation in the left lower lobe.

BOX 33-1 Case Definition of Severe Acute Respiratory Syndrome

Suspect Case

1. A person presenting after 1 November 2002 with history of high fever (>38°C) and cough or breathing difficulty, and one or more of the following exposures during the 10 days before onset of symptoms:
   - Close contact with a person who is a suspect or probable case of SARS
   - History of travel to an area with recent local transmission of SARS
   - Residing in an area with recent local transmission of SARS
2. A person with an unexplained acute respiratory illness resulting in death after 1 November 2002, but on whom no autopsy has been performed, and one or more of the following exposures during the 10 days before onset of symptoms:
   - Close contact with a person who is a suspect or probable case of SARS
   - History of travel to an area with recent local transmission of SARS
   - Residing in an area with recent local transmission of SARS

Probable Case

1. A suspect case with radiographic evidence of infiltrates consistent with pneumonia or respiratory distress syndrome on chest radiograph
2. A suspect case of SARS that is positive for SARS coronavirus by one or more assays
3. A suspect case with autopsy findings consistent with the pathology of respiratory distress syndrome without an identifiable cause

after fever onset and then dropping to 62.5% at a mean of 14 days after fever onset.[21]

■ TREATMENT

The treatment of children with SARS is largely based on adult experience and has not been subject to controlled trials. The actual pathogenesis is poorly understood. SARS predominantly presents radiologically with ground-glass opacification and pathologically as revealed from autopsy results of fatal adult cases, diffuse alveolar damage, hyaline membrane formation, and scanty interstitial inflammatory-cell infiltrates.[22] Treatment during the outbreak therefore include agents against SARS-CoV as well as anti-inflammatory therapy to prevent viral replication-induced pneumonitis and subsequent pulmonary fibrosis.[23] Our initial practice is to treat children with suspect SARS with antibiotics covering organisms associated with both common bacterial and atypical pneumonia (e.g., *Streptococcus pneumoniae* and *Mycoplasma*). We would add oral ribavirin 40 to 60 mg/kg/day in three 8-hourly doses if a definite contact history makes SARS very likely. If the symptoms, especially fever and general well-being, do not respond to the treatment within 48 hours, corticosteroid will be commenced in the form of oral prednisolone 1 to 2 mg/kg/day in two divided doses or IV hydrocortisone 1 to 2 mg/kg/dose every 6 hours. If fever persists or when there is clinical deterioration or progressive chest radiograph change, pulse methylprednisolone 10 mg/kg/dose will be given every 24 hours for up to three doses, depending on clinical response. Oral ribavirin will at the same time be changed to 20 to 60 mg/kg/day intravenously given every 8 hours. Steroid will be continued for a total of 2 weeks in the form of prednisolone 1 to 2 mg/kg/day or hydrocortisone 1 to 2 mg/kg/dose every 6 hours after methylprednisolone. If the child's condition improves, the steroid will then be reduced to half the dose and gradually tapered off over a week. However, if the chest radiograph is still abnormal by day 21, low-dose steroid will be continued for a longer time and slowly tapered off according to clinical and radiologic assessment. In the younger children in whom the infection appears to run a milder course, an obvious question is whether treatment with either medication, either alone or in combination, is of any benefit. This question can only be answered by properly conducted randomized controlled trial.

The use of ribavirin has received considerable criticism from overseas and experts in Hong Kong; lack of in vitro antiviral efficacy[24] and common adverse reactions such as hemolysis[25] have been their major concerns. The efficacy of other possible agents against SARS-CoV such as Kaletra (ritonavir 400 mg and lopinavir 100 mg) has been assessed. The combination when used with concomitant ribavirin yielded significantly better clinical outcome in adult patients.[26] There are also strong advocates for not using corticosteroids at all, for fear of secondary sepsis and other complications (such as avascular necrosis). Not only is the efficacy of steroid therapy unproven in SARS, its timing and dosage regimens are also controversial. The general consensus is now to consider steroid therapy as second-line treatment to be reserved for those with severe or worsening disease.

Our policy requires that all patients with SARS, including children, be discharged home 21 days after the onset of symptoms provided their condition permits. Studies in adults suggest that over 50% of patients continue to excrete the virus in their stool and urine 3 weeks after onset of illness.[5] It is possible that the same might apply to children; therefore, instructions should be given to the parents on the proper disposal of excreta so as to prevent further transmission of the disease in the community.

■ PROGNOSIS, OUTCOME, AND SEQUELAE

The course of illness in adults has been described as triphasic.[27] Patients are relatively stable within the first week, which is the active viral replication phase. In the second week, about 80% of the patients will develop progressive pneumonic changes with increasing oxygen requirement ("immune response phase"). About 25% will develop acute respiratory distress syndrome, requiring intensive care unit admission. The mortality rate has been reported to be over 15% in adults, while the mortality rate may be as high as 50% for the elderly with comorbidities.[14] The clinical course in young children is markedly different. None of those younger than 12 years of age required intensive care unit admission, and most never required supplementary oxygen. In contrast, some adolescents may have a more progressive course, though less aggressive than that seen in adult patients. No fatalities among the pediatric age group were reported.

We have studied the radiologic and pulmonary function outcome of 47 serologically confirmed SARS pediatric patients at 6 months from diagnosis. Persistent radiologic abnormalities in the form of air trapping and ground-glass opacification were found

in 34% of the study group. Need for oxygen supplementation and lymphopenia during the course of illness were found to be risk factors predisposing an individual to such abnormal radiology. Those with persistent radiologic abnormality had lung function similar to those with normal CT thorax. However, their oxygen consumption at peak exercise was significantly reduced compared with those with normal radiographs.

We will continue to see the effects of SARS on children long after the epidemic is over. Many children have experienced quarantine-imposed separation from their families and are not yet mature enough to understand the rationale. Some have lost many family members within a relatively short time period and have had their normal routines destroyed. In addition, they are bombarded daily with images of the disease in the form of the ubiquitous surgical masks, unprecedented media coverage, and community upheaval. The psychologic impact of this epidemic may become the major long-term sequelae as time goes by.

■ INFECTION CONTROL

Severe acute respiratory syndrome is a highly contagious disease, and the virus can remain stable and viable in urine and feces for as long as 4 days.[28] Transmission can occur via large droplets, by direct contact with infectious material, or by contact with fomites contaminated by infectious material.[27] In a few instances, potential airborne transmission was reported in association with endotracheal intubation, nebulized medications, and noninvasive positive pressure ventilation of SARS patients. Nosocomial transmission of the disease can effectively be stopped by enforcement of routine standard, contact, and droplet precautions in all clinical areas, and additional airborne precautions in all high-risk areas. During the SARS period, we adopted the policy of having a dedicated team of doctors and nurses providing care to all patients admitted to the designated SARS areas. We also have separate wards for patient triage, confirmed SARS cases, and step-down of patients in whom SARS has been ruled out. Designated changing rooms and areas for gowning and ungowning are also identified. We have summarized our experience in isolation procedures and the use of personal protection equipment in a recently published article.[29] An important lesson that we learned from this SARS epidemic relates to the need to enhance infection control programs in hospitals. A reliable alert mechanism, good communication among hospital staff members, efficient surveillance infrastructure, and continuing education to promote importance of appropriate patient care practices (especially hand washing) are vital ingredients for a successful infection control program. There are still many unanswered questions about the virus; its other possible modes of transmission, its infectivity during the incubation period and after clinical recovery, and whether it will become an endemic disease will have to be established.

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