

ORIGINAL ARTICLE

Identification of Severe Acute Respiratory Syndrome in Canada

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ABSTRACT

BACKGROUND

Severe acute respiratory syndrome (SARS) is a condition of unknown cause that has recently been recognized in patients in Asia, North America, and Europe. This report summarizes the initial epidemiologic findings, clinical description, and diagnostic findings that followed the identification of SARS in Canada.

METHODS

SARS was first identified in Canada in early March 2003. We collected epidemiologic, clinical, and diagnostic data from each of the first 10 cases prospectively as they were identified. Specimens from all cases were sent to local, provincial, national, and international laboratories for studies to identify an etiologic agent.

RESULTS

The patients ranged from 24 to 78 years old; 60 percent were men. Transmission occurred only after close contact. The most common presenting symptoms were fever (in 100 percent of cases) and malaise (in 70 percent), followed by nonproductive cough (in 100 percent) and dyspnea (in 80 percent) associated with infiltrates on chest radiography (in 100 percent). Lymphopenia (in 89 percent of those for whom data were available), elevated lactate dehydrogenase levels (in 80 percent), elevated aspartate aminotransferase levels (in 78 percent), and elevated creatinine kinase levels (in 56 percent) were common. Empirical therapy most commonly included antibiotics, oseltamivir, and intravenous ribavirin. Mechanical ventilation was required in five patients. Three patients died, and five have had clinical improvement. The results of laboratory investigations were negative or not clinically significant except for the amplification of human metapneumovirus from respiratory specimens from five of nine patients and the isolation and amplification of a novel coronavirus from five of nine patients. In four cases both pathogens were isolated.

CONCLUSIONS

SARS is a condition associated with substantial morbidity and mortality. It appears to be of viral origin, with patterns suggesting droplet or contact transmission. The role of human metapneumovirus, a novel coronavirus, or both requires further investigation.

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SEVERE ACUTE RESPIRATORY SYNDROME (SARS) is a condition of unknown cause that has recently been recognized in patients in Asia, North America, and Europe. As defined by the World Health Organization (WHO), a suspected case is disease in a person with a documented fever (temperature, $>38^{\circ}\text{C}$), lower respiratory tract symptoms, and contact with a person believed to have had SARS or a history of travel to a geographic area where there has been documented transmission of the illness. A suspected case that involves chest radiographic findings of pneumonia, acute respiratory distress syndrome, or an unexplained respiratory illness resulting in death with autopsy results demonstrating the pathology of acute respiratory distress syndrome (ARDS) without an identifiable cause is considered a probable case.¹

This report summarizes the initial epidemiologic findings, clinical description, and diagnostic findings that followed the identification of SARS in Canada.

METHODS AND RESULTS

DESCRIPTION OF THE OUTBREAK

Toronto

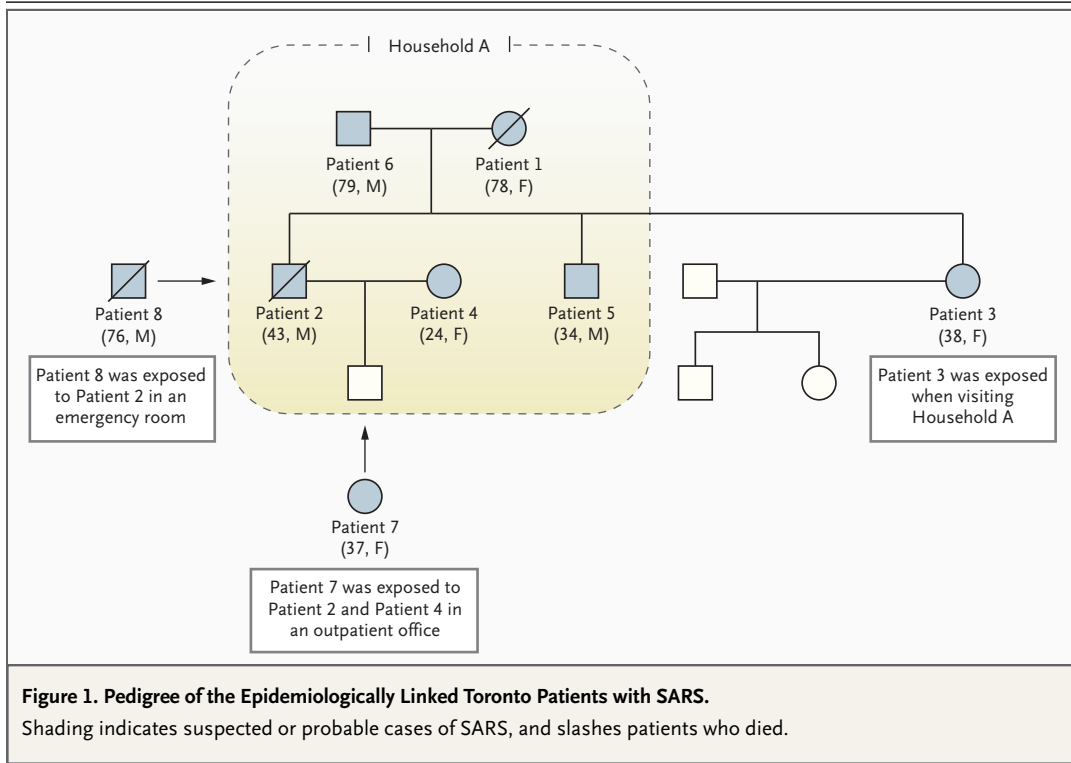
The first cases in Toronto were linked to members of a multigenerational family of Hong Kong descent who live in Toronto (Fig. 1 and 2). The Toronto index case (Patient 1) and her husband traveled to Hong Kong to visit relatives from February 13 through February 23, 2003. While in Hong Kong visiting their son, Patient 1 and her husband stayed at Hotel A from February 18 through February 21. Another hotel guest, who eventually was identified as the source patient for SARS in Hong Kong, also stayed on the same floor at Hotel A.² Patient 1 and her husband stayed in the hotel only at night, spending the days visiting their son. They returned to their apartment in Toronto, which they shared with two sons, a daughter-in-law, and a five-month-old grandson (Household A), on February 23, 2003.

Patient 1, a 78-year-old woman with a history of type 2 diabetes and coronary heart disease, had fever, anorexia, myalgias, a sore throat, and mild nonproductive cough two days after returning home. Three days later, her family physician noted pharyngeal erythema but no other abnormalities on physical examination. An oral antibiotic was prescribed, and she was sent home. Two days later,

she noted the development of increasing cough with dyspnea. She died three days later, on March 5, at home, nine days after the onset of her illness. An autopsy was not performed.

The index patient's 43-year-old son (Patient 2), who had an underlying history of type 2 diabetes and hypertension, had fever and diaphoresis on February 27, two days after his mother first noted symptoms. Within approximately five days he became afebrile, but concurrently, a nonproductive cough, chest pain, and dyspnea developed. A chest radiograph revealed moderate air-space disease in the right middle and lower lobes, for which he received antibiotics. Because of persistent symptoms, he was assessed at a hospital and noted to have a fever (temperature, 39.8°C) and an oxygen saturation of 82 percent while breathing room air. A chest radiograph revealed bibasilar air-space disease. He was admitted to the hospital with a diagnosis of community-acquired pneumonia and was supported with noninvasive ventilation and treated with broad-spectrum antibiotics. Antituberculous medication and airborne precautions were added when tuberculosis was considered after the first day of his admission. Contact precautions were also added, given uncertainty about the underlying infectious agent. By day 2 of his admission, his respiratory status had deteriorated, and he was intubated and received mechanical ventilation. Despite intensive physiological support, multiorgan dysfunction syndrome developed, and he died on March 13, 2003, 6 days after admission, and 15 days after becoming ill. All routine investigations for etiologic agents were negative. At autopsy, the lung tissue revealed diffuse alveolar damage consistent with pathologic manifestations of acute respiratory distress syndrome. Intraalveolar and interstitial mononuclear cells suggesting a possible viral cause were also noted, but no viral cytopathic effect was seen. Examination of the liver revealed microvesicular fatty change, focal hemorrhages, and hepatocyte necrosis with scattered acidophilic bodies, but no viral inclusions were seen. The spleen showed large areas of probable ischemic necrosis and some atypical lymphocytes in periarteriolar sheaths. Further information on the evaluation for specific pathogens is given below.

On March 8 and 9, because of concern about possible tuberculosis in the family, the remaining five adult family members and their three children (5 months old, 9 years old, and 17 years old), who had all been exposed to the index patient, under-



went screening chest radiography. All had fever, cough, dyspnea, or all three, as well as abnormal chest radiographs, except for the three children and the husband of Patient 3, who were and continue to be asymptomatic with normal chest radiographs. SARS was considered to be a possible explanation for these abnormalities and for the deaths of Patient 1 and Patient 2, who in retrospect met the criteria for probable SARS. (Patient 1 met almost all of the criteria, although an autopsy and microbiologic investigations were not completed to rule out identifiable causes.) In the light of this possible explanation, each of the symptomatic adults was reassessed on March 13. One met the criteria for suspected SARS (Patient 4), and three met the criteria for probable SARS (Patient 3, Patient 5, and Patient 6). All four were admitted to the hospital, three of them to intensive care units; one patient required mechanical ventilation. All four were treated with broad-spectrum antibiotics, oseltamivir, and intravenous ribavirin and have recovered fully, with the exception of two who continue to have mild dyspnea on exertion approximately three weeks after the onset of their illness.

As a result of media attention, three additional

cases of SARS were identified. The first case was in a previously healthy 37-year-old female family physician of Asian descent (Patient 7) who saw Patient 2 and his wife (Patient 4) on March 6, when they were both symptomatic. Patient 7 had a severe headache on March 9, followed by fevers (temperatures of up to 40°C), myalgias, and malaise. Four days later, a nonproductive cough developed, and she was noted to have fever (temperature, 38.5°C) and tachypnea with an oxygen saturation of 100 percent on room air. Chest radiography revealed a subtle left basilar infiltrate. She was admitted to a medical ward with a diagnosis of suspected SARS and has subsequently recovered, coincident with receiving broad-spectrum antibiotics, oseltamivir, and intravenous ribavirin.

The second additional identified case was in a 76-year-old man of non-Asian descent (Patient 8) who had a history of type 2 diabetes, coronary heart disease, and hypertension and who was evaluated at the hospital to which Patient 2 was admitted. Patient 8 was assessed in the emergency department on March 7 for atrial fibrillation and observed overnight on a gurney separated by a cotton curtain 1 to 2 m from Patient 2, who was being held overnight

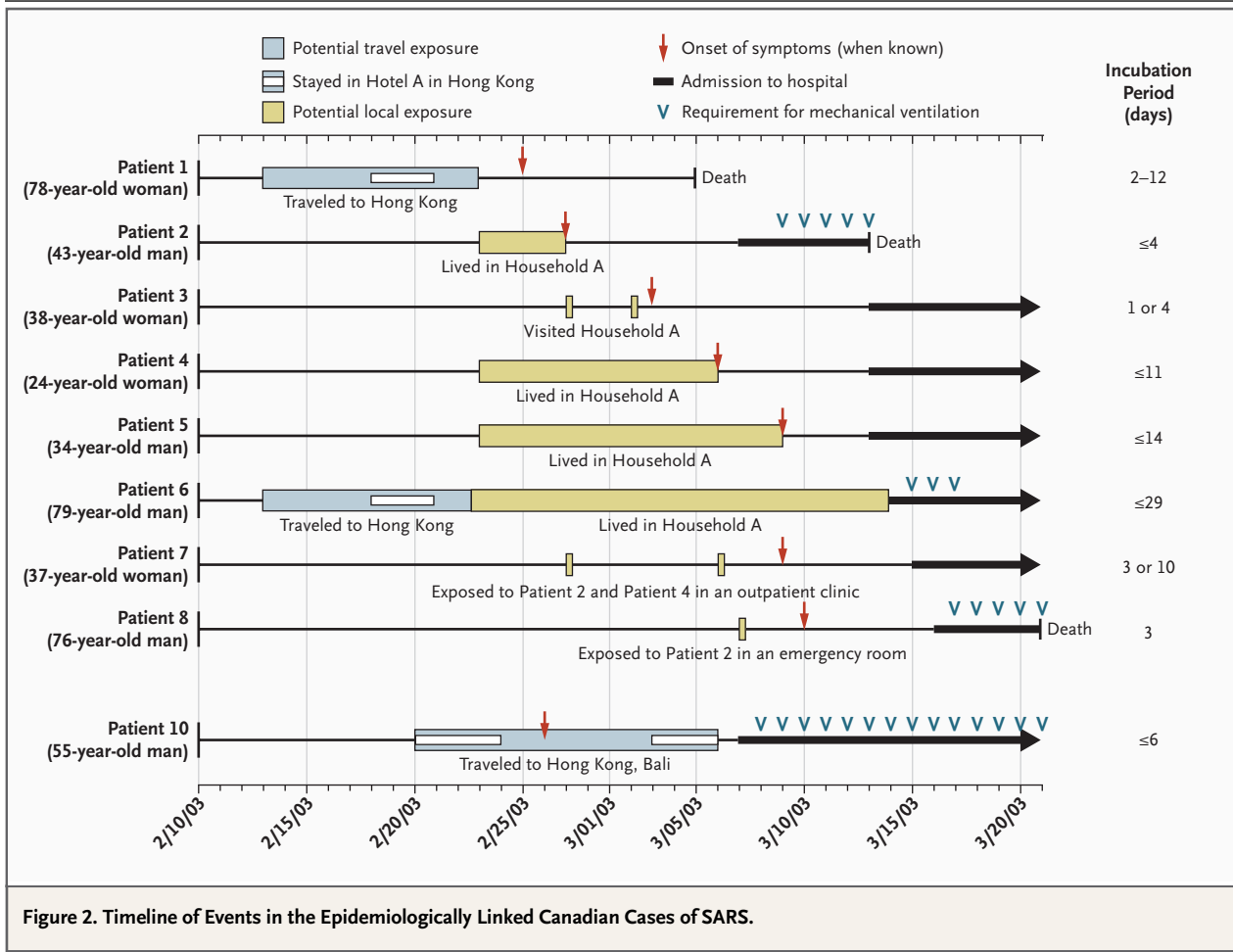


Figure 2. Timeline of Events in the Epidemiologically Linked Canadian Cases of SARS.

without respiratory or contact precautions awaiting an inpatient hospital bed. Patient 8 was discharged home on March 8, and two days later he had fever (temperatures of up to 40°C), diaphoresis, and fatigue. A chest radiograph revealed right-upper-lobe and bibasilar interstitial infiltrates; despite antibiotic treatment, a nonproductive cough and worsening dyspnea subsequently developed, along with hypothermia (temperature, 36.6°C) and an oxygen saturation of 70 percent on room air. He was admitted to the intensive care unit with a diagnosis of probable SARS and required intubation and ventilation. Despite receiving broad-spectrum antibiotics, oseltamivir, intravenous ribavirin, and intensive support, he died on March 21, 5 days after admission and 12 days after the onset of his illness. An autopsy was performed, the results of which are currently pending.

The third additional case (in Patient 9) was unre-

lated to this family cluster. He is a 62-year-old man of non-Asian descent with a history of atrial fibrillation who had chest pain, sore throat, and lightheadedness, followed by cough, dyspnea, and fever, while traveling in Southeast Asia in early March. On his return to Toronto on March 14, he was admitted to the hospital with a diagnosis of probable SARS and was treated with broad-spectrum antibiotics, oseltamivir, and intravenous ribavirin. Two days after admission, his respiratory status worsened and he required intubation and ventilation. His condition has since stabilized and is slowly improving, but he continues to require ventilatory support 16 days after the onset of his illness.

Vancouver

The only case in Vancouver was in Patient 10, a 55-year-old, previously healthy man who traveled with his wife to Hong Kong and Bali from February 20

through March 6, 2003. While visiting Hong Kong from February 20 to February 24, Patient 10 and his wife also stayed in Hotel A, but on a different floor from Patient 1, Patient 6, and the hotel guest who was eventually identified as the source patient for SARS in Hong Kong. When in the hotel, Patient 10 and his wife did not eat at a common dining facility, nor did they entertain or visit other guests in the hotel. While traveling, two days after leaving Hong Kong, Patient 10 had malaise followed two days later by fever (temperature, 39.4°C), chills, and headache. Progressive dyspnea and a nonproductive cough developed a day later. After returning to Vancouver on March 7, he was assessed and found to have a temperature of 38.5°C, an oxygen saturation of 45 percent on room air, and mixed air-space and reticular opacification diffusely on chest radiography. He was admitted to the intensive care unit, and within 24 hours he required intubation and ventilation to maintain adequate oxygenation. He was soon recognized as having probable SARS and has been treated with broad-spectrum antibiotics. He remains in intensive care on ventilatory support 30 days after the onset of his illness.

SUMMARY OF CLINICAL FEATURES AND INITIAL INVESTIGATIONS

A summary of the clinical features and initial investigations of the first 10 cases of SARS identified in Canada (8 probable and 2 suspected) is given in Table 1. All of the patients were adults, ranging from 24 to 78 years of age. Six of the 10 were men. Eight of the 10 were of Asian descent. Three had a diagnosis of type 2 diabetes mellitus (Patient 1, Patient 2, and Patient 8); two had underlying pulmonary disease (asthma in Patient 3 and chronic cough of unclear cause in Patient 6); and four had a history of smoking (Patient 2, Patient 6, Patient 8, and Patient 9) although none still smoked. Given the patients who had a defined exposure time (Patient 3, Patient 7, and Patient 8), the incubation period can be estimated to range from 3 to 10 days. However, we are unable to exclude the possibility of a one-day incubation period in Patient 3.

The presenting symptoms included fever in all cases and nonspecific symptoms such as malaise (7 of 10 cases) and myalgias (2 of 10 cases). Three of the 10 patients had chest pain, 3 had sore throat, and 3 had headache as part of their initial presentation. Although a nonproductive cough (in all 10 cases) and dyspnea (8 of 10 cases) were common, these respiratory symptoms were not the present-

Table 1. Clinical Features of the Canadian Patients with SARS at Presentation.

Variable	Value
	<i>no./ no. with results (%)</i>
Symptoms	
Fever	10/10 (100)*
Nonproductive cough	10/10 (100)
Dyspnea	8/10 (80)
Malaise	7/10 (70)
Diarrhea	5/10 (50)
Chest pain	3/10 (30)
Headache	3/10 (30)
Sore throat	3/10 (30)
Myalgias	2/10 (20)
Vomiting	1/10 (10)
Investigations	
Infiltrate on chest radiography	9/9 (100)
Oxygen saturation on room air <95%	7/9 (78)
Leukopenia (cell count <4×10 ⁹ /liter)	2/9 (22)
Lymphopenia (cell count <1.5×10 ⁹ /liter)	8/9 (89)
Thrombocytopenia (cell count <130×10 ⁹ /liter)	3/9 (33)
Lactate dehydrogenase (above upper limit of normal)	4/5 (80)
Aspartate aminotransferase (>1.5× upper limit of normal)	7/9 (78)
Alanine aminotransferase (>1.5× upper limit of normal)	5/9 (56)
Creatine kinase (above upper limit of normal)	5/9 (56)

* Although all 10 patients had a history of fever at presentation to the hospital, on examination only 5 of 9 were febrile (temperature, 38.4 to 40°C); 1 had a low-grade fever (temperature, 37.9°C), and 3 had hypothermia (temperature, 35.5 to 36.5°C).

ing symptoms in 5 cases. In three patients the fevers had improved by the time respiratory symptoms occurred. Five of the 10 patients had diarrhea, and 1 had vomiting although 4 of these patients were also taking medications frequently associated with gastrointestinal side effects. No patient had a rash.

On presentation to the hospital, five of nine patients were febrile (temperature, 38.4 to 40°C), one had a low-grade fever (temperature, 37.9°C), and three had hypothermia (temperature, 35.5 to 36.5°C). Tachycardia (in five of nine cases), tachypnea (in seven of nine), and borderline low blood pressure (in five of nine) were common. Oxygen saturation while breathing room air was less than 95 percent in seven of nine patients. Physical examination was normal in all patients outside the respiratory system. Crackles were noted at the bases symmetrically (in four of eight patients) or asymmetrically (in one of eight), with bronchial breath sounds or egophony in two. Chest radiographs revealed abnormalities in all of the nine patients who underwent radiography. In all but three patients, changes were bilateral and predominantly in the basal lung zones. Abnormalities were subtle at first in five of the nine patients, primarily involving a reticular interstitial pattern. For two of these patients, subsequent chest radiographs were read as normal. All other patients had progressive symmetric involvement of predominantly air-space disease on subsequent radiographs. Pleural effusions were not seen. A representative series of chest radiographs is shown in Figure 3.

The most common laboratory abnormalities noted included lymphopenia, elevated lactate dehydrogenase levels, elevated aspartate aminotransferase levels, and elevated creatine kinase levels. Other less common abnormalities included mild thrombocytopenia and mild leukopenia.

CASE MANAGEMENT

All seven patients who presented to the hospital in Toronto and were recognized as having suspected or probable SARS were treated empirically with recommended doses of oral oseltamivir and broad-spectrum antibiotics, as well as intravenous ribavirin in the dosing schedule recommended for the treatment of viral hemorrhagic fever (a loading dose of 2 g, followed by 1 g every six hours for four days, then 500 mg every eight hours for another four to six days).³ The three other patients were treated with empirical broad-spectrum antibiotics alone. All cases were managed with use of respiratory and contact precautions as soon as the diagnosis of suspected or probable SARS had been considered.

CLINICAL COURSE

Five of the patients with SARS required mechanical ventilation for worsening respiratory failure at one

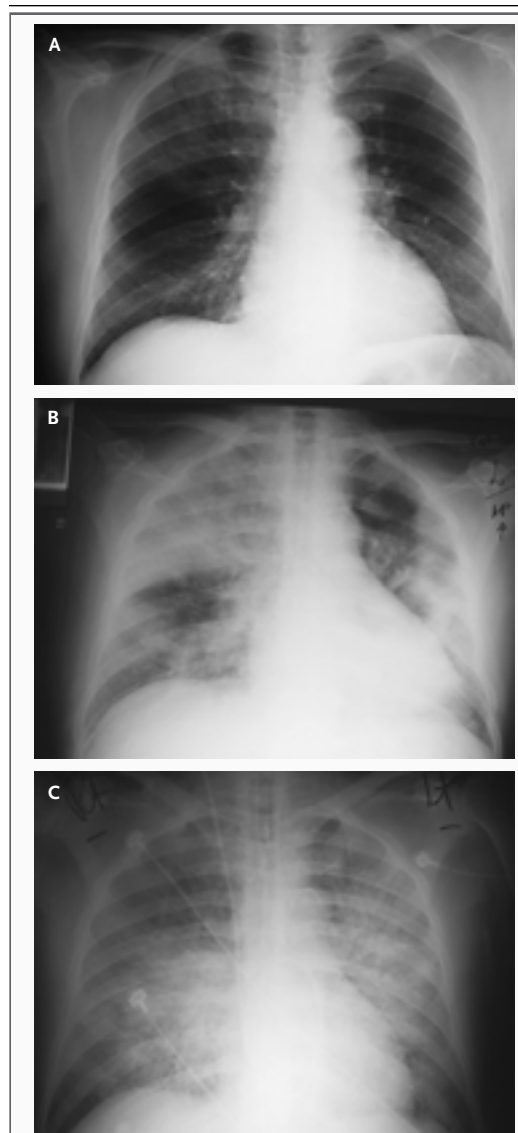


Figure 3. The Course of Disease in Patient 8.

Patient 8, a 76-year-old man, was exposed to Patient 2 on March 7, had fever (temperatures of up to 40°C), diaphoresis, and fatigue three days later on March 10. A chest radiograph obtained on March 14 revealed right-upper-lobe and bibasilar interstitial infiltrates (Panel A). He subsequently noted a nonproductive cough and increasing dyspnea and was admitted to the hospital on March 16. A chest radiograph obtained on March 17 revealed bilateral patchy air-space disease with relative sparing of the right lung base and left upper lobe (Panel B). He was transferred to the intensive care unit and was intubated and received mechanical ventilation because of respiratory distress. Progressive respiratory failure and worsening of the findings on chest radiography occurred on March 20 (Panel C), and the patient died on March 21.

point in their illness, and two of these patients have died (Patient 2 and Patient 8). Patient 2 initially received noninvasive ventilation and was then intubated and received mechanical ventilation until his death four days later. Tidal volumes were 500 to 700 ml, and minute ventilation largely ranged between 10 and 15 liters per minute. Peak inspiratory pressures ranged from 17 to 42 cm of water but were generally less than 35 cm of water, with positive end-expiratory pressure levels of 5 to 15 cm of water. The ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) in the first 96 hours was generally more than 150, but it decreased thereafter to between 100 and 150; the PaO_2 never dropped below 71 mm Hg. Patient 8 was intubated and received ventilation with tidal volumes of 500 to 750 ml. The FiO_2 ranged from 0.9 to 1.0, with PaO_2 : FiO_2 ratios of 56 to 85 despite positive end-expiratory pressure levels of 14 cm of water. Peak inspiratory pressures generally ranged from 24 to 38 cm of water, and the partial pressure of carbon dioxide increased from about 25 to about 50 mm Hg over a period of four days despite increases in minute ventilation from about 15 to 20 liters per minute. Although both patients had markedly abnormal PaO_2 : FiO_2 ratios, they were never extremely hypoxemic and probably did not die of severe hypoxemia.

Patient 1 also died at home, increasing the total number of deaths to 3 among the 10 patients. All of the deaths occurred in patients who had an underlying immunocompromised state (type 2 diabetes).

Of the three patients who were treated with broad-spectrum antibiotics alone, two died and one remains in intensive care requiring mechanical ventilation. Of the seven patients who were treated with intravenous ribavirin and oral oseltamivir in addition to broad-spectrum antibacterial therapy, one died and one remains in intensive care requiring mechanical ventilation but with signs of clinical improvement. The other five, including one who had required mechanical ventilation, showed improvement within the first five days of treatment. They have all since recovered fully, with the exception of two who remain mildly dyspneic on exertion approximately three weeks after the onset of their illness.

LABORATORY INVESTIGATIONS

Histopathological and microbiologic investigations of specimens received were conducted at local, national, and international laboratories. Histo-

pathological testing was completed on autopsy tissue from Patient 2. Routine and specialized microbiologic investigations were completed on all specimens received in 9 of the 10 cases. (No specimens were sent from Patient 1, who died before being recognized as having SARS and in whom an autopsy was not performed.)

HISTOPATHOLOGICAL INVESTIGATIONS

Autopsy tissue from Patient 2 was subjected to immunohistochemical tests for influenza virus A and B, respiratory syncytial virus, adenovirus, hendra and nipah viruses, hantavirus, measles virus, enterovirus, flaviviruses, old world arenavirus, typhus and spotted fever rickettsia, coxiella species, *Yersinia pestis*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*. All were negative.

MICROBIOLOGIC INVESTIGATIONS

Bacterial and Fungal Examination

Routine bacterial and fungal examination was completed on all blood, respiratory, and urine specimens from 9 of the 10 patients, yielding negative results. Specifically, cultures as well as direct examination (where appropriate) were completed on all blood, respiratory, and urine specimens received, yielding negative results. In addition, cultures for legionella species, direct fluorescent antibody testing against legionella species on all respiratory specimens received, and testing for the presence of *Legionella pneumophila* serogroup 1 antigen in urine specimens received have been negative.

To date, bacterial molecular testing has been completed on all respiratory specimens received from 6 of the 10 patients, yielding negative results. Specifically, DNA was extracted, and polymerase-chain-reaction (PCR) detection for targets specific for *L. pneumophila*, *M. pneumoniae*, *C. pneumoniae*, *C. psittaci*, chlamydia at the genus level, *Y. pestis*, *Bacillus anthracis*, and 16S rRNA was negative.

Virologic Examination

Routine direct virologic examination of all respiratory and stool specimens received from 9 of the 10 patients was completed, yielding negative results. This included negative electron-microscopical examination and negative direct fluorescent antibody testing against influenza virus A and B, parainfluenzaviruses 1, 2, and 3, adenovirus, and respiratory syncytial virus in all specimens, with the exception of one subsequently unconfirmed positive direct

fluorescent antibody result for influenza virus B in a specimen from Patient 10.

Viral molecular testing has been completed on all respiratory and blood specimens received from 9 of the 10 patients, yielding mostly negative results. Specifically, DNA was extracted and PCR was completed for targets specific to various DNA viruses, yielding negative results for adenoviruses, parvoviruses, circoviruses, herpesviruses, and orthopoxviruses. In addition, RNA was extracted and reverse-transcription-PCR (RT-PCR) was completed for targets specific to various RNA viruses, including influenza virus A and B, respiratory syncytial virus, parainfluenza virus subtypes 1, 2, 3, and 4, human metapneumovirus, filoviruses (Ebola and Marburg viruses), arenaviruses, measles virus, mumps virus, hantaviruses, and Crimean-Congo hemorrhagic fever virus, yielding negative results.

Further studies were completed on all respiratory specimens received from 9 of the 10 patients. These included viral cultures (including inoculation onto cell culture and into embryonated hen eggs and intracerebral inoculation of suckling mice), immune electron microscopy of nasopharyngeal swabs and bronchoalveolar fluids with serum obtained during the convalescent phase from Patient 10, RT-PCR for conserved portions of the polymerase gene of RNA viruses, and nested RT-PCR with genus-specific degenerative primers for paramyxoviruses and bunyaviruses. Results for all of these tests have been negative, with two exceptions. Human metapneumovirus was amplified by nested RT-PCR from bronchoalveolar-lavage fluid and nasopharyngeal swabs from five of nine patients with SARS and from a nasopharyngeal swab from an asymptomatic contact of one of the patients in Toronto (Patient 3) with use of the following primers: 5'CTTTGGACTTAATGACAGATG3' and 5'GTCTTCCTGTGCTAACTTTG3'.⁴ For confirmation of these positive findings, the amplicons were sequenced and found to be unique, ruling out the possibility of cross-contamination in the laboratory.

In addition, a novel coronavirus was isolated from Vero cell cultures inoculated with respiratory specimens from five of nine patients with SARS. Four of these patients had specimens from which metapneumovirus was also identified. A cytopathic effect on the Vero cell cultures was noted on day 6 of incubation. On the basis of collaboration with investigators in Hong Kong and at the Centers for Disease Control and Prevention in Atlanta, who reported isolating a novel coronavirus from patients

with SARS in other areas of the world, RT-PCR was completed targeting conserved regions of the coronavirus polymerase gene using the following primer pairs: 5'CAGAGCCATGCCTAACATG3' and 5'AATGTTTACGCAGGTAAGCG3'. A novel coronavirus identical to that reported by the Centers for Disease Control and Prevention² was amplified from all five cultures. In addition, nested RT-PCR using the same primers plus 5'TGTTAAACCAGGTGGAAC3' and 5'CCTGTGTTGTAGATTGCG3' amplified the coronavirus directly from bronchoalveolar-lavage fluid from three of nine patients tested, all of whom also had coronavirus isolated from cell culture as described above.

At a different laboratory, a coronavirus was also identified independently by amplification directly from bronchoalveolar-lavage fluid from three of six patients tested. All three of these patients had coronavirus isolated from cell culture and amplification as described above. Reverse transcription was completed using the primer 5'GCATAGGCAGTAGTTGCATC3', followed by PCR targeting a highly conserved region of the coronavirus polymerase gene with use of the paired primers 5'TGATGGGATGGGACTATCCTAAGTGTA3' and 5'TTGCATCACCAGTGTGCGCCACCAGGTT3'. One of the amplicons was sequenced, and although the nucleotide sequence was different from that of any known coronaviruses, the deduced amino acid sequence had a high degree of homology (78 percent) to the polymerase amino acid sequence of several coronaviruses. Phylogenetic analysis suggests that this is a novel virus that is not closely related to any of the known clusters of coronaviruses (groups 1, 2, and 3).

Further studies are currently being completed to help determine whether the human metapneumovirus and a novel coronavirus, either alone or in combination, are the cause of SARS or whether other thus far undetected pathogens are possibly responsible. The possibility that coinfection of either virus with another agent may be responsible for SARS cannot be excluded.

CONTACT TRACING

As of March 30, 2003, in the Greater Toronto area, contact tracing has identified an additional 100 patients as having probable or suspected SARS. The ethnic background of these patients has varied widely. To date, one additional death has been reported. Transmission has been limited to close contacts of patients (i.e., household members or health

care workers who were not using contact or respiratory precautions). Case-finding measures have also identified additional persons with symptoms suggestive of SARS who have returned from travel to areas outside Canada where there has been documented transmission of SARS.

DISCUSSION

The identification of SARS in Canada only a few weeks after an outbreak on another continent exemplifies the ease with which infectious agents can be transmitted in this era of international travel. It also demonstrates the importance and value of information and alert systems such as the Department of Communicable Disease Surveillance Response of the World Health Organization and the Disease Outbreak News Web site (<http://www.who.int/csr/don>) and the ProMED-mail (Program for Monitoring Emerging Diseases) reporting network sponsored by the International Society for Infectious Diseases (<http://www.promedmail.org>).⁵

Epidemiologic investigations and laboratory studies suggest that most patients with disease meeting the definition of SARS in both Toronto and Vancouver can be linked to a common source and to common potential causative agents. On the basis of preliminary investigations, it appears that this syndrome may be due in part to the newly described respiratory viral pathogen, human metapneumovirus,⁶ to a novel coronavirus, or both.

Evidence of the role of human metapneumovirus includes its amplification from respiratory specimens from five of nine Canadian patients with SARS and one asymptomatic contact and the identification of a metapneumovirus from respiratory specimens from other non-Canadian patients with SARS (John Tam, Department of Microbiology, Chinese University of Hong Kong: personal communication). In addition, the range of clinical findings, from asymptomatic disease to severe pneumonia and death, is similar to that described in human metapneumovirus infection.⁷ On the other hand, the severity with which the Canadian cases of SARS presented and the high attack rate of SARS among close contacts have not been described in patients with human metapneumovirus infection, suggesting that human metapneumovirus alone may not be responsible for SARS, that a genetic variant of the human metapneumovirus is potentially responsible, or that human metapneumovirus is not related to SARS but

is an incidental finding. Indeed, we know little about the prevalence of asymptomatic carriage of human metapneumovirus, and such information would be helpful in interpreting the meaning of our amplification of this virus in patients meeting the criteria for SARS.^{8,9}

The novel coronavirus identified in five of nine Canadian cases may also be a possible causative agent of SARS. Further evidence includes its identification by other investigators around the world from specimens from other patients with SARS and reports of positive immunofluorescence antibody tests in serum from patients from whom the coronavirus was isolated.² In addition, known human coronaviruses are recognized to cause respiratory infection, albeit typically less severe than that described in the Canadian patients with SARS.¹⁰ Finally, coronaviruses are known to infect both animals and humans, and it is logical to consider that the emergence of a new disease may be related to the emergence of a novel coronavirus that originated with a limited range of animal hosts and evolved to involve an altered range that now includes humans.¹¹ Although one can speculate about the possible roles of both coronaviruses and human metapneumovirus in SARS, it is currently not clear what role, if any, either of these viruses has in causing SARS. Further collaborative investigations are needed.

The illnesses described in the Canadian patients with SARS ranged from a febrile respiratory disease not associated with hypoxemia to severe pneumonia with significant respiratory dysfunction requiring intubation and mechanical ventilation and leading to death. Factors that may account for this variation in disease severity include genetic predisposition, age, underlying illness, smoking status, previous immunity, and coinfection with more than one pathogen. Within the Toronto family cluster of SARS cases, all patients who had severe enough disease to require supplemental oxygenation were genetically related; although this fact could represent a possible underlying genetic predisposition to severe disease, contact was most likely closest among these persons. Advanced age and the presence of underlying medical illnesses, which have been reported to be associated with more severe disease in patients infected with other respiratory viruses, including human metapneumovirus and coronaviruses, may also be risk factors for more severe disease in SARS.^{7,12} Indeed, all of the Canadian patients with SARS who either re-

quired intubation or died had underlying medical illnesses or were older than 55 years of age. Tobacco smoking, a known risk factor for other respiratory infections,¹³ may also be a risk factor for more severe SARS. Of the four Canadian patients who had a history of smoking, all required mechanical ventilation, as compared with only one of the six nonsmokers. Lack of previous immunity to the underlying etiologic agent or agents of SARS may also be a risk factor for more severe manifestations of disease, as may coinfection with more than one pathogen. Coinfection has been associated with increased severity of other respiratory viral illnesses. For example, Greensill et al.¹⁴ studied 10 infants with severe respiratory syncytial virus bronchiolitis who had no other risk factors for severe disease and found that 9 (90 percent) were coinfecting with human metapneumovirus. Similarly, in SARS, human metapneumovirus or another pathogen may have the role of a copathogen, increasing the underlying severity of disease secondary to a novel coronavirus or another yet-to-be-identified pathogen.

The mechanism of transmission of the agent or agents causing SARS is not yet understood. However, the fact that transmission has been limited to only close contacts of patients, such as household members, health care workers, or other patients who were not protected with contact or respiratory precautions, suggests that either droplet secretions or direct or indirect contact probably has a role. However, the apparent ease of transmission in some cases is of concern. Although both the index patient in Toronto and the patient in Vancouver stayed in the same hotel in Hong Kong during the period when at least one other person with SARS was a guest, they had minimal exposure to other guests. Although airborne transmission is a possibility that cannot be completely ruled out in this example, there were probably many opportunities for indirect contact as well. Supporting droplet secretions or direct or indirect contact as the most likely mode of transmission is the fact that, to date, follow-up of all contacts of patients with SARS has not

revealed secondary transmission that cannot be explained by these routes.

Treatment recommendations based on this small case series are obviously limited. However, given the possibility that human metapneumovirus or a coronavirus may be a possible causative agent and given the observed mortality rate, it may be prudent until there is further understanding of the underlying cause of SARS to consider empirical treatment with an antiviral agent, such as ribavirin. Ribavirin is a ribonucleoside analogue that induces lethal mutagenesis of RNA viral genomes and has broad-spectrum activity against RNA viruses¹⁵ including respiratory syncytial virus,¹⁶ a pneumovirus related to human metapneumoviruses, and coronaviruses.^{11,17} Although the condition of five of seven (71 percent) of the Canadian patients with SARS who have been treated with ribavirin has improved with therapy, the patients were treated with an array of therapeutic agents, and it is unclear whether ribavirin affected the clinical outcome. Indeed, the efficacy of ribavirin against SARS has not been established, and it cannot currently be considered the standard of care. The patients who received mechanical ventilation fulfilled the diagnostic criteria for ARDS with diffuse infiltrates on chest radiography and hypoxemia without evidence of left ventricular failure.¹⁸ There is no definite therapy for ARDS; therapy is supportive,¹⁹ with the use of mechanical ventilation to improve oxygenation and to decrease the work of breathing. Noninvasive ventilation was used in one patient (Patient 2) but he required intubation within 24 hours owing to worsening respiratory failure. The best approach for ventilating patients with SARS is not known, but it seems reasonable to adopt a lung-protective strategy that has been shown to decrease mortality in patients with ARDS,²⁰ perhaps by preventing the development of multiorgan dysfunction syndrome.^{21,22}

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APPENDIX

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