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ABSTRACT. *Objective.* **To study the epidemiologic, clinical, laboratory, and radiologic features, prognostic indicators, and short-term to medium-term outcomes for children with severe acute respiratory syndrome (SARS) and to validate the performance characteristics of a clinical case definition, calculated with respect to SARS-associated coronavirus (SARS-CoV) seroconversion.**

Methods. **Children <18 years of age, from a single-site outbreak, who satisfied a clinical case definition for SARS, with subsequent serologic confirmation, were treated according to a standard protocol and prospectively monitored.**

Results. **Forty-four children were included. The median age was 12 years. Forty-two children (95.5%) demonstrated an epidemiologic link. Fever, cough, malaise, coryza, sputum production, headache, myalgia, lymphopenia, and elevated lactate dehydrogenase levels were common presenting features. Radiographic findings were nonspecific, but high-resolution computed tomography of the thorax was an early diagnostic aid. A specific reverse transcription-polymerase chain reaction assay for SARS-CoV yielded positive results for <50% of children. Of 9 children who developed hypoxemia, 8 were treated with methylprednisolone. Of 5 children who received intensive care, 3 required assisted ventilation. All children recovered, and serious adverse events in response to treatment were not observed. The outcomes at 3 to 6 months after disease onset, including exercise tolerance, pulmonary functions, and psychologic status, were favorable. An age of >12 years was associated with methylprednisolone therapy for severe illness. After exclusion of the only infant, an age of >12 years was associated with oxygen requirements. Sore throat, high neutrophil count at presentation, and peak neutrophilia were independent factors predicting severe illness. The clinical case definition demonstrated good sensitivity, specificity, and positive and negative predictive values (97.8%, 92.7%, 88%, and 98.7%, respectively) for diagnostic accuracy.**

Conclusions. **Children are susceptible to SARS-CoV infection. Teenagers resemble adults with respect to disease progression and may develop severe illness. The short-term to medium-term outcomes are good. Sore throat and initial and peak neutrophilia seem to be predictors of severe illness. Our clinical case definition performed well in the epidemic.** *Pediatrics* **2004; 113:e535–e543. URL: http://www.pediatrics.org/cgi/content/full/113/6/e535;** ***severe acute respiratory syndrome, SARS, children.***

ABBREVIATIONS. SARS, severe acute respiratory syndrome; SARS-CoV, SARS-associated coronavirus; CXR, chest radiograph; HRCT, high-resolution computed tomography; NPA, nasopharyngeal aspirate; RSV, respiratory syncytial virus; RT-PCR, reverse transcription-polymerase chain reaction; WHO, World Health Organization.

Hong Kong was struck by an epidemic of severe acute respiratory syndrome (SARS) from March to June 2003. A total of 1755 infected individuals were reported.[1] Although the majority were adults, 121 children (6.9%) <18 years of age were registered, yielding an age-specific attack rate of 8.9 cases per 100 000 persons <18 years of age and a case fatality rate of 0%. A total of 89 hospitalized children in Hong Kong demonstrated serologic evidence of infection by the SARS-associated coronavirus (SARS-CoV) (e-SARS database, Hospital Authority, Hong Kong Special Administrative Region, data on file).

Published articles on pediatric SARS have focused on reporting the demographic, clinical, laboratory, and radiologic characteristics. Definitive virologic data, prognostic indicators, and short-term to medium-term follow-up information were lacking in those preliminary reports.[2–4]

We prospectively monitored a cohort of 44 children with laboratory confirmation of SARS who were treated at a referral center for pediatric infectious diseases that admitted the largest number of pediatric patients with SARS in Hong Kong. Their epidemiologic links; clinical, laboratory, and radiologic features; and outcomes 3 to 6 months after disease onset are reported. The prognostic factors for severe illness and validation of a clinical case definition are described also.

METHODS

Patients

Children <18 years of age who were hospitalized in Princess Margaret Hospital (Hong Kong) during the period of March 14 to June 10, 2003, and who satisfied a clinical case definition for SARS were classified as having clinical SARS and were included in this

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study. Children who were referred with a diagnosis of suspected SARS during the same period but did not meet the clinical case definition were classified as having clinical non-SARS. Patients were classified as having laboratory SARS or laboratory non-SARS according to their SARS-CoV serologic findings.

Clinical Case Definition

The initial World Health Organization (WHO) case definitions of suspected and probable SARS were meant for surveillance.[5] Children in this study were classified as having clinical SARS if they satisfied the following diagnostic criteria: fever (rectal temperature of ≥38.5°C or oral temperature of ≥38°C), chest radiograph (CXR) findings of pulmonary infiltrates or acute respiratory distress syndrome, and suspected or probable contact with a person under investigation for or diagnosed as having SARS or exposure to a locality with suspected or documented community transmission of SARS, through either travel or residence, within 10 days of the onset of symptoms, as well as ≥1 of the following: chills, malaise, myalgia, muscle fatigue, cough, dyspnea, tachypnea, hypoxia, lymphopenia, decreasing lymphocyte count, or failure to respond, in terms of fever and general well-being, to antibiotics covering the usual pathogens of community-acquired pneumonia (eg, a broad-spectrum β-lactam plus a macrolide) after 2 days of therapy.

Radiologic Investigations

Serial CXRs were obtained after admission, using designated portable radiograph machines, until radiologic resolution. In the absence of abnormal findings but the presence of a definite history of contact, high-resolution computed tomography (HRCT) of the thorax was performed to facilitate diagnosis. Strict droplet and contact precautions were observed during transport of the patient to and from the computed tomography suite. Meticulous disinfection of the computed tomography suite was performed after the scheduled session, designated for suspected SARS patients only. Patients who required oxygen supplementation were offered HRCT examination of the thorax 3 to 6 months after disease onset.

Microbiologic Investigations

Bacterial culture of the blood was performed. Nasopharyngeal aspirates (NPAs) were used for rapid antigen detection of influenza A and B, respiratory syncytial virus (RSV), adenovirus, and parainfluenza types 1, 2, and 3, with direct immunofluorescence assays. NPA specimens were inoculated into different cell lines for isolation of respiratory viruses, including Vero E6 cells for specific isolation of SARS-CoV. Rapid diagnosis using reverse transcription-polymerase chain reaction (RT-PCR) targeting specific segments of the SARS-CoV genome was performed with RNA extracted from NPA and stool samples as described.[6,7] Serologic studies included *Mycoplasma pneumoniae* IgM and paired acute and convalescent sera for IgG against *M pneumoniae*, *Chlamydia pneumoniae*, *Chlamydia psittaci*, *Legionella pneumophila*, influenza A and B, RSV, adenovirus, and parainfluenza types 1, 2, and 3. Laboratory confirmation of SARS was made with detection of a ≥4-fold increase in convalescent antibody titers against SARS-CoV at least 21 days after disease onset, using an indirect fluorescent antibody assay.[8] Isolation of SARS-CoV from NPA or stool specimens in cell culture was similarly confirmatory.

Treatment

The treatment strategy for children with clinical SARS was modeled after the initial experience with adult patients. A regimen including antibiotics and ribavirin, with or without corticosteroids, in various combinations at different stages of the disease was used as described.[2] Significant adverse events related to treatment were recorded. Children who presented with psychologic, emotional, or behavioral disturbances during hospitalization or after discharge were referred to clinical psychologists for assessment and intervention.

Follow-up Monitoring

Children were evaluated 1 to 2 weeks after discharge and again 3 to 6 months after disease onset for assessment of their physical and psychologic status.

Statistical Analyses

Analyses were conducted with SAS software, version 6.12 (SAS, Cary, NC). Categorical variables were compared by using the χ^2 test with Yates' correction. Associations were assessed with the unpaired, 2-tailed t test for continuous variables. When the sample size was too small, Fisher's exact test was used. Univariate analyses of probable risk factors for severe illness were performed. Multivariate analysis with stepwise logistic regression was performed to identify independent risk factors for severe illness. $P < .05$ was considered significant.

RESULTS

Patients and Clinical Findings

Fifty children <18 years of age who met the clinical case definition for SARS were identified. During the same period, 89 children were hospitalized because of suspected SARS but were classified as having clinical non-SARS.

Of the 50 children with clinical SARS and the 89 children with clinical non-SARS who were prospectively studied, acute and convalescent serologic results were available for all 50 children and 77 children, respectively. Forty-four children with clinical SARS and only 1 child with clinical non-SARS demonstrated SARS-CoV seroconversion. Six children with clinical SARS did not demonstrate seroconversion 29 to 36 days after disease onset. Five of those patients had no direct contact with a person under investigation for or diagnosed as having SARS. The only child in the clinical non-SARS group with laboratory SARS had no contact history and presented with fever, coryza, sore throat, and cough. His CXR results were normal.

All 44 children with clinical and laboratory SARS were included for additional analyses. They came from 41 families, with a total of 76 affected members. None of the patients was immunocompromised. The demographic and epidemiologic characteristics are summarized in Table 1. An epidemiologic link could be established for 42 children (95.5%), including 31 children (70.5%) who were victims of a point-source major outbreak in the Amoy Gardens residential complex, in which 321 persons were involved.[9] During the epidemic in Hong Kong, ~60% of all children with serologically confirmed SARS were involved in the point-source outbreak.

The clinical features of the children are presented in Table 2. Forty children (90.9%) presented with ≥3 clinical features, and 22 children (50%) exhibited ≥5 features including fever. Headache ($P = .015$) and myalgia ($P = .002$) were significantly more common among children >12 years of age. Coryza ($P = .03$) was significantly more common among children ≤12 years of age. The youngest patient, a premature infant 50 days of age, presented with hypothermia, with subsequent fever, respiratory distress, and cyanotic attack.[10]

The mean duration of fever before admission was 3.7 ± 0.6 days (range: 0-12 days; median: 3 days). Wheezing was absent in physical examinations for all children, and inspiratory crackles were never prominent. No child developed skin rash, lymphadenopathy, hepatosplenomegaly, or clinical bleeding. The hematologic and biochemical findings are presented in Table 3. A significant proportion of chil-

TABLE 1. Demographic Characteristics and Epidemiologic Links for Children With SARS

	No. of Patients
Demographic characteristics (N = 44)	
Gender	
Male	20 (45.5%)
Female	24 (54.5%)
Age	
Mean	12.2 ± 4.1 y
Median	12 y
Range	50 d to 17.9 years
Age distribution	
<1 y	1 (2.3%)
1–5 y	2 (4.5%)
6–10 y	10 (22.7%)
11–17 y	31 (70.5%)
Ethnicity	
Chinese	43 (97.7%)
Filipino	1 (2.3%)
Comorbidity	5* (11.4%)
Epidemiologic link (N = 44)	
Point-source outbreak	31 (70.5%)
Household contact	6 (13.6%)
Social contact	3 (6.8%)
Hospital contact	2 (4.5%)
No contact history	2 (4.5%)
Travel history	0

* Asthma, 1; epilepsy, 1; autism, 1; Turner syndrome, eczema, and allergic rhinitis, 1; glucose-6-phosphate dehydrogenase deficiency and allergic rhinitis, 1.

dren exhibited leukopenia, lymphopenia, thrombocytopenia, and mild prolongation of activated partial thromboplastin time. Progressive lymphopenia was significantly more common among children ≤12 years of age (P = .038). For children >12 years of age, peak lymphopenia was recorded at presentation. Thrombocytopenia was significantly more common among children >12 years of age during the course of illness (P = .012). Reactive thrombocytosis after recovery was significantly more common among children ≤12 years of age (P = .029). Initial biochemical results were normal for the majority of children, but some children exhibited elevated lactate dehydrogenase and alanine aminotransferase levels.

The primary radiologic abnormality was airspace disease, either ground-glass opacity or focal consolidation with peripheral or mixed central/peripheral distribution. Rapid progression to unilateral multifocal or bilateral involvement, with reductions in lung volumes in the second week of illness, was typical for patients who developed respiratory distress (Fig 1, A and B). Two children demonstrated initially normal CXR results, but HRCT of the thorax revealed a small area of focal, subpleural, pneumonic consolidation involving the right lower lobe in both cases (Fig 1, C and D). Complete resolution of the airspace opacity on CXRs required >1 month for the most severely affected children. At 151 to 165 days after disease onset, residual minor, subpleural, ground-glass opacities and/or minor air trapping with expiration were still evident in HRCT examinations for 6 of 8 children who had received oxygen therapy. The persistent abnormalities were noted more commonly in the lower lobes. No evidence of pulmonary fibrosis, bronchial wall thickening, bronchiectasis, or lung volume loss was noted for these children in follow-up assessments.

TABLE 2. Presenting Clinical Features Among Children With SARS

Presenting Feature	No. of Cases (%)
Fever	44 (100)
Cough	28 (63.6)
Malaise	24 (54.5)
Coryza	19 (43.2)
Sputum production	16 (36.4)
Headache	16 (36.4)
Myalgia	16 (36.4)
Nausea and/or vomiting	13 (29.5)
Chills or rigor	12 (27.3)
Diarrhea	9 (20.5)
Sore throat	6 (13.6)
Dizziness	5 (11.4)
Dyspnea	4 (9.1)
Abdominal pain	4 (9.1)
Poor feeding/anorexia	4 (9.1)
Lethargy	3 (6.8)
Chest pain	1 (2.3)
Cyanotic attack	1 (2.3)

Presenting Feature	No. of Cases		P Value
	Age ≤12 y (N = 23)	Age >12 y (N = 21)	
Cough	15	13	1
Malaise	9	15	.065
Coryza	14	5	.03
Sputum production	8	8	1
Headache	4	12	.015
Myalgia	3	13	.002
Nausea and/or vomiting	5	8	.39
Chills or rigor	4	8	.23
Diarrhea	5	4	1
Sore throat	2	4	.57
Dizziness	1	4	.29
Dyspnea	2	2	1
Abdominal pain	1	3	.53
Poor feeding/anorexia	3	1	.66
Lethargy	1	2	.93
Chest pain	1	0	1
Cyanotic attack	1	0	1

Forty-four children with clinical SARS demonstrated SARS-CoV seroconversion >21 days after disease onset. A ≥4-fold increase in indirect fluorescent antibody titers for SARS-CoA was recorded as early as 8 days after onset for the youngest patient despite his prematurity.[10] Persistence of antibody titers was demonstrated 4 to 6 months after disease onset, although approximately one third of children demonstrated decreases in indirect fluorescent antibody titers of one half or more.

Positive RT-PCR results for SARS-CoV in NPAs were documented for only 21 children (47.7%). For most children, NPA specimens were obtained within 7 days after disease onset. Only 7 children (15.9%) demonstrated successful isolation of the virus from NPA cultures. Positive RT-PCR results for stool samples were noted for 17 children (38.6%), from as early as day 7 of disease to as late as day 41. For none of the children was SARS-CoV isolated from stool samples. RT-PCR and viral culture detection rates did not vary significantly with age and severity of illness.

For 2 children classified as having clinical and laboratory SARS, other pathogens were identified. One exhibited influenza B seroconversion, but no

TABLE 3. Laboratory Findings for Children With SARS

Laboratory Abnormality	At Presentation *N* (%)	During Course of Illness *N* (%)
Total white blood cell count of $<4 \times 10^9$ cells/L	15 (34.1)	21 (47.7)
Absolute lymphocyte count of $<1.5 \times 10^9$ cells/L	34 (77.3)	38 (86.4)
Absolute neutrophil count of $>7 \times 10^9$ cells/L	3 (6.8)	23 (52.3)
Platelet count of $<150 \times 10^9$ cells/L	12 (27.3)	12 (27.3)
Hemoglobin level of <10 g/dL	1 (2.3)	2 (4.5)
Alanine aminotransferase level of >40 IU/L	7 (15.9)	21 (47.7)
Albumin level of <35 g/L	1 (2.3)	6 (13.6)
Globulin level of >35 g/L	7 (15.9)	9 (20.5)
Creatine kinase level of >245 IU/L	3 (6.8)	4 (9.1)
Lactate dehydrogenase level of >230 IU/L	24 (54.5)	28 (63.6)
Activated partial thromboplastin time of >35 s	17 (38.6)	17 (38.6)

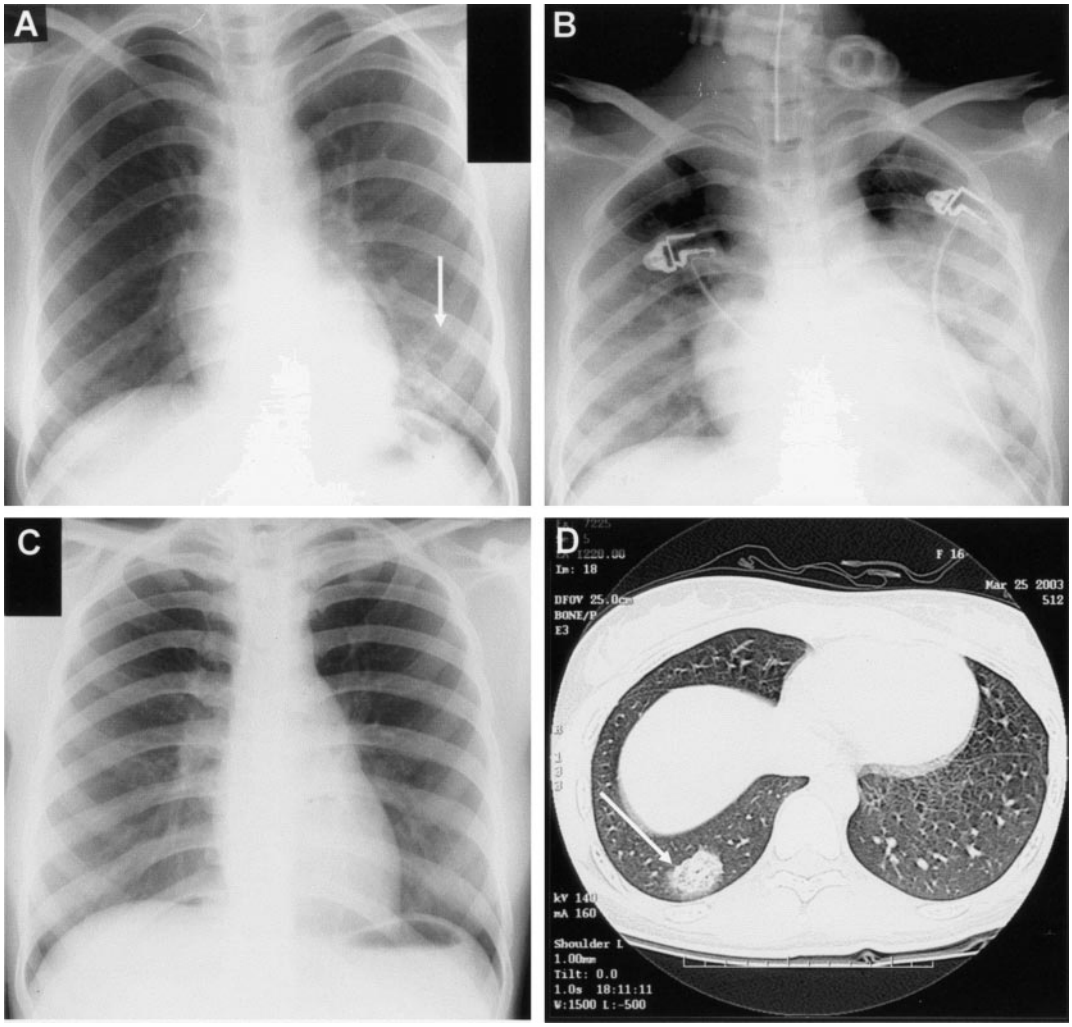

Fig 1. CXRs and HRCT scans of the thorax for 2 children with SARS. A, Admission CXR for a 15-year-old girl, showing left lower lobe consolidation 3 days after the onset of fever. B, Progressive radiographic deterioration, resulting in widespread bilateral consolidation at the time of intubation and mechanical ventilation for the same patient, 12 days after the onset of fever. C, Normal CXR findings for a 16-year-old girl obtained at admission, 2 days after the onset of fever. D, HRCT scan of the thorax for the same patient, showing peripheral, subpleural, focal consolidation in the right lower lobe that was not evident on CXRs.

virus was isolated from NPA cultures. The other exhibited *C pneumoniae* seroconversion and isolation of herpes simplex virus type 1 from throat cultures on days 4 and 36 of illness, which probably represented intermittent asymptomatic shedding as a result of reactivation of latent infection. For the only child classified as having clinical non-SARS but laboratory SARS, influenza A subtype H3N2 was isolated from the NPA culture on day 3 of illness. A direct immunofluorescence assay for influenza A antigen yielded positive results for the same specimen. Seroconversion to influenza A was also documented. Of the 6 children classified as having clinical SARS but laboratory non-SARS, 4 demonstrated an identifiable pathogen (influenza A in 2 cases, parainfluenza type 2 in 1 case, and *M pneumoniae* in 1 case).

Treatment and Outcomes

Forty-two children (95.5%) were treated with ribavirin. Thirty-seven children (84.1%) were administered corticosteroids. High-dose methylprednisolone was administered to 9 children (20.5%), in addition to prednisolone or hydrocortisone, at a mean of 8.3 ± 3.5 days after the onset of fever (range: 3–15 days; median: 8 days). Children >12 years of age were more likely to require methylprednisolone because of severe illness (odds ratio: 13.5; 95% confidence interval: 2.1–87.2; $P = .016$).

Nine children (20.5%), including the only infant, developed hypoxemia at a mean of 6.2 ± 2.7 days after the onset of fever (range: 3-10 days) and required oxygen supplementation. All patients except the premature infant were treated with methylprednisolone. The need for oxygen was not significantly different between children ≤12 years of age and those >12 years of age ($P = .099$). However, if the only infant was excluded from the analysis, then age of >12 years was significantly associated with oxygen requirement (odds ratio: 12.8; 95% confidence interval: 1.4–117.1; $P = .023$).

Five children (11.4%) required intensive care, including the premature infant and 4 children >12 years of age. Three patients (6.8%) required assisted ventilation, in the form of continuous positive airway pressure for the premature infant, bilevel positive airway pressure for a 15-year-old younger twin sister, and bilevel positive airway pressure with subsequent intubation and intermittent positive-pressure ventilation for the older twin sister.[11]

A close temporal relationship was observed between clinical and radiologic improvement and methylprednisolone administration among the most severely affected children. There were no deaths. The mean total duration of fever was 7.1 ± 3.1 days (range: 1–17 days: median: 7 days). Serious adverse events in response to treatment were not observed. Two adolescents who had received intensive care developed transient visual and/or auditory hallucinations, which lasted for a few hours, when their prednisolone dosages were tapered shortly before discharge. Their symptoms readily resolved with emotional support and psychologic counseling.

Forty-one children (93.2%) were monitored successfully. Eleven (26.8%) reported mild decreases in exercise tolerance, which lasted 1 week to 3 months after discharge. Pulmonary function tests were performed for 6 of the 9 children who required oxygen therapy. Consent was not obtained for 3 children. Four of the children demonstrated normal pulmonary function test results 151 to 165 days after disease onset. Two children exhibited findings suggesting hyperactive airways responsive to bronchodilator administration 143 to 153 days after disease onset. However, premorbid pulmonary function measurements were not available for comparison.

Nine children (22%) experienced vague muscle weakness, which lasted 1 week to 1 month after discharge. Seventeen children (41.5%) reported increased shedding or diffuse thinning of hair, generally 2 to 3 months after disease onset. One of those children had not been treated with ribavirin or corticosteroid. None developed alopecia areata or alopecia totalis. Hair shedding was self-limiting, and all patients recovered spontaneously within 1 to 3 months. Acute telogen effluvium, manifested by excessive loss of normal club hairs, was the likely cause.

Six children (14.6%) reported transient mild decreases in attention span and/or forgetfulness after recovery. No permanent memory loss was evident in follow-up assessments. Emotional lability was observed for 8 children (19.5%), lasting 1 week to 2 months after discharge. Four children (9.8%) seemed to have depressed moods, which lasted 1 week to 1 month after discharge. Two of those children had lost one of their parents during the epidemic. Both children were referred to a clinical psychologist for bereavement counseling. Ten affected family members of the cohort of 44 children with clinical and laboratory SARS died.

Proactive clinical psychologic services consisting of telephone contacts, psychoeducation on coping, and screening of psychologic functioning with a mailed standard questionnaire were rendered to the children 1 and 3 months after discharge. The psychologic effects of SARS and mood states were assessed. No overt psychologic disturbances were evident in the returned screening questionnaires at 3 months after discharge.

Risk Factors for Severe Disease

The following parameters were identified in univariate analyses to be significantly associated with oxygen therapy: sore throat at presentation, dyspnea at presentation, lowest absolute lymphocyte count, peak neutrophil count of $>10 \times 10^9$ cells per L, peak alanine aminotransferase level of >80 IU/L, and the use of methylprednisolone. Similarly, sore throat at presentation, initial total white blood cell count of $>10 \times 10^9$ cells per L, initial absolute neutrophil count of $>7 \times 10^9$ cells per L, peak neutrophil count of $>10 \times 10^9$ cells per L, and the use of methylprednisolone were significantly associated with the need for intensive care (Table 4).

Multivariate analysis with stepwise logistic regression suggested that sore throat (adjusted odds ratio: 12.8; 95% confidence interval: 1.3–124.1; $P = .03$) and peak neutrophil count of $>10 \times 10^9$ cells per L (adjusted odds ratio: 11.7; 95% confidence interval: 1.8–77.5; $P = .01$) were probable independent risk factors for severe disease leading to oxygen requirement. Similarly, sore throat (adjusted odds ratio: 24.9; 95% confidence interval: 1.8–342.3; $P = .02$) and initial absolute neutrophil count of $>7 \times 10^9$ cells per L (adjusted odds ratio: 39.1; 95% confidence interval: 1.5–999; $P = .03$) were probable independent risk factors for intensive care requirement.

Diagnostic Accuracy

To validate the diagnostic accuracy of the clinical case definition, using laboratory SARS as confirmation, a 2 × 2 table was constructed, from which the sensitivity (97.8%), specificity (92.7%), positive predictive value (88%), and negative predicative value

TABLE 4. Univariate Analysis of Factors Associated With Severe Illness Among Children With SARS

Variable	No. of Cases		*P* Value	Odds Ratio (95% Confidence Interval)
	Need for Oxygen ($N = 9$)	No Need for Oxygen ($N = 35$)		
Presenting clinical feature				
Sore throat	4	2	.01	13.2 (2.4–71.8)
Dyspnea	3	1	.03	17.0 (2.3–123.2)
Most abnormal laboratory finding				
Lowest absolute lymphocyte count ($\times 10^9$ cells/L)	0.5 ± 0.2	0.9 ± 0.5	<.01	(0.15–0.63)†
Peak neutrophil count of $>10 \times 10^9$ cells/L	6	5	<.01	12.0 (2.7–55.0)
Peak alanine aminotransferase level of >80 IU/L	5	5	.03	7.5 (1.6–34.2)
Use of methylprednisolone	8	1	<.01	272.0 (38.8–1907)

Variable	No. of Cases		*P* Value	Odds Ratio (95% Confidence Interval)
	Need for ICU Care ($N = 5$)	No Need for ICU Care ($N = 39$)		
Presenting clinical feature, sore throat	3	3	.01	18.0 (3.0–107.4)
Initial laboratory finding				
Total white blood cell count of $>10 \times 10^9$ cells/L	2	1	.03	25.3 (3.3–196.7)
Absolute neutrophil count of $>7 \times 10^9$ cells/L	2	1	.03	25.3 (3.3–196.7)
Most abnormal laboratory finding, peak neutrophil count of $>10 \times 10^9$ cells/L	4	7	.01	18.3 (2.7–123.5)
Use of methylprednisolone	4	5	<.01	27.2 (4.2–176.1)

ICU indicates intensive care unit.
† 95% confidence interval of mean difference.

(98.7%) were derived (Table 5). Six children were overdiagnosed. Only 1 child with SARS was missed with the clinical case definition. The missed child exhibited normal CXR findings and would have been missed with the WHO case definition for probable SARS. Four of the 6 overdiagnosed children fulfilled the WHO case definition for probable SARS, with fever, cough, and pulmonary infiltrates evident on CXRs. They would have been overdiagnosed with WHO criteria as well. The remaining 2 children did not present with cough. Applying the WHO case definition for our cohort of 44 children would result in missing 15 children (34%) who did not present with cough, shortness of breath, or difficulty breathing.

DISCUSSION

The clinical features of SARS among children are nonspecific. Application of the original WHO surveillance case definition or the current WHO clinical case definition is likely to miss a considerable number of patients who do not present with cough, shortness of breath, or difficulty breathing.[5,12] In adult series, cough as a presenting feature occurs in 29% to 100% of cases, with shortness of breath in 4% to 80%.[6,8,13–15] In pediatric series, including the present cohort, cough is a presenting feature for 43% to 91% of children and shortness of breath for 9% to 40%.[2–4] The WHO case definitions would have excluded 34% of the children with laboratory-confirmed SARS in the present cohort, which is the largest single-center, pediatric case series reported to date. The lack of sensitivity of the WHO case definitions for both adult and pediatric patients is disturbing, with respect to the effects on case management at the point of care.[4,16]

TABLE 5. Performance Characteristics of a Clinical Case Definition for SARS Among Children

	Clinical SARS, *N*	Clinical Non-SARS, *N*
Laboratory SARS	44	1
Laboratory non-SARS	6	76

Sensitivity (44 of 45 cases) = 0.978; specificity (76 of 82 cases) = 0.927; positive predictive value (44 of 50 cases) = 0.88; negative predictive value (76 of 77 cases) = 0.987.

Physical examination findings may not be contributory in the differential diagnosis of SARS, and radiographic findings are also not diagnostic. However, despite normal or equivocal CXR findings, HRCT for demonstration of early focal consolidation should be considered if SARS is suspected. The most common initial laboratory abnormalities among children include lymphopenia, leukopenia, thrombocytopenia, elevated lactate dehydrogenase levels, and mildly prolonged activated partial thromboplastin time. In contrast, adult patients commonly present with elevated alanine aminotransferase, creatine kinase, and D-dimer levels, in addition to the aforementioned findings.[6,8,13–15] Whether the age difference in laboratory abnormalities is attributable to more pronounced inflammatory responses among adults remains to be determined. Progressive lymphopenia and neutrophilia during the course of illness might be attributable to disease progression or the administration of corticosteroids. However, because most of our children (84%) had been treated with corticosteroids in one form or another, it is difficult to establish a direct causal relationship in the absence of control data. Progressive lymphopenia was more common among children ≤12 years of age. For children >12 years of age, 8 of whom had received high-dose methylprednisolone, peak lymphopenia was recorded at the time of presentation.

This is indirect evidence that the lympholytic effect of corticosteroids might not be prominent in our cohort. Children ≤12 years of age commonly demonstrate reactive thrombocytosis after recovery from SARS. This phenomenon is sometimes observed among children recovering from systemic viral infections and is probably not related to the use of corticosteroids.

Coinfection among children with SARS is uncommon. Three children with laboratory SARS in our study exhibited microbiologic evidence of coinfection, with influenza A virus, influenza B virus, and *C pneumoniae*. It remains unknown whether cocirculation of 2 pathogens occurs, infection with 1 pathogen predisposes individuals to infection by another pathogen, or copathogens are important in the pathogenesis of SARS among some patients. The detection of both SARS-CoV and human metapneumovirus for 6 of 48 adult patients with SARS in a teaching hospital in Hong Kong is intriguing.[17] However, it is unlikely that copathogens had any role in the worldwide outbreak of SARS.

Ribavirin was chosen as an empiric antiviral agent for SARS therapy in the dire situation of a major outbreak of a life-threatening infection, before the etiologic agent was even identified. Ribavirin was the antiviral agent with the broadest spectrum of activity that was commercially available then, when SARS was thought to be caused by a novel virus. It has been demonstrated that ribavirin has an immunomodulatory effect, which might be an additional advantage when ribavirin is used as an antiviral agent.[18,19] The use of ribavirin in SARS was reviewed by van Vonderen et al.[20] It was learned later that ribavirin has minimal in vitro antiviral effects on SARS-CoV, as tested in reference laboratories in the United States and Canada.[21] A recent report of the in vitro antiviral activity of interferon-β against SARS-CoV is encouraging.[22]

The preliminary postmortem findings of macrophage infiltration and diffuse alveolar destruction in the lungs of adult patients with SARS are reminiscent of cytokine dysregulation.[23] The HRCT finding of bronchiolitis obliterans-organizing pneumonia (an inflammatory condition that is responsive to corticosteroid therapy) in the lungs of adult patients with SARS has reinforced to physicians the usefulness of glucocorticoids in SARS therapy, with their potent antiinflammatory and immunomodulatory actions.[13] The rationale for the use of ribavirin and corticosteroids among children was based on the initial apparent success of the combination in the treatment of adults.[13] Moreover, because corticosteroids were advocated for control of the probable immune hyperactivation phase in the pathogenesis of SARS, the addition of broad antiviral coverage to reduce the likelihood of secondary opportunistic viral infections after the use of high-dose corticosteroid seemed reasonable.

In retrospect, we do not think that ribavirin alone has any significant effect in arresting disease progression. Corticosteroids are also probably unnecessary for patients who do not develop significant respiratory compromise. With hindsight, the use of corticosteroids in less severe SARS cases and for the early management of SARS during the phase of active viral replication was probably inappropriate. In our experience, a close temporal relationship exists between clinical and radiologic improvement and methylprednisolone administration among the most severely affected children with hypoxemia, who are threatened by impending acute respiratory failure during the phase of immune hyperactivation. We cannot categorically recommend this treatment strategy because of the small number of children treated and the lack of objective evidence from a controlled trial. The possibility of spontaneous recovery without the use of corticosteroids, as exemplified by the Toronto series, cannot be excluded.[4] Nevertheless, there might be a place for the future use of methylprednisolone as rescue therapy for patients who have clearly experienced failure of the best supportive care, because its use could be life saving. The optimal dosage and best timing for administration are unknown. The roles of other, more selective, antiinflammatory or immunomodulating agents remain to be explored.

Although a period of vague muscle weakness and mild reduction in exercise tolerance was experienced by approximately one fourth of the children after recovery, the prognosis in the follow-up period was good, as reflected by physical examination results and normal findings of lung function tests performed 5 months after onset for the most severely affected teenagers. Muscle weakness after recovery may be attributable to the catabolic effect of the infection, as reflected by significant weight loss and/or physical deconditioning during hospitalization. The effects of corticosteroids on muscles cannot be excluded. Whether airway hyperreactivity, as demonstrated in 2 children, occurs as a transient or permanent sequela remains to be determined. The absence of permanent structural damage in the lung parenchyma, as indicated by HRCT, is reassuring. In contrast, some adult patients have developed pulmonary fibrosis despite recovery from the primary illness.[24]

The diffuse thinning and shedding of hair among two fifths of children was self-limiting, although it was initially distressing for some older girls. We do not consider the phenomenon to be drug-related. Ribavirin is not known to cause alopecia, and glucocorticoids cause hirsutism or hypertrichosis instead. The condition is probably secondary to the acute insult of SARS. Telogen effluvium secondary to febrile systemic illness, critical care, and severe psychologic stress in life-threatening situations is well described.[25–27] The timing of hair loss at 2 to 3 months after disease onset is consistent with the typical description. It is indisputable that SARS presents as a life-threatening event, both physically and psychologically.

Psychologic disturbances observed among children recovering from SARS are probably multifactorial. The psychologic effects of separation, despair in an intimidating hospital environment with stringent

isolation precautions, and bereavement and family disintegration after the death of close adult family members are immense. Some of the mood changes and transient hallucinations experienced by a few patients might be related to corticosteroid administration. No frank psychosis or serious psychologic sequelae were evident in follow-up monitoring. Continued monitoring for a delayed onset of psychologic problems among children is essential. The role of clinical psychologists in the rehabilitation of children, both during hospitalization and after discharge, cannot be overemphasized.

Previous preliminary reports of SARS among children did not indicate risk factors for severe illness.[2–4] Although the validity of the multivariate analysis is limited by the small number of children in our cohort, it seems that sore throat, high neutrophil count at presentation, and peak neutrophilia are independent prognostic indicators for severe illness in terms of requirements for oxygen and intensive care. Furthermore, children >12 years of age are more likely to require methylprednisolone treatment because of severe illness. Whether sore throat at presentation is associated with a higher viral load remains to be determined. However, our data suggested that the presence of sore throat was not significantly associated with detection of the virus with either RT-PCR ($P = .52$) or culture ($P = .51$). The finding is intriguing but may be incidental, given the small number of patients. Neutrophilia at presentation probably reflects a greater degree of inflammation. Neutrophilia developing during the course of illness may be secondary to corticosteroid administration, but peak neutrophilia was already established at admission, before any specific therapy was instituted, for 2 of 9 children who subsequently required oxygen. In adult series, the independent predictors of severe illness are advanced age, high initial absolute neutrophil counts, high initial or peak lactate dehydrogenase levels, and positive RT-PCR results for NPA samples.[7,13,28,29]

Our clinical case definition has very good sensitivity (97.8%) and specificity (92.7%) in field testing and served us well during the SARS outbreak. However, early in an outbreak, an epidemiologic clue might not be available to satisfy the requirement in the case definition, even for an actual case. It should be emphasized that the predictive values of our clinical case definition have not been validated in a nonoutbreak situation in which disease prevalence is low. It is also worth noting that the SARS epidemic in Hong Kong did not overlap with the peak season for either influenza or RSV (the winter months of January to March and the summer months of June to August, respectively). If SARS were to reemerge during the peak season for influenza or RSV, it is likely that more false-positive case assignments would occur, with poorer specificity and lower positive predictive value as a result. Moreover, paired serologic results were not available for 12 of 89 children in the clinical non-SARS category, and the performance indices for the clinical case definition might be affected significantly by the missing data.

CONCLUSIONS

Children are susceptible to infection by SARS-CoV. Young children generally experience milder disease, compared with children >12 years of age. Adolescents should be monitored closely for clinical and radiologic deterioration, because they resemble adults with respect to disease progression. Rapid diagnosis with the first-generation RT-PCR assay has not been satisfactory. No specific treatment regimen exists to date, which underscores the importance of providing good supportive care including oxygen and assisted ventilation. The short-term to medium-term outcomes for children who recover from SARS seem good. Sore throat and initial and peak neutrophilia seem to be predictors of severe illness. Many children do not meet the clinical case definition proposed by WHO. An epidemiologic link seems to be the single most important clue to diagnosis. Our clinical case definition demonstrated excellent performance when used in an outbreak setting.

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