

SARS in Newborns and Children

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Key Words

Severe acute respiratory syndrome · Coronavirus

Abstract

The severe acute respiratory syndrome (SARS) is a highly contagious infection caused by a newly discovered strain of coronavirus (SARS-CoV). Infants born to pregnant women with SARS did not appear to acquire the infection through vertical transmission. Some newborn infants, however, developed severe intrauterine growth retardation and life-threatening gastrointestinal complications. It is now known that the clinical course and prognosis are different between paediatric and adult SARS patients. Young children (<12 years), in general, run a less aggressive clinical course than do teenage and adult patients. Thus far, no fatalities have been reported in the paediatric age group (≤ 18 years). This review describes the current understanding of the clinical manifestations, diagnostic tests, immunological profiles, patient management and outcomes of SARS-CoV infection in the paediatric population.

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Introduction

The severe acute respiratory syndrome (SARS) is an emerging infectious disease caused by a newly discovered strain of coronavirus (SARS-CoV) [1, 2]. In early spring 2003, an outbreak of SARS in Southeast Asia shocked the world [3] and paralysed the economy of the region. Up to December 2003, 8,098 people have been affected worldwide, of whom 774 died of respiratory failure or complications associated with SARS [4]. In Hong Kong, 1,755 adult (>18 years) and paediatric patients (≤ 18 years) were infected by the coronavirus [5]. About 5% were young children (<12 years) and teenagers (12–18 years). Despite a high mortality rate in the adult population (9.6–16.7%) [4, 5], there were no fatalities in the paediatric age group [6–8]. The available data suggest that the clinical course of SARS in paediatric patients is different compared with adults. Young children, in particular, appeared to have a milder form of the disease [6–8]. This review describes the current understanding of SARS-CoV infection in newborns and children.

Newborns Born to Mothers with SARS

During the SARS outbreak between March and June 2003 in Hong Kong, 12 pregnant women were infected with SARS-CoV [9]. Seven presented in the first trimes-

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ter, and 5 in the late second and third trimester. All pregnant women had high fever ($\geq 38^{\circ}\text{C}$), lymphopenia and radiological features consistent with air-space consolidation and bronchopneumonia. All except one received ribavirin and corticosteroid treatment. Four patients required mechanical ventilation because of deteriorating pulmonary function, 3 of whom died from respiratory failure or sepsis [9].

Four and 2 of the pregnant women who presented in the first trimester had spontaneous miscarriages and termination of pregnancies, respectively [9]. The only newborn survivor in the first trimester group was delivered at term and had a normal weight at birth. In addition, all newborns in the second and third trimester group survived [10]. Of the latter group of infants, 3 were delivered by emergency Caesarean section during the acute phase of illness, between 26 and 32 weeks' gestation, and the other 2 were delivered in the convalescent phase at 33 weeks' gestation and term, respectively. Although all the mothers had pneumonia and confirmed SARS, a systematic search for SARS-CoV, including serial reverse-transcriptase polymerase chain reaction (RT-PCR) assays and viral cultures on blood, body secretions (endotracheal aspirates and oronasal secretions), excreta (urine, stool and ileostomy or jejunostomy fluids) and other body fluids (peritoneal, gastric and cerebrospinal fluids) did not demonstrate the presence of SARS-CoV in any of the newborns. The amniotic fluid samples were also negative for SARS-CoV. The acute and convalescent serological titres of the infants did not show a 4-fold increase in antibody concentration to SARS-CoV [10]. None of the newborns was found to be dysmorphic at birth, and all of them followed a clinical course typical of infants with similar gestations. Our data suggest that these infants are not shedding the virus and have not been clinically infected [10].

Two other important clinical observations are noted in this cohort of infants. First, the 2 pregnancies (second and third trimester group) that did not require early obstetric intervention developed oligohydramnios and severe intrauterine growth retardation. Whether these findings were attributable to the severe maternal respiratory illness resulting in circulatory insufficiency and hypoxaemia of the fetus, placental insufficiency secondary to placental tissue infarction as evidenced by the thrombotic and fibrotic changes in the stem and terminal villi [9], prolonged use of high dose corticosteroids or antiviral agents or some other unknown factors, remains to be determined. Second, the severe gastrointestinal complications in the most premature infants are also worrying. The 26 and 28 weeks' gestation infants developed jejunal perfora-

tion and necrotising enterocolitis, respectively [10]. Although such complications might have been coincidental, it could be related to the adverse perinatal events and/or the effects of prostaglandin modulating drugs, including high dose antenatal systemic corticosteroids and postnatal usage of indomethacin, disrupting the gastrointestinal mucosal integrity [11]. The current evidence does not support a direct aetiological role of SARS-CoV in causing these adverse gastrointestinal events.

SARS in Young Children and Teenage Patients

Contact History

The majority of young children and teenage patients had a definitive contact history with adult SARS patients, usually an immediate family member [6–8]. It is now believed that the virus is transmitted through droplets, close person-to-person contact and possibly also through direct contact by sharing communal facilities [3]. However, it is intriguing to learn that many of these children had been attending school at the time of presentation, but there was no evidence that they spread the infection to their classmates [6]. Whether this phenomenon is associated with a low viral load shed by infected paediatric patients during the early symptomatic period requires further investigation.

Clinical Manifestations

The clinical manifestations of SARS in young children and teenage patients have been described in detail in recent published reports [6–8]. Fever is the most frequently encountered symptom [6–8]. Other non-specific features, including lethargy, rhinorrhoea, headache, dizziness, myalgia, chills and rigors, have also been observed. Nausea, abdominal pain, diarrhoea and vomiting, sore throat and febrile convulsions are less commonly encountered. Respiratory signs and symptoms also tend to be vague. Cough, predominantly unproductive in nature, is found in more than half of the patients. Tachypnoea, dyspnoea, hypoxaemia and crepitations on chest auscultation are seldom noted and mainly affect the more severe cases [6–8].

The clinical course of SARS in the majority of paediatric patients follows a 'biphasic' rather than the 'triphasic' pattern as described in adult cases [12]. The viral replication phase (phase 1) is associated with an increase in body viral load [13], and the patient often presents with fever and other systemic features. This phase usually lasts for a few days after the onset of fever. The onset of the immu-

nopathological phase (phase 2) is marked by persistent or recurrence of fever, hypoxaemia and progression of pneumonia with new infiltrations in chest radiographs [12]. The deterioration in clinical condition corresponds to the period when the body viral load is expected to fall, and progression of pulmonary disease is believed to be mediated by exaggerated host immunological reaction [14]. Young children and the majority of teenage patients have relatively mild disease and seldom progress to the 'adult respiratory distress syndrome (ARDS)' stage (phase 3).

In general, young children (<12 years) appear to run a milder and shorter clinical course, and often present with cough and rhinorrhoea indistinguishable from upper respiratory tract infection caused by other viruses [6–8]. In contrast, teenage patients present with more constitutional features such as headache, lethargy, myalgia, chills, rigors, and lower respiratory tract signs, resembling those of adult SARS patients [3, 6]. Their clinical courses also tend to be more protracted and severe.

Laboratory Investigations

The most consistent haematological finding is lymphopenia which is found in over 90% of patients [6, 7]. Other haematological abnormalities such as thrombocytopenia, coagulopathy and elevated D-dimer levels are also observed [6–8].

Raised circulating lactic dehydrogenase level is the most frequently encountered abnormal biochemical finding [6, 7]. Teenage patients with severe clinical involvement tend to have more deranged laboratory indices and they take longer to resolve [7]. Transient elevation of serum creatine phosphokinase and transaminases, with normal bilirubin level, may also occur in a proportion of patients.

Key cytokines and chemokines were serially monitored using flow cytometry in 8 paediatric SARS patients admitted to the Prince of Wales Hospital. There was marked elevation of circulating interleukin (IL)-1 β levels suggesting selective caspase-1-dependent pathway activation in infected macrophages [15]. Conversely, IL-6 and tumour necrosis factor (TNF) α , which were markedly increased in avian H5N1 influenza infection [16, 17], were only mildly raised in the acute phase of SARS [15]. In addition, our data suggest that other chemokines, interferon- γ -inducible protein-10 (IP-10) and monokine induced by interferon- γ (MIG), were substantially elevated soon after the onset of fever [unpubl. data]. The activation of predominant type 1 T-helper lymphocyte (Th1)-mediated immune response facilitates viral clearance and may explain the rapid recovery of the paediatric cases.

Diagnostic Tests

RT-PCR has been used extensively for detection of SARS-CoV during the early phase of the outbreak. Although the test is specific, the sensitivity is about 55% [18]. The yield appears to be highest in nasopharyngeal aspirate and stool samples. To date, paired acute and convalescent serological titres provide the definitive test for diagnosis of SARS [14]. However, seroconversion is a late process and the diagnosis can only be made retrospectively. Thus, the development of a rapid diagnostic test will be most desirable and will greatly improve the clinical management of suspected cases. One-step real-time quantitative RT-PCR has been developed for SARS-CoV RNA quantification, and was used for the 8 paediatric patients admitted to the Prince of Wales Hospital, Hong Kong. The assay detected SARS-CoV RNA in the plasma of all patients [13]. The overall detection rate of the test in adult patients is about 75–78% [19]. The high detection rate of SARS-CoV in plasma during the first week of illness in paediatric patients and the quick turnaround time of 4–6 h make this plasma-based test a potentially useful rapid diagnostic tool for clinical practice.

Radiological Investigations

The initial radiological findings in children can be normal or show features compatible with air-space disease (fig. 1) [6, 7, 20]. Various abnormalities, including focal consolidation, ground glass opacities, linear atelectasis and peribronchial thickening have been reported [6, 7, 20]. Similar to the adult disease, these abnormal changes are concentrated predominantly in the lower lobes [20]. High-resolution computed tomography (CT) scanning of the chest was not routinely performed in paediatric SARS patients, and was reserved for children with (i) high suspicion of SARS-CoV infection; (ii) positive contact history, and (iii) normal or equivocal initial chest radiographs. Again, air-space consolidation is the most frequent finding on chest CT (fig. 2a, b), and this investigation has been shown to be useful in demonstrating the lung lesions a few days before they are radiologically apparent. The radiological abnormalities associated with SARS are often non-specific and indistinguishable from lower respiratory tract infection due to other viruses. These images can only provide information on the severity of pulmonary involvement and cannot be used as a specific investigation for diagnosis of SARS.

Management

The management of SARS consists of (i) effective triaging for in-patients; (ii) good infection control measures, and (iii) specific treatment for the disease.



Fig. 1. A chest radiograph of an 8-year-old boy with SARS. The patient presented with fever, dry cough, and chills and rigor. The chest radiograph revealed an area of ill-defined air-space opacification in the left lower zone with loss of the left heart silhouette. Another smaller opacity is present at the right upper zone (arrows).

An effective triage policy for fever patients is vital for preventing cross infection amongst in-patients. Our experience suggests that many isolation rooms and cubicles are needed for separating different categories of patients such as those who are febrile, those with contact history and those with radiological features suggestive of bronchopneumonia [21, 22]. The ultimate organisation of patient cohorting depends on the geographical configuration of the paediatric ward and neonatal unit of individual hospitals [21, 22]. In addition, visiting is restricted for children with fever and is not allowed for suspected or probable cases of SARS [21, 22]. Towards the latter half of the outbreak, a videophone system was installed in the SARS areas to enable parents to communicate and to see their children in real time.

The infection control measures in the paediatric ward and neonatal unit are targeted at preventing contact, droplet and aerosol spread of the virus. Disposable water-resistant protective gowns and masks should be worn in all high-risk areas. Face shield and goggle, in addition to the regular protective gear, are recommended for performing high-risk procedures such as tracheal intubation, attending delivery and collection of potentially contami-



Fig. 2. High-resolution computed tomography (CT) scan of thorax of the same patient as in figure 1 showing multifocal areas of mixed ground glass and air-space consolidation in the lingular segment of the left lower lobe (a), and the peripheral region of the right upper lobe (b).

nated specimens. The use of nebulisers, high-flow oxygen masks and continuous positive airway pressure ventilation are prohibited outside the incubator or in an open ward [21, 22]. Staff must change gloves and wash or alcohol-rub hands after contact with each patient.

It is important that frontline paediatricians do not miss community-acquired pneumonia or systemic infections due to other treatable microorganisms [23]. Patients with fever and pneumonia are treated with a cephalosporin and a macrolide antibiotic. Most non-SARS patients

improve and become afebrile within 1 week. The specific treatment regimen for paediatric SARS patients is largely extrapolated from the adult protocol [3, 12]. In principle, antiviral agents should be prescribed for phase 1, and immunomodulating therapy for phase 2 of the disease. During the outbreak, ribavirin and corticosteroids were used as a combined therapy for acute treatment [6, 7]. Intravenous pulsed methylprednisolone was reserved for those who had progressive clinical and/or radiological deterioration in the second phase. Despite the apparent encouraging response to the treatment regimen, there is no evidence that ribavirin is effective *in vitro* against SARS-CoV. It is possible that high circulating IP-10 and MIG levels are effective in recruiting inflammatory cells for eradicating the virus in the acute phase [unpubl. data]. Although anecdotal experience supports the use of corticosteroids in severely affected patients [24], their use may be associated with serious adverse effects [25]. Whether children with mild or moderate SARS should be subjected to such potentially toxic treatment requires to be tested by future randomised clinical trials. Our latest study on cytokines does not support the use of TNF α monoclonal antibody for treatment of this category of patients [15]. New antiviral agents and immunomodulating drugs, such as kaletra and interferon-1 β , are currently under investigation.

Outcomes

In contrast to the high fatality rates in adults with SARS [4, 5], there was no death in the paediatric popula-

tion in Hong Kong and Canada [6–8]. Less than 4% of children required mechanical ventilation in Hong Kong and most were teenage patients. We are closely monitoring the late postviral complications and long-term pulmonary function of these children.

Conclusions

The most important question to answer regarding pregnant women with SARS is whether SARS-CoV can be transmitted vertically to the fetus to cause bronchopneumonia or systemic viral infection. Our data suggest that the coronavirus is unlikely to be transferred via the intrauterine route, and none of the newborn infants was shedding the virus or developed SARS-CoV infection [10]. However, their abdominal signs and symptoms should be carefully monitored after delivery, and growth and neurodevelopment deserve long-term follow-up. Although a recent report suggests that young infants with SARS could become ill and require supplemental oxygen [26], young children, in general, develop a milder form of disease with a less aggressive clinical course than that of teenage and adult patients [6–8]. The understanding of the genome sequence of the SARS-CoV [27–30], the immunological profiles [15], and the natural history of the disease in different age groups [6–8, 12, 24] may hopefully facilitate the development of rapid and accurate diagnostic tests, treatments and vaccines to fight against this highly contagious and potentially devastating disease.

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