Research letters

Clinical presentations and outcome of severe acute respiratory syndrome in children

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Hong Kong has been severely affected by severe acute respiratory syndrome (SARS). Contact in households and health-care settings is thought to be important for transmission, putting children at particular risk. Most data so far, however, have been for adults. We prospectively followed up the first ten children with SARS managed during the early phase of the epidemic in Hong Kong. All the children had been in close contact with infected adults. Persistent fever, cough, progressive radiographic changes of chest and lymphopenia were noted in all patients. The children were treated with high-dose ribavirin, oral prednisolone, or intravenous methylprednisolone, with no short-term adverse effects. Four teenagers required oxygen therapy and two needed assisted ventilation. None of the younger children required oxygen supplementation. Compared with adults and teenagers, SARS seems to have a less aggressive clinical course in younger children.

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Since late February, 2003, WHO has received reports of outbreaks of a severe form of atypical pneumonia in Vietnam, Hong Kong, and Singapore. Hong Kong is the most severely affected city. WHO has referred to this unusual form of severe pneumonia as severe acute respiratory syndrome (SARS).[1] The surveillance case definition of SARS is: history of high fever (>38°C); one or more respiratory symptoms, including cough, shortness of breath, and difficulty breathing; and close contact within 10 days before onset of symptoms with a person who has been diagnosed with SARS, history of travel within 10 days before onset before symptoms to an area with reported foci of SARS transmission, or both.[1] Household contact and contacts in health-care settings are believed to be important routes of transmission.[2,3] This transmission route could put children at particular risk, but most data available so far have been in adults. We therefore decided to report our experience in treating children with SARS.

Between March 13 and 28, 2003, ten children with suspected SARS were admitted to and managed at the Prince of Wales and Princess Margaret Hospitals, Hong Kong. We prospectively followed up the clinical, laboratory, and radiological profiles and treatment outcomes of these children. Microbiological investigations were done to detect common bacterial and viral pathogens associated with community-acquired pneumonia.

We treated all patients with combined corticosteroids, antivirals, and antibacterial agents. Intravenous cefotaxime, oral clarithromycin, and oral ribavirin (40 mg/kg daily, given in two or three doses) were started if a diagnosis of SARS was suspected on admission. Oral prednisolone (0·5 mg/kg daily at Prince of Wales Hospital, and 2·0 mg/kg daily at Princess Margaret Hospital) was added if fever persisted after 48 h. In addition, we treated patients who had moderate symptoms of high fluctuating fever and notable malaise with intravenous ribavirin (20 mg/kg daily, given in three doses) and hydrocortisone (2 mg/kg every 6 h) immediately after admission. For patients who had persistent fever and progressive worsening clinically or radiologically, we used pulse intravenous methylprednisolone (10–20 mg/kg). Ribavirin was administered for 1–2 weeks and corticosteroid dose was tapered over 2–4 weeks.

All children satisfied the WHO case definition for SARS and all had been in close contact with infected adults. The demographic, clinical, and laboratory data are shown in the table. Fever was a consistent symptom in all children, and lasted for a median duration of 6 days (range 3–11). There was no clinically significant drop in haemoglobin concentrations during treatment with ribavirin. In eight patients, corticosteroid was added to the regimen when fever did not subside. Pulse methylprednisolone was given to one young child (patient 2) and four teenagers (patients 6–9). Within 2 days of corticosteroid administration, all but one patient (patient 9) became afebrile. The same four teenagers developed respiratory distress and oxygen desaturation on day 5, 4, 6 and 7, respectively, after the onset of fever. These children were placed under strict isolation for 21 days and became asymptomatic before discharge.

Nine children had abnormal chest radiographs on presentation. The primary abnormality was air-space opacification. Of the five children aged 12 years or younger (patients 1–5), four presented with focal segmental consolidation. Patient 2 had ill-defined patchy consolidation, but CT of the thorax showed multifocal air-space consolidation. All these patients had mild progressive consolidative change on serial chest radiographs but complete resolution was achieved within 14 days. The typical radiographic changes in one patient are shown in the figure. Three of the five teenagers (patients 7–9) presented with bilateral lower-lobe opacification at presentation, which progressed rapidly within days. Despite clinical improvement, these consolidative changes persisted into the 2nd week of the illness. Patient 10 showed no abnormality on chest radiography at presentation, but high-resolution CT confirmed focal consolidation in the right lower lobe. In CT of the thorax in patients 2 and 6, the characteristic features of peripheral and alveolar opacities simulated the radiological appearances of bronchiolitis obliterans organising pneumonia. Four teenagers required supplemental oxygen, one required bi-level positive airway pressure and intermittent positive-pressure ventilation. Respiratory distress developed 4–7 days after presentation.

Lymphopenia ($0{\cdot}3$–$3{\cdot}0\times10^9$/L) was reported in all patients, but the teenagers were generally more severely affected than the younger children. Lymphopenia mostly occurred between days 3 and 7, after the onset of fever. No bacteria, fungi, mycoplasma, chlamydia, or common respiratory viruses were detected by the laboratory investigations. Coronavirus was isolated by viral culture from the nasopharyngeal aspirates of patients 2 and 3. Reverse-transcriptase PCR targeting the novel coronavirus present in the nasopharyngeal aspirate samples was positive in four of six children tested (patients 1, 7, 9, and 10).

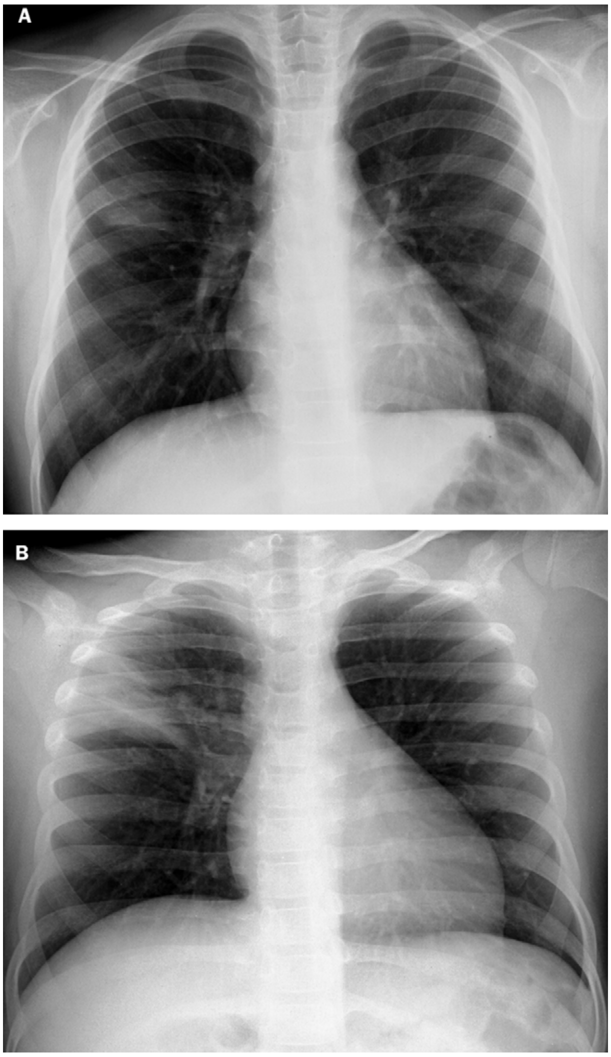
	Patient number									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Age (years)	1·5	2·2	5·1	6·2	7·5	13·2	13·3	15·6	15·6	16·4
Sex (M/F)	F	M	F	F	M	F	F	F	F	F
Clinical features										
Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dyspnoea	No	No	No	No	No	Yes	Yes	Yes	Yes	No
Runny nose	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	No
Cough	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Sore throat	No	No	No	No	No	No	Yes	Yes	Yes	No
Chills/rigors	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Myalgia	No	No	No	No	No	No	Yes	Yes	Yes	Yes
Headache	No	No	No	No	No	No	Yes	Yes	Yes	Yes
Other	··	Febrile convulsion	··	··	Dizziness	Nausea	Abdominal pain	··	Nausea	··
Contact history	Community outbreak	Grandmother	Grandmother	Family doctor	Parents	Health-care worker	Community outbreak	Mother*	Mother*	Health-care worker
Laboratory findings										
Lowest lymphocyte count ($\times10^9$/L)	3·0 (day 3)	1·1 (day 3)	1·1 (day 4)	1·1 (day 3)	1·2 (day 3)	0·8 (day 6)	0.7 (day 4)	0·4 (day 6)	0·3 (day 11)	0·4 (day 7)
Lowest platelet count ($\times10^9$/L)	345	216	143	196	131	178	147	136	131	209
Highest serum LDH (U/L)†	376	308	324	273	332	286	676	392	431	208
Highest serum ALT (U/L))‡	29	35	25	12	38	45	44	95	65	168
Radiological findings										
Initial chest radiograph	Right lower-zone focal	Right perihilar	Left middle-zone consolidation	Left upper-zone consolidation	Right upper-zone consolidation	Right lower-zone consolidation	Left and right lower-zone consolidation	Left lower-zone consolid-ation	Left lower-zone consolid-ation	Normal
Progressive changes of chest radiograph	Increased right lower-zone consol-idation (day 2)	Progress to involve right upper zone (day 8)	Increased left middle-zone consolidation (day 5)	Increased left upper-zone consolidation (day 4)	Increased right upper-zone consol-idation (day 5)	Increased right lower-zone consol-idation (day 5)	Increased right and left upper-zone consolidation (day 6)	Diffuse confluence left and right lower zones (day 9)	Diffuse confluence right and left lower zones (day 11)	Normal
Findings on CT of thorax	None	Bilateral multifocal air space consol-idations	None	None	None	None	None	None	None	Consolid-ation at right basal segments
Treatment and outcome										
Oral ribavirin	Prescribed	Prescribed	Prescribed	Prescribed	Prescribed	Prescribed	Not prescribed	Not prescribed	Not prescribed	Prescribed
IV ribavirin	Not prescribed	Prescribed	Not prescribed	Not prescribed	Not prescribed	Prescribed	Prescribed	Prescribed	Prescribed	Not prescribed
Oral prednis-olone/IV hydrocortisone	Not prescribed	Prescribed	Prescribed	Not prescribed	Prescribed	Prescribed	Not prescribed	Prescribed	Prescribed	Prescribed
IV pulse methyl-prednisolone	Not prescribed	Twice (day 10)	Not prescribed	Not prescribed	Not prescribed	Once (day 6)	Three times (days 4–6)	Once (day 6)	Once (day 7)	Not prescribed
Duration of fever (days)	4	6	7	3	6	6	5	10	11	4
Ventilatory support	Not prescribed	Not prescribed	Not prescribed	Not prescribed	Not prescribed	Nasal cannula (days 5–9)	Nasal cannula (days 4–10)	Face mask (days 7–8; 12–15), BiPAP (days 8–12)	Face mask (days 7–10; 13-19), IPPV (days 10–13)	Not prescribed
Maximum oxygen requirement	Air	Air	Air	Air	Air	2 L/min	3 L/min	50%	50%	Air

LDH=lactic dehydrogenase. ALT=alanine aminotransferase. IV=intravenous. BiPAP=bi-level positive airway pressure. IPPV=intermittent positive pressure ventilation. *Mother of twin sisters (patients 8 and 9) is health-care assistant. †Normal range 110–230 U/L. ‡Normal range 1–40 U/L.

Clinical features and treatment outcomes among SARS children

We noted two distinct patterns of clinical presentation among the children we studied. Teenage patients presented with symptoms of malaise, myalgia, chill, and rigor similar to those of adults,[2,3] whereas the younger children presented mainly with cough and runny nose, and none had chills, rigor, or myalgia. The clinical course was much milder and shorter among younger patients, and radiological changes were milder and generally resolved more quickly than in the teenagers. All paediatric patients had clinically important lymphopenia,[3] but it was more severe among the teenage children. However, since young children normally have higher lymphocyte counts than adults, the interpretation of results must take into account the patients' ages.[4] Furthermore, lymphopenia frequently resolves when the disease is improving.

We adopted a treatment regimen of ribavirin and steroids similar to that used in adult SARS patients.[2,3] Ribavirin is a broad-spectrum antiviral agent and has been used for treatment of severe respiratory syncytial virus infection in



Serial chest radiographs of patient 5, who presented with fever and cough

A=ill-defined air-space consolidation in periphery of right upper lobe and abutting horizontal fissure. B=Increased consolidation in right upper zone on day 5.

children.[5] Among our patients, short-term use of high-dose ribavirin was well tolerated and had no major short-term adverse effects such as severe haemolytic anaemia. In addition, high-dose corticosteroid was used in combination with the antiviral agent because severe immune-mediated damage of lung tissue was reported in postmortem examination of SARS patients.[3]

Eight of the ten children had been attending school at the time of presentation. There was no evidence that they had spread the infection to their classmates. This finding is in sharp contrast to the experience reported among adults that SARS carries a very high infectivity rate.[2,3] At the time of our study, 22 adults had died in Hong Kong.[3] During the study period, around 30 children were suspected as having SARS in Hong Kong. So far, no child has died. Our preliminary findings suggest that young children develop a milder form of the disease with a less-aggressive clinical course than do teenagers and adults.

1 WHO. Case definition for surveillance of severe acute respiratory syndrome SARS. http://www.who.int/csr/sars/casedefinition (accessed April 24, 2003).

2 Peiris JSM, Lai ST, Poon LLM, et al, and members of the SARS study group. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; **361:** 1319–25.

3 Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. http://content.nejm.org/cgi/reprint/NEJMoa030685v2.pdf (accessed April 24, 2003).

4 Cairo M, Brancho F. Blood and blood-forming tissues. In: Rudolph AM, ed. Rudolph's Pediatrics, 21st edn. New York: McGraw Hill, 2002: 1548.

5 Smith DW, Frankel LR, Mathers LH, Tang AT, Ariagno RL, Prober CG. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. *N Engl J Med* 1991; **325:** 24–29.

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