Children Hospitalized With Severe Acute Respiratory Syndrome-Related Illness in Toronto

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ABSTRACT. *Objective.* An outbreak of severe acute respiratory syndrome (SARS) occurred in the greater Toronto area between February and June 2003. We describe the clinical, laboratory, and epidemiologic features of children who were admitted to the Hospital for Sick Children, Toronto, with a presumptive diagnosis of suspect or probable SARS.

Methods. A prospective investigational study protocol was established for the management of children with a presumptive diagnosis of suspect or probable SARS. All were ultimately classified as having probable SARS, suspect SARS, or another cause on the basis of their epidemiologic exposure, clinical and radiologic features, and results of microbiologic investigations.

Results. Twenty-five children were included; 10 were classified as probable SARS and 5 were classified as suspect SARS, and in 10 another cause was identified. The exposure consisted of direct contact with at least 1 adult probable SARS case in 11 children, travel from a World Health Organization-designated affected area in Asia in 9 children, and presence in a Toronto area hospital in which secondary SARS spread had occurred in 5 children. The predominant clinical manifestations of probable cases were fever, cough, and rhinorrhea. With the exception of 1 teenager, none of the children developed respiratory distress or an oxygen requirement, and all made full recoveries. Mild focal alveolar infiltrates were the predominant chest radiograph abnormality. Lymphopenia; neutropenia; thrombocytopenia; and elevated alanine aminotransferase, aspartate aminotransferase, and creatine kinase were present in some cases. Nasopharyngeal swab specimens were negative for the SARS-associated coronavirus by an in-house reverse transcriptase-polymerase chain reaction in all 25 children.

Conclusions. Our results indicate that SARS is a relatively mild and nonspecific respiratory illness in previously healthy young children. The presence of fever in conjunction with a SARS exposure history should prompt one to consider SARS as a possible diagnosis in children irrespective of the presence or absence of respiratory symptoms. Reverse-transcriptase polymerase chain reaction analysis of nasopharyngeal specimens seems to be of little utility for the diagnosis of SARS during the early symptomatic phase of this illness in young children. *Pediatrics* 2003;112:e261–e268. URL: http://www.pediatrics.org/cgi/content/full/112/4/e261; *severe acute respiratory syndrome, reverse-transcriptase polymerase chain reaction, probable SARS, suspect SARS.*

ABBREVIATIONS. SARS, severe acute respiratory syndrome; WHO, World Health Organization; RT-PCR, reverse-transcriptase polymerase chain reaction; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine kinase.

Severe acute respiratory syndrome (SARS) was first described in an American businessman who was hospitalized in Hanoi, Vietnam, in late February 2003 by Dr Carlo Urbani, a World Health Organization (WHO) communicable diseases expert (sadly, Dr Urbani himself died of SARS on March 29, 2003).[1] The WHO issued a global health alert describing this syndrome on March 12, 2003.[2] By June 30, 2003, a total of 8447 probable cases of SARS were reported to the WHO from >30 countries.[3] The majority of cases occurred in China (*n* = 5327), Hong Kong (*n* = 1755), Taiwan (*n* = 678), Canada (*n* = 252), and Singapore (*n* = 206). An overall mortality rate of approximately 9.5% is suggested by WHO surveillance data.

A novel coronavirus has been implicated in several clinical studies as the likely cause of SARS.[4–8] In these studies, the SARS-associated coronavirus was isolated in Vero-cell culture and detected by reverse-transcriptase polymerase chain reaction (RT-PCR) in respiratory samples taken from patients with suspected SARS. Furthermore, the illness has now been reproduced in cynomolgus macaques inoculated with Vero cell-cultured SARS-associated coronavirus, and the virus subsequently isolated from these animals was found to be identical to that inoculated, as shown by negative-contrast electron microscopy and RT-PCR.[9] Thus, the modified Koch's postulates set forth by Rivers[9,10] for viral diseases seem to have been satisfied. The genome of the SARS-associated coronavirus has now been fully sequenced, and phy-

logenetic analysis indicates that it is not closely related to the 3 previously known coronavirus groups.[11,12]

The clinical, laboratory, and radiologic features of SARS have been described principally in adults.[4,5,8,13,14] There is a paucity of pediatric data; a preliminary report out of Hong Kong describing 10 cases of pediatric SARS suggested that younger children may have milder disease than teenagers and adults.[15] The purpose of the present report is to describe the clinical, laboratory, and epidemiologic features of children who were admitted to the Hospital for Sick Children, Toronto, with a presumptive diagnosis of suspect or probable SARS.

METHODS

Study Population and Setting

Between February and June 2003, an outbreak of SARS occurred in the greater Toronto area.[4,13] All children who were admitted to the Hospital for Sick Children during this period with a presumptive diagnosis of suspect or probable SARS were included. The Hospital for Sick Children, the largest pediatric referral center in the greater Toronto area, serves a population of approximately 1.2 million children and youths. The hospital has 350 acute care beds, 31 of which are negative-pressure isolation rooms.

SARS-Related Definitions

Suspect SARS was defined by the presence of fever (>38°C orally) and a history of potential exposure to SARS during the 10 days preceding the onset of symptoms. A child was considered to have probable SARS when he or she fulfilled the criteria for suspect SARS and had chest radiograph findings suggestive of lower respiratory tract disease (mild peribronchial thickening was not considered evidence of lower respiratory tract disease). The WHO surveillance case definition requirement for cough or difficulty in breathing was removed because of early clinical experience indicating that SARS is a relatively mild illness in children and concern that some SARS cases would be missed if the WHO criteria were followed strictly.[16] Potential exposure to SARS was defined by documented close contact with a person fulfilling the WHO definition of suspect or probable SARS or history of travel from a SARS-affected area in Asia or having been in a hospital in the greater Toronto area in which secondary SARS transmission had occurred.

During the course of hospitalization, children were reclassified into 3 groups (probable SARS, suspect SARS, and other cause) in a manner similar to that recently recommended by the WHO.[16] A child was considered to have probable SARS when he or she fulfilled the aforementioned criteria for suspect SARS, had radiographic changes suggestive of lower respiratory tract disease or evidence of a severe progressive respiratory illness (including decreased oxygen saturation) suggestive of atypical pneumonia or acute respiratory distress syndrome, and no other potential causative agent was identified. In the absence of chest radiograph changes suggestive of lower respiratory tract disease or severe progressive respiratory illness, a child was classified as suspect SARS when no other potential causative agent was identified. The other cause category included all children for whom a firm non-SARS causative diagnosis was established.

Study Design and Protocol

A prospective investigational study protocol was established for the management of children who were admitted with a diagnosis of suspect or probable SARS by the Pediatric SARS Investigation Team. The study was approved by the Research Ethics Board of the Hospital for Sick Children. All children who fulfilled criteria for suspect or probable SARS were admitted and placed in single negative-pressure isolation rooms. Strict airborne and droplet infection control precautions were implemented for all cases; this included the use of an N-95 mask, face shield or goggles, cap, gown, and gloves for any patient contact. Direct contact with patients was restricted to a small number of SARS management team members. Parents of children hospitalized with suspect or probable SARS were not permitted to stay with or visit their children and were quarantined at home by public health authorities. No visitors were permitted. A record of all health care workers and support staff who came in contact with these patients was maintained in the patient's chart.

A standard set of investigations, including a portable chest radiograph and laboratory tests, were performed on all patients at the time of admission. Routine laboratory investigations included a complete blood count and differential, venous blood gases, serum electrolytes, creatinine, urea, bilirubin, γ-glutamyl transferase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase (CPK). Follow-up complete blood counts were performed every 2 to 4 days on patients who received intravenous ribavirin. Follow-up chest radiographs and blood work, other than the complete blood counts in those on ribavirin, and any investigations not listed in the protocol were performed at the discretion of the managing physician.

Microbiologic investigations, performed within 24 hours of admission, included a nasopharyngeal swab for direct antigen detection and culture of common respiratory viruses (respiratory syncytial virus, influenza A and B, parainfluenza 1–3, and adenovirus), a nasopharyngeal swab for SARS-associated coronavirus RT-PCR, a throat swab for bacterial culture, a throat swab for *Mycoplasma pneumoniae* PCR, a stool sample for electron microscopy, and 2 blood cultures. Direct antigen detection for common respiratory viruses was performed by means of direct immunofluorescence microscopy, and culture for these same viruses was performed using AGMK, MDCK, and Hep-2 cell lines. *M pneumoniae* PCR was performed using the P1–1 and P1–3 primers for the P1 adhesin gene as previously described.[17] Blood and throat swab bacterial cultures and stool for electron microscopy were performed using standard microbiologic methods.

RT-PCR for the SARS-associated coronavirus was performed using a modified version of a previously published assay.[4] Primers were directed at a highly conserved region of the POL-1B gene of the coronaviruses. Reverse transcription was done using the primer 5′-GCATAGGCAGTAGTTGCATC-3′, and PCR was done using the primers 5′-TGATGGGTTGGGACTATCCTAAATG-TGA-3′ and 5′-GTAGTTGCATCACCGGAAGTTGTGCCACC-3′. The expected amplicon size was 220 bp. The reverse transcription master mix was prepared by mixing 4 μL of reverse transcription buffer, 0.5 μL of RNasin (Promega, Mississauga, Ontario), 2 μL of dithiothreitol (100 mM), 1 μL dNTP mix (10 mM each), 1.5 μL of the coronavirus primer, and 1 μL of Superscript II (Life Technologies, Burlington, Ontario). The reverse transcription reaction was conducted by heating a 10-μL RNA aliquot to 65°C for 2 minutes, cooling it on ice, adding 10 μL of the reverse transcription reaction mix, and incubating at 42°C for 60 minutes. The PCR reaction was performed in a total volume of 50 μL containing 5 μL of reaction buffer, 1.25 μL of dNTP mix (10 mM each), 2 μL of each PCR primer (10 μm stock), 1 μL of Advantage 2 polymerase mix (Clontech, Mississauga, Ontario), 28.75 μL of double-distilled H₂O, and 10 μL of reverse transcription reaction mixture, all of which was overlaid with mineral oil. The PCR was done using a Robocycler 40 thermal cycler (Stratagene, La Jolla, CA). Thirty-seven cycles, each consisting of denaturation at 99°C for 35 seconds, annealing at 50°C for 90 seconds, and elongation at 68°C for 90 seconds, were performed. Reactions were analyzed by agarose gel electrophoresis.

The analytical sensitivity of the assay was measured using a serial dilution of RNA extracted from a lung biopsy sample of a patient with SARS. The viral load of the lung tissue had been quantified with the Real Art HPA-coronavirus RT-PCR (Artus, San Francisco, CA), and the analytical sensitivity of our RT-PCR assay was estimated at approximately 10 genome copies. The identity of the amplicon was verified by cleavage with the restriction enzyme *Alu* I and/or by sequencing the amplicon.

Clinical samples were run in batches. Each batch included a positive control consisting of an aliquot of serially diluted RNA from a lung tissue infected with the SARS-associated coronavirus (see above), which was reextracted and subjected to RT-PCR, 1 negative control consisting of double-distilled water used as a template for RNA extraction and RT-PCR, and 1 negative control consisting of double-distilled water used as a template for RT-PCR. Strict adherence to previously described precautions against PCR contamination was maintained.[18]

Ribavirin therapy was considered for all children who were

admitted with a presumptive diagnosis of suspect or probable SARS, particularly in the presence of chest radiograph abnormalities and/or a strong history of close contact with 1 or more probable SARS cases. Dosing of intravenous ribavirin was based on the dosing regimen recommended for several viral hemorrhagic fever syndromes.[19–21] The recommended dosing schedule included a loading dose of 33 mg/kg, followed by 16 mg/kg administered every 6 hours for a total of 4 days (16 doses), and then 8 mg/kg administered every 8 hours for a total of 3 days (9 doses). Standard antimicrobial therapy for community-acquired pneumonia or other focal infections was administered at the discretion of the treating physician.

RESULTS

Baseline Characteristics and Epidemiology

Twenty-five children were admitted to the Hospital for Sick Children with a presumptive diagnosis of suspect or probable SARS between March 14 and June 15, 2003. The majority of these admissions occurred between March 24 and April 4 (Fig 1). The median age of this cohort was 2.25 years (range: 5 months to 17.5 years). Sixty percent were female. With the exception of 1 child with recurrent acute otitis media and bilateral tympanostomy tubes, all were previously healthy. Ten were reclassified as probable SARS, 5 as suspect SARS, and 10 as other cause.

Eleven children had documented exposure to 1 or more people with probable SARS (Table 1); in all 11 cases, the SARS contacts were household and other adult family members. Eight of these children, including 7 with probable SARS and 1 with suspect SARS, were exposed to 2 or more probable SARS cases. The household contacts of 3 children, all of whom were classified as probable cases, were health care workers. In 9 children, the mode of exposure was travel from a WHO-reported affected area in Asia within 10 days of symptom onset; 6 from China, including 4 from Guangdong province and 2 from Beijing, 1 from Hong Kong, 1 from Singapore, and 1 from Vietnam. Two of these children, from Guangdong province in China, were classified as probable SARS. In the other 7 travel-related exposures, a firm alternative diagnosis was established. Five children

TABLE 1. Epidemiologic Exposure According to SARS Category

Exposure	Probable SARS	Suspect SARS	Other Cause
Direct contact*	8	1	2
Travel†	2	0	7
Hospital‡	0	4	1

* Defined as having cared for, lived with, or had face-to-face (within 1 m) contact with a suspect or probable SARS case (as defined by the WHO).
† Refers to travel from or residence in a WHO-designated SARS-affected area.
‡ Refers to presence in a Toronto area hospital at a time when secondary transmission of SARS had been documented.

had been admitted to or had visited a Toronto hospital at a time in which secondary SARS spread was subsequently documented to have occurred; none of these children met the case definition for probable SARS.

Clinical Manifestations

The median time from last possible SARS exposure to onset of symptoms for children with probable SARS was 5 days (range: 0–12 days). For children with suspect SARS and other causes, a median of 3 days and 0.5 days had elapsed between the time of last possible exposure and symptom onset (range: 0–13 days and 0–8 days, respectively). For the group as a whole, the duration of symptoms before admission ranged from several hours to as long as 5 days; 76% (19 of 25) were admitted to the hospital within 24 hours of symptom onset.

The epidemiologic exposure as well as clinical and laboratory features of children with probable and suspect SARS are illustrated in Tables 2 and 3. In general, the clinical manifestations of children in whom a non-SARS cause was identified did not differ substantially from children with probable and suspect SARS. Fever (38.0°C or higher) was the initial clinical manifestation in 7 probable (70%), 5 suspect (100%), and 9 other cause (90%) cases. Respiratory
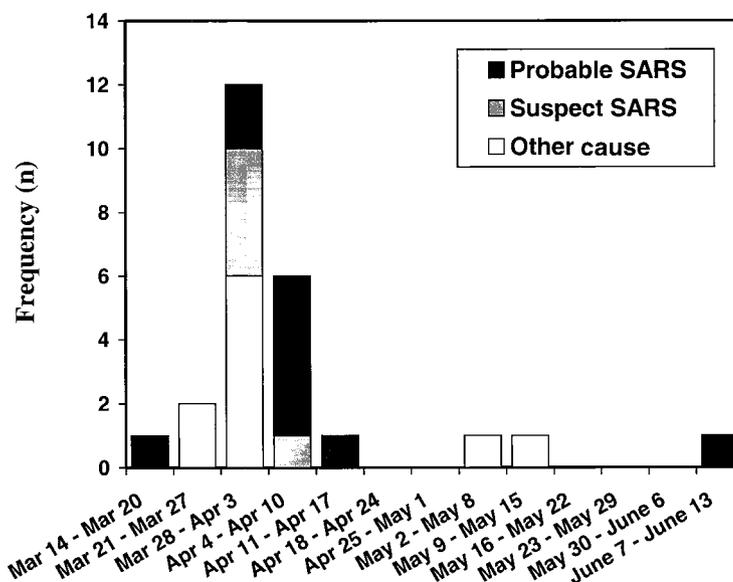
Fig 1. Number of SARS-related hospital admissions per week according to final SARS category.

TABLE 2. Clinical and Laboratory Features of Children With Probable SARS

Case	Age	Sex	Exposure*	Tmax	Clinical Manifestations†	Chest Radiograph Findings	Laboratory Abnormalities‡
1	17.5	F	1 household contact	40.1°C	Cough, dyspnea, hypoxemia, bilateral crackles	Dense RML and LLL infiltrates	Leukopenia (2.70×10^9/L); lymphopenia (0.81×10^9/L); thrombocytopenia (130×10^9/L); elevated AST, ALT (236 U/L, 187 U/L); elevated CPK (457 U/L); elevated LDH (>2150 U/L)
2	12	F	>2 household contacts	38.1°C	Cough, diarrhea	LLL infiltrate	None
3	11	M	2 household contacts	38.5°C	Headache, chills	RLL infiltrate	Lymphopenia (1.39×10^9/L)
4	6	M	2 household contacts	38.2°C	Sore throat, vomiting	Patchy lower lobe infiltrate, peribronchial thickening	Lymphopenia (1.30×10^9/L); neutropenia (0.33×10^9/L); elevated AST (61 U/L); elevated LDH (1012 U/L)
5	4.5	F	>2 household contacts	38.7°C	Cough, rhinorrhea, bilateral crackles	Patchy RUL infiltrate, peribronchial thickening	None
6	2.9	M	2 household contacts	41.0°C	Cough, rhinorrhea	LLL infiltrate, peribronchial thickening	None
7	2.4	M	>2 household contacts	38.2°C	Lethargy	RLL infiltrate	Leukopenia (2.4×10^9/L); lymphopenia (0.74×10^9/L); neutropenia (0.63×10^9/L)
8	1.3	F	Travel from Guangdong Province, China	40.0°C	Cough	Patchy RUL infiltrate, peribronchial thickening	None
9	1.2	F	Travel from Guangdong Province, China	38.°C	Cough, rhinorrhea, bilateral crackles, diarrhea, vomiting	Moderate bilateral perihilar peribronchial thickening	None
10	0.4	M	>2 household contacts	38.3°C	Rhinorrhea	Patchy RUL and RLL infiltrates	Neutropenia (0.65×10^9/L); elevated ALT (74 U/L)

Tmax indicates highest documented temperature; RML, right middle lobe; RLL, right lower lobe; RUL, right upper lobe; LLL, left lower lobe.
* All known household contacts were adults (parents and other relatives).
† Fever was present in all cases
‡ The most abnormal result is shown.

TABLE 3. Clinical and Laboratory Features of Children With Suspect SARS*

Case	Age	Sex	Exposure	Tmax	Clinical Manifestations†	Laboratory Abnormalities‡
1	16	F	Hospital	39.0°C	Cough, chills, fatigue	None
2	5	F	2 household contacts§	40.3°C	Cough	Leukopenia (3.10×10^9/L); neutropenia (1.00×10^9/L); lymphopenia (1.30×10^9/L)
3	3	F	Hospital	40.1°C	Vomiting, diarrhea, lethargy	Lymphopenia (1.39×10^9/L); elevated AST (62 U/L)
4	1.8	M	Hospital	38.1°C	Cough, rhinorrhea	None
5	1.2	F	Hospital	39.7°C	Diarrhea	Elevated AST (81 U/L)

* By definition, none of these children had chest radiograph finding suggestive of lower respiratory tract disease (other than mild peribronchial thickening).
† Fever was present in all cases.
‡ The most abnormal result is shown.
§ All known household contacts were adults (parents and other relatives).

symptoms occurred in 8 probable (80%), 3 suspect (60%), and 7 other cause cases (70%). The onset of respiratory symptoms preceded fever in 3 probable cases (30%) and coincided with the onset of fever in 2 probable (20%) and 6 other cause cases (60%). Headache, lethargy, vomiting, and diarrhea were observed in a minority of cases. Irritability and myalgia were not identified in any of the children in this cohort.

Chest Radiograph and Laboratory Findings

Relatively minor nonspecific focal alveolar infiltrates were the predominant radiologic abnormality noted in 8 of 10 probable SARS cases (Fig 2). Bilateral progressive lower lobe infiltrates were observed in 1 case; this 17.5-year-old female was the only patient to manifest respiratory distress and an oxygen requirement (patient 1, Table 2). Moderate bilateral perihilar peribronchial thickening was the sole radiologic abnormality in 1 probable case. By definition, there were no chest radiograph abnormalities suggestive of lower respiratory tract disease (other than mild peribronchial thickening) in children who were categorized as having suspect SARS. One child in the other cause category demonstrated multifocal patchy infiltrates in the perihilar and lower lung regions.

The remaining 9 children in this category had normal chest radiographs.

Laboratory findings are shown in Tables 2 to 4. Lymphopenia ($<1.5 \times 10^9$/L) was the most common hematologic abnormality occurring in 4 probable, 2 suspect, and 2 other cause cases. Neutropenia ($<1.5 \times 10^9$/L) was noted in 3 children with probable SARS, 1 child with suspect SARS, and 2 children with other causes. Mild thrombocytopenia was seen in 1 patient in each of the 3 categories. Elevated ALT and/or AST was detected in 3 children with probable SARS, 2 children with suspect SARS, and 5 children with other causes. With the exception of 1 probable SARS case (patient 1, Table 2) the elevation in ALT and AST was minimal (40–100 U/L). An elevated CPK was observed in 1 probable case (patient 1, Table 2). A high lactate dehydrogenase level was seen in 2 of 5 probable SARS cases tested (patients 1 and 4, Table 2) and 1 of 3 other cause cases tested. RT-PCR for the SARS-associated coronavirus on nasopharyngeal swab specimens was negative in all 25 children.

A non-SARS causative agent was identified in 10 children (other cause category). In 7 of these children, common respiratory viruses were identified by culture and/or antigen detection of respiratory sam-
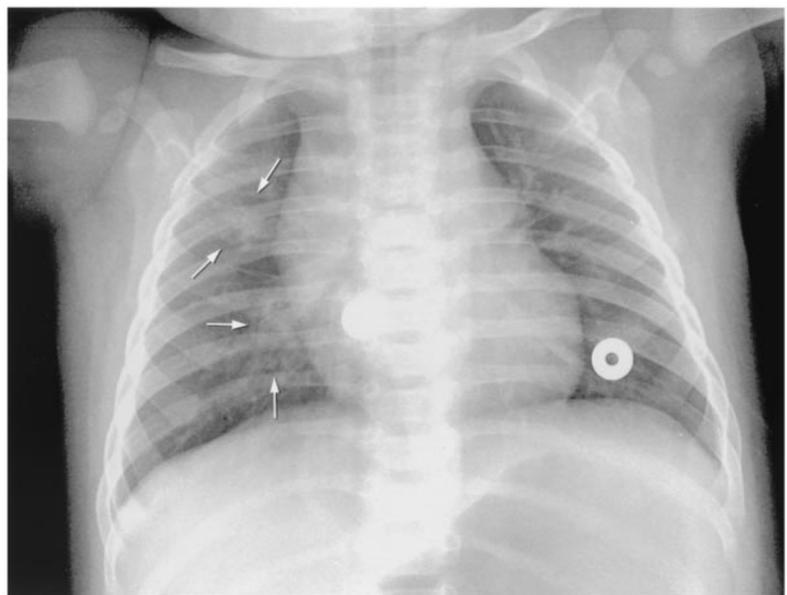
Fig 2. Chest radiograph of a 5-month-old male infant demonstrating ill-defined patchy infiltrates in the right upper lobe and superior segment of the right lower lobe. The infant presented with fever and nasal congestion after prolonged household contact with several symptomatic adult family members who were subsequently confirmed to have SARS.

TABLE 4. Selected Laboratory Features at Time of Admission*

Parameter	Probable SARS (n = 10)	Suspect SARS (n = 5)	Other Cause (n = 10)	P Value†
White blood cell count (× 10⁹/L)	5.75 (2.40–20.30)	7.70 (6.30–10.20)	9.75 (4.00–38.00)	.15
Absolute neutrophil count (× 10⁹/L)	2.55 (1.11–10.90)	5.00 (3.90–8.30)	5.58 (0.11–29.30)	.06
Absolute lymphocyte count (× 10⁹/L)	1.90 (0.74–11.25)	1.90 (1.30–3.70)	3.20 (0.42–7.60)	.57
Hemoglobin (g/L)	113 (91–150)	130 (105–134)	114 (102–142)	.93
Platelet count (× 10⁹/L)	275 (131–593)	300 (230–349)	245 (154–421)	.71
Sodium (mEq/L)	138 (135–143)	135 (135–140)	139 (133–142)	.41
AST (U/L)	41 (23–97)	40 (18–81)	45 (22–65)	.93
ALT (U/L)	20 (6–74)	11 (3–41)	19 (3–72)	.46
CPK (U/L)	117 (56–457)	79 (28–114)	78 (56–284)	.37

* Reported as median (range); the median age of probable SARS (3.7 years; range: 5 months to 17.5 years), suspect SARS (2.25 years; range: 1.2 to 16 years), and other cause (2.1 years; range: 6 months to 12 years) cases was similar ($P = .48$, analysis of variance).
† Kruskal-Wallis test comparing probable SARS cases with other cause cases; comparison of other cause cases with pooled results of probable and possible cases also did not reveal significant differences.

ples; these included influenza A (n = 3), adenovirus (n = 2), parainfluenza 3 (n = 1), and respiratory syncytial virus (n = 1). All 7 presented with fever and respiratory symptoms. *Streptococcus pneumoniae* bacteremia, primary varicella zoster virus infection, and rotavirus diarrhea were each implicated as the likely cause of symptoms in 1 other cause case.

Antimicrobial Therapy

Ribavirin was administered intravenously to 10 children (1 also received aerosolized ribavirin). In all but 2, the decision to initiate ribavirin was based on the finding of chest radiograph infiltrates and a preliminary diagnosis of probable SARS. The 2 children who received ribavirin despite normal chest radiographs had heavy household exposure to >1 probable SARS case (patient 3, Table 2, and patient 2, Table 3). Of the 10 children initiated on ribavirin therapy, 8 were ultimately classified as probable SARS, 1 as suspect SARS, and 1 as other cause. The duration of ribavirin therapy ranged from 2 to 10 days (median 7 days). Hemolytic anemia occurred in 1 probable case (patient 1, Table 2), but this was of mild degree and did not necessitate discontinuation of the drug. No other ribavirin-associated adverse effects were noted. Corticosteroids were not administered to any of the children in this cohort. A full course of antibiotic therapy (clarithromycin) for community-acquired pneumonia was given to 6 probable cases and 1 other cause case.

Course in Hospital and Outcome

The clinical course of most children was mild and brief in duration. Only 1 child (a teenager) with probable SARS developed respiratory distress and required oxygen supplementation (patient 1, Table 2). None of the children required ventilatory support or intensive care admission. The duration of fever ranged from 1 to 6 days (median: 1 day) for children with probable SARS, 1 to 3 days (median: 1 day) for children with suspect SARS, and 1 to 4 days (median: 2 days) for children with other causes. The duration of cough ranged from 0 to 10 days (median: 2 days) for children with probable SARS, 0 to 3 days (median: 1 day) for children with suspect SARS, and 0 to 4 days (median: 1 day) for children with other causes. The median duration of hospitalization for the entire cohort was 4 days (range: 1–25 days). For both prob-

able and suspect cases, the duration of hospitalization ranged from 2 to 25 days (median: 8 days and 3 days, respectively). Two siblings, 1 with probable SARS and 1 with suspect SARS, were hospitalized for 25 days principally as a result of their parents' prolonged hospitalization. The older of these 2 children (patient 3, Table 2) had a second febrile episode that lasted 3 days beginning 11 days into his admission; he had no other symptoms during this episode, but a patchy right lower lobe infiltrate was demonstrated.

DISCUSSION

The most striking observation from this cohort was the apparent nonspecific and mild nature of SARS-related illness in young children. The clinical, laboratory, and radiologic features were indistinguishable from those typically observed in infections caused by common respiratory pathogens such as respiratory syncytial virus and influenza. One infant with probable SARS presented with typical features of bronchiolitis. None of the children in this cohort, with the exception of a 17.5-year-old girl, developed respiratory distress or required oxygen supplementation, and in most, chest radiograph findings tended to be mild and nonspecific. Similarly, compared with teenagers and adults,[7,8,13–15] laboratory abnormalities such as lymphopenia, thrombocytopenia, and elevation in CPK and liver transaminase levels seemed to be mild in degree in young children. In fact, such abnormalities were observed in similar frequency in probable, suspect, and other cause cases. Our findings are generally consistent with those described for 10 children with probable SARS in Hong Kong.[15] In that cohort, 4 of 5 teenagers required oxygen supplementation, whereas all those younger than 10 years did not.

Two children in our cohort, classified as probable SARS because of household exposure, fever, and the presence of chest radiograph infiltrates, lacked respiratory symptoms throughout the course of their illness. Cough occurred in only 6 of 10 probable SARS cases. The chest radiograph changes of 1 of these children, who had prolonged household exposure to SARS (both parents with probable SARS), became apparent only during a second febrile episode that developed 11 days into hospitalization (patient 3, Table 2). His younger sister (patient 2, Table 3) had

fever, mild respiratory symptoms, and a normal chest radiograph. These observations suggest that the WHO surveillance case definition may not be sufficiently sensitive for young children. Specifically, the requirement for respiratory symptoms (cough or difficulty breathing) to qualify as a suspect case and the requirement for progressive respiratory disease or radiographic abnormalities to qualify as a probable case may not be appropriate in the pediatric setting. Our results suggest that, in children, the presence of fever in conjunction with an appropriate exposure history should lead one to consider the possibility of SARS. If SARS were to become an endemic disease, it would be necessary to treat any child with unexplained fever as a potential case of SARS until proved otherwise.

The relatively mild nature of SARS in young children raises intriguing questions regarding the pathophysiology and spread of this disease. In particular, the role of the host immune response to the offending agent in the disease process requires investigation. The demonstration of bilateral peripheral air-space ground-glass consolidation reminiscent of bronchiolitis obliterans organizing pneumonia (on computed tomography scanning) and the similarity of histologic features (pulmonary edema with hyaline membrane formation) of SARS to those of early adult respiratory distress syndrome are consistent with a disease that has an immune-mediated component.[14] It was, in part, these observations that led physicians in Hong Kong to use corticosteroids in addition to antimicrobial therapy in the management of SARS.[14]

Preliminary data suggest that children pose a lower risk of transmitting SARS than do adults.[15] In a report out of Hong Kong, there was no evidence of transmission by 8 children who had probable SARS and whose symptoms began while they were attending school. In our institution, no health care workers contracted SARS, and, as far as we know, there has been no documented transmission of SARS to health care workers from children. Whether this is attributable to a lower viral burden or to other factors remains to be determined.

Early in the epidemic, intravenous ribavirin was advocated in the treatment of adults and children with SARS in part because of its broad-spectrum in vitro activity against RNA viruses[19,22–24] and in part because of its efficacy in treatment of some viral hemorrhagic fever syndromes.[20,21] However, preliminary in vitro susceptibility testing undertaken by Health Canada's National Microbiology Laboratory and the US Army Medical Research Institute of Infectious Diseases suggests that ribavirin has no demonstrable activity against the SARS-associated coronavirus at concentrations effective for Lassa fever virus and other hemorrhagic fever viruses.[25] In addition, there is no convincing evidence that ribavirin is effective in reducing intensive care admissions, need for ventilatory support, or mortality among adult SARS patients.[13] At present, ribavirin is not recommended for the routine management of SARS in Canada.[25] The potential role of aerosolized ribavirin remains undefined.

The RT-PCR used in this cohort is an improved version of the coronavirus RT-PCR previously developed in our laboratory.[4] The primer sequences have been slightly modified, taking into account the recently published SARS-associated coronavirus genomic sequence.[11] The sensitivity of the new version of the test has been improved by 3 orders of magnitude. The original version was able to detect the presence of the SARS-associated coronavirus in bronchoalveolar lavage and/or lung biopsy specimens of some severely affected adult SARS patients.[4,26] In a Hong Kong cohort, the presence of SARS-associated coronavirus RNA was detected in nasopharyngeal specimens of 50% (22 of 44) of adults with probable SARS using a different RT-PCR assay.[8] In the only pediatric study published to date, the SARS-associated coronavirus was detected in nasopharyngeal specimens of 4 children, 3 of whom were teenagers.[15] The failure to detect coronavirus by RT-PCR in nasopharyngeal swab specimens in our cohort of predominantly young children may be related to poor sensitivity of the assay in the setting of mild disease (low viral load). Alternatively, it is conceivable that the SARS-associated coronavirus is only transiently present in the upper airway. The possibility that none of the children in our cohort was infected with the SARS-associated coronavirus cannot be excluded with certainty in the absence of serologic data, but this possibility seems extremely unlikely in view of the strong epidemiologic link of many of these cases to SARS. An intriguing observation is the recent finding that the SARS-associated coronavirus can be detected by RT-PCR in the blood, stool, and urine of some affected patients; the ultimate role that this will play in routine diagnosis remains to be seen.

The main limitation of the present study was the reliance on clinical and epidemiologic criteria to classify children as to their likelihood of having SARS. It is possible that some of the children in our cohort who were classified as probable SARS did not in fact have this disease, whereas others, classified as suspect SARS, may have been true SARS cases. It is also possible that some of the children in the other cause category had co-infections with the SARS-associated coronavirus. Despite the limitations of our classification strategy, we believe that its utility is supported by the fact that the majority of those with the strongest epidemiologic links to SARS were ultimately classified as probable SARS cases, whereas most of those with weak epidemiologic links ended up in the other cause category. Notwithstanding this observation, it will be important to revisit our classification strategy once reliable serologic assays become available. In this regard, we have been collecting and storing acute and convalescent blood samples for future analysis.

CONCLUSIONS

Our results suggest that SARS is a relatively mild and nonspecific respiratory illness in young children. The clinical features observed in teenagers seem to be more in line with those of adults. The WHO surveillance case definition for SARS may not be

sufficiently sensitive for young children; we suggest that the presence of fever in conjunction with an appropriate SARS exposure history should prompt one to consider SARS as a possible diagnosis in children irrespective of the presence or absence of respiratory symptoms. The failure to detect the SARS-associated coronavirus in nasopharyngeal swab specimens using RT-PCR in our cohort suggests that the quantity of virus present in the upper airway of young children during the early symptomatic phase of SARS is extremely low. The type of specimens and timing of collection of specimens that will provide the best diagnostic yield in children remain to be established.

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