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25th November 2003

Dr. the Hon. Law Chi Kwong, JP
Chairman
Select Committee to inquire into the handling of
the Severe Acute Respiratory Syndrome outbreak by
the Government and Hospital Authority
3/F, Citibank Tower
3 Garden Road, Central
Hong Kong

Dear Dr. the Hon. Law,

Re: SARS

Thank you for giving me the opportunity to submit my views on the SARS outbreak. The following is an account of the outbreak from my perspective. The same account had been submitted to the SARS Expert Committee and Hospital Authority Review Panel on SARS outbreak.

We first came face to face with this new disease was on 10 March 2003, when 18 health care workers at the Prince of Wales Hospital reported sick. Through telephone reports, we learnt that no less than 50 of the hospital's health care workers were actually suffering from a febrile illness. On 11 March, a special clinic was established at the hospital to screen affected staff and a special observation ward was set up to cohort these patients. A substantial number of staff were found to have patchy consolidation on their chest x-rays. The clinical features of these patients have been described in our publication in the New England Journal of Medicine. (appendix 1) As all those infected had either tended patients in Ward 8A or visited there, it was thought likely that the ward contained a source of infection. Ward 8A was therefore closed to new admissions and staff and visitors were instructed to wear masks.

At that moment in time the clinical entity of SARS had not yet been described. The disease was not given a name yet, but generally referred to

as "atypical pneumonia". Faculty members were however aware that we were dealing with a highly infectious condition with potentially serious consequences. On the afternoon of 12 March, I took the decision to close all medical wards to medical students, and by the evening, as more staff and students were admitted with the illness, the precautions were upgraded to include suspending all clinical teaching at the Prince of Wales Hospital, and declaring the hospital out of bounds for all medical students. By 14 March, to curtail cross infection, clinical teaching at all hospitals was suspended. On 17 March, I suspended all non-clinical activities at the Prince of Wales Hospital and moved non-clinical academic services supporting staff to the main campus. As a result of these actions, and the concerted efforts of the SARS Task Force of the University, there was fortunately no cross infection amongst our medical students, no spread of infection onto the University campus and no staff of the University, apart from those medical staff directly exposed to Ward 8A, became infected.

When the first wave of patients were admitted, there was nothing known about the causation, mode of spread, clinical course, treatment or prognosis of this previously undescribed condition. The clinical team under Professor Joseph Sung and the Intensive Care Unit under Professor Gavin Joynt, worked out an effective protocol for patient management, whilst our colleagues in the laboratory worked hard to identify the infective agent, and devised diagnostic tests for the condition. Our infection control team under Professor Augustine Cheng updated and upgraded infection control protocols as more information became available. We learned, at great cost, that previously innocuous and routine clinical procedures such as the use of nebulisers and endotracheal intubation posed great risk to our colleagues. (appendix 2) We shared information about this new disease with our colleagues both in Hong Kong and internationally as they became available. Some of the data have been published in scientific journals (appendix 3 - 9) and more are in the pipeline.

Let me now turn to the spread of the disease in the community. From the very beginning, faculty members were cognizant of the dangers that this highly contagious and deadly condition posed to our community. Indeed during the first meeting with hospital management on 12 March, faculty members warned, in the presence of Dr Ko Wing Man, of the need to close the Prince of Wales Hospital to the public. The Department of Health sent Dr TK Au to assist with the investigation of the outbreak at the Prince of Wales Hospital. On 13 March, during the evening ward round, one of our infected nurses told Dr Fung Hong, Professor Joseph Sung, Dr Philip Li and myself that he suspected that one of the young male patients could be the source of the outbreak. Investigation by Prince of Wales staff rapidly confirmed that he was indeed the source of the Prince of Wales Hospital outbreak. By 14 March, I was sufficiently concerned to call in Professor Wong Tze-wai of our Department of Community and Family Medicine and asked him to assist with the epidemiological investigation. During a meeting with the hospital management, Professor Wong confirmed that provisions for quarantining patients and contacts already existed in public health legislation. On the same day, we received a preliminary WHO report from Hanoi. Senior staff became alarmed at the high requirement for ventilatory support and the high interim mortality. Professor Joseph Sung also obtained information from colleagues in Guangzhou indicating that they had been dealing with a highly infectious pneumonia with a high mortality. The clinical features of the Hanoi and Guangzhou cases were identical to the ones we saw at the Prince of Wales Hospital. We realized we

had a potentially disastrous situation on our hands. At this point in time the official line appeared to be one of reassurance to the public that there is no imminent threat of a community outbreak. Faculty members debated how best to control the infection into the community but recognized that, as long as the Department of Health was making every effort to downplay the seriousness of the situation, it would be impossible to implement effective measures, as patients (and contacts) could not be detained in hospital against their wish.

By 17 March, there were more than 100 cases admitted to the hospital. Having discussed the matter with senior staff in the faculty, I saw the need to inform the public of the seriousness of the situation, and the risk of a community outbreak.

Frustrated with the lack of progress of the epidemiological investigations by the Department of Health of the outbreak at the hospital, I called in research nurses from our university to assist on 19 March. We were able to quickly uncover cases where the infection had spread in the community. It was felt that it was the faculty's duty to warn the public but there was also concern that confusion would result if such a warning was not endorsed by the Department of Health. Dr Fung Hong shared our views. I therefore phoned Dr Margaret Chan at around 6 pm and at the same time faxed her a letter expressing my grave concern, urging her to "urgently consider all possible measures including quarantine of patients and contacts to contain the outbreak before it was too late." (appendix 10) The Director did not seem to be convinced but commented over the phone that she was privy to confidential information from the mainland, that she and her Department had expertise in epidemiology and that there was no cause for concern. I have yet to receive a reply to my letter from Dr Chan.

By 20 March, two general practitioners came down with the infection after seeing patients with SARS. By that evening, the consensus amongst senior members of the faculty was that something more needed to be done to warn our colleagues and the community. Given the response of Dr Margaret Chan to my appeal the day before, it was agreed that another avenue of communication needed to be sought. The faculty debated whether to go to the public in a high profile manner, but decided that confrontation would not be in the best interest of the community, as the government alone had the mechanisms for infection control for our community. We therefore, through Dr Fung Hong, asked Dr William Ho to come to the Prince of Wales Hospital and presented to him the data that was available. We managed to convince him of the seriousness of the situation. This episode was well described in Dr Ho's subsequent letter to the Hospital Authority staff. (appendix 11)

The faculty held an emergency executive committee meeting to discuss the course of action on 21 March. Dr Fung Hong and Professor Wong Tze-wai were also at that meeting. The meeting resolved that it was the duty of the Faculty to warn the public and our colleagues in private practice that SARS has already spread to the community. The Faculty sent a delegation to Dr CH Leong to express our grave concern, and to take measures to protect the community and other health care professionals. A copy of the confirmed minutes of the meeting is enclosed (appendix 12). Professors TF Fok, Tony Chung and Peter Cameron met with Dr CH Leong at the HA Headquarters at

around 1 pm. Dr Leong agreed that immediate action needed to be taken to warn the public. He also agreed to discuss the matter with Dr EK Yeoh urgently. On the same evening, the faculty posted a warning message on the website of the Public Doctors' Association, and sent out the same message to all Hong Kong Medical Association members. (appendix 13)

I am all too cognizant of the havoc that SARS has wreaked in Hong Kong and the whole world. I am haunted by the fact that close to 400 of our loyal health care workers contracted the disease while on duty and eight of them died. I am grateful for the opportunity to present the faculty's viewpoint to the investigation committee. We must learn from this very bitter experience and improve our systems so that we are ready for the next attack. May I end by making two observations?

1) Apart from human factors, the delay in responding to the crisis in the beginning resulted from the artificial separation of the Department of Health (responsible for disease control and prevention) and the Hospital Authority (responsible for hospital medicine). The gulf between these two institutions, both in administration and culture, prevented a rapid, concerted response as the epidemic unfolded.

2) The Prince of Wales Hospital is outdated, dilapidated and ill equipped to deal with an infectious disease outbreak such as SARS. The professionalism and dedication of health care team (including the administrators) cannot compensate for the lack of isolation facilities, poorly designed wards, antiquated air conditioning systems and overcrowding. Our gallant doctors, nurses and health care assistants paid dearly for their selfless sacrifice.

Best regards,

Yours sincerely,

SC Sydney Chung
Dean

SC/cm

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Major Outbreak of Severe Acute Respiratory Syndrome in Hong Kong

Nelson Lee, M.D., David Hui, M.D., Alan Wu, M.D., Paul Chan, M.D., Peter Cameron, M.D., Gavin M. Joynt, M.D., Anil Ahuja, M.D., Man Yee Yung, B.Sc., C.B. Leung, M.D., K.F. To, M.D., S.F. Lui, M.D., C.C. Szeto, M.D., Sydney Chung, M.D., and Joseph J.Y. Sung, M.D.

ABSTRACT

BACKGROUND

There has been an outbreak of the severe acute respiratory syndrome (SARS) worldwide. We report the clinical, laboratory, and radiologic features of 138 cases of suspected SARS during a hospital outbreak in Hong Kong.

METHODS

From March 11 to 25, 2003, all patients with suspected SARS after exposure to an index patient or ward were admitted to the isolation wards of the Prince of Wales Hospital. Their demographic, clinical, laboratory, and radiologic characteristics were analyzed. Clinical end points included the need for intensive care and death. Univariate and multivariate analyses were performed.

RESULTS

There were 66 male patients and 72 female patients in this cohort, 69 of whom were health care workers. The most common symptoms included fever (in 100 percent of the patients); chills, rigors, or both (73.2 percent); and myalgia (60.9 percent). Cough and headache were also reported in more than 50 percent of the patients. Other common findings were lymphopenia (in 69.6 percent), thrombocytopenia (44.8 percent), and elevated lactate dehydrogenase and creatine kinase levels (71.0 percent and 32.1 percent, respectively). Peripheral air-space consolidation was commonly observed on thoracic computed tomographic scanning. A total of 32 patients (23.2 percent) were admitted to the intensive care unit; 5 patients died, all of whom had coexisting conditions. In a multivariate analysis, the independent predictors of an adverse outcome were advanced age (odds ratio per decade of life, 1.80; 95 percent confidence interval, 1.16 to 2.81; P=0.009), a high peak lactate dehydrogenase level (odds ratio per 100 U per liter, 2.09; 95 percent confidence interval, 1.28 to 3.42; P=0.003), and an absolute neutrophil count that exceeded the upper limit of the normal range on presentation (odds ratio, 1.60; 95 percent confidence interval, 1.03 to 2.50; P=0.04).

CONCLUSIONS

SARS is a serious respiratory illness that led to significant morbidity and mortality in our cohort.

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IN MARCH 2003, THERE WAS AN OUTBREAK of atypical pneumonia in Hong Kong. As of March 27, there were 367 reported cases in Hong Kong and more than 1400 cases worldwide.[1] The disease may progress rapidly and often results in the acute respiratory distress syndrome (ARDS). As of this writing, there have been 10 deaths in Hong Kong related to the illness, which the World Health Organization (WHO) has named the severe acute respiratory syndrome (SARS). Globally, there have been at least 53 deaths related to SARS.[1] Schools have been closed in Hong Kong, and more than 1000 people who had a history of contact with a patient with SARS were quarantined.

We describe the clinical, laboratory, and radiologic features of patients with SARS who were seen at the Prince of Wales Hospital, Hong Kong. These patients were either health care workers in a medical ward of the hospital or persons who had a history of contact with an index patient or exposure to the same medical ward. We also included patients who had contracted the disease through direct contact with these cases.

METHODS

On March 10, 18 health care workers in a medical ward of the Prince of Wales Hospital reported that they were ill. Through telephone contact, more than 50 of the hospital's health care workers were identified as having had a febrile illness over the previous few days. On March 11, 23 of them were admitted to an isolation ward in the hospital. A team of "atypical pneumonia physicians" was formed to take responsibility for screening of suspected cases and subsequent management. The team included physicians from the Department of Medicine and Therapeutics (infectious disease, respiratory medicine, and general medicine), the Department of Emergency Medicine, and the intensive care unit (ICU). Clinical findings and laboratory data were documented prospectively.

Since the etiologic agent was not known at the onset of the outbreak, the diagnosis was based on clinical symptoms and the ruling out of common bacterial and viral pathogens that cause pneumonia. On the basis of the criteria for SARS that have been established by the Centers for Disease Control and Prevention (CDC),[2] our case definition was a fever (temperature, >38°C), a chest radiograph (a plain radiograph, a computed tomographic [CT] image of the thorax, or both) showing evidence of consolidation with or without respiratory symptoms (e.g., cough and shortness of breath), and a history of exposure to an index patient suspected to have SARS or direct contact with a person who became ill after exposure to an index patient.

All patients were initially admitted to medical wards with isolation facilities. Initial investigations included a complete blood count (with a differential count), clotting profile (prothrombin time, activated partial-thromboplastin time, international normalized ratio, D-dimer) and serum biochemical measurements (including electrolytes, renal-function and liver-function values, creatine kinase, and lactate dehydrogenase). These studies and chest radiography were performed daily until the fever had subsided for three days. Nasopharyngeal-aspirate samples obtained from all study patients were screened for common viruses, including influenzavirus A and B, respiratory syncytial virus, adenovirus, and parainfluenzavirus types 1, 2, and 3, with the use of commercial immunofluorescence assays. In addition, virus culture was performed with the use of various cell lines (LLC-MK2, MDCK, Hep2, human embryonic lung fibroblast, Buffalo green-monkey kidney, and Vero cells). In addition, multiplex reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays for influenzavirus A, influenzavirus B, and respiratory syncytial virus were performed in 65 randomly selected patients. Electron microscopy was used to study nasopharyngeal aspirates in selected cases. Sputum cultures and blood cultures were performed in all cases to complete the microbiologic workup. PCR assays for mycoplasma and *Chlamydia pneumoniae* were performed in 65 randomly selected patients. A legionella urinary antigen assay was performed in the first 25 patients.

Initial treatment included cefotaxime and clarithromycin (or levofloxacin) to target common pathogens causing community-acquired pneumonia, according to current recommendations.[3,4] Oseltamivir (Tamiflu) was also given initially to treat possible influenza infection. If fever persisted for more than 48 hours and the blood count showed leukopenia, thrombocytopenia, or both, oral ribavirin (1.2 g three times a day) and corticosteroid therapy (prednisolone at a dose of 1 mg per kilogram of body weight per day) was given as a combined regimen. Patients with persistent fever and worsening lung opacities were given intravenous ribavirin (400 mg every eight hours) and corticosteroid therapy (an additional two to three pulses of 0.5 g of methylprednisolone daily). Patients in whom hypoxemia developed were given oxygen through a nasal can-

nula. Patients were admitted to the ICU if respiratory failure developed, as evidenced by an arterial oxygen saturation of less than 90 percent while the patient was receiving 50 percent supplemental oxygen, a respiratory rate that exceeded 35 breaths per minute, or both.

An epidemiologic study was conducted shortly after the outbreak. We identified our index patient, whose exposure history has been described elsewhere.[5] He was a 26-year-old ethnic Chinese man who was admitted to the Prince of Wales Hospital on March 4, 2003, with a high temperature, myalgia, and cough. His chest radiograph showed an ill-defined air-space opacity in the periphery of the right upper lobe. He was treated with amoxicillin–clavulanate and clarithromycin. All bacteriologic and virologic tests were unrevealing. The right lung opacity progressed to bilateral consolidation. After seven days of antibiotic therapy, his fever gradually diminished, and the lung opacities started to resolve. During this period, he was treated with albuterol (0.5 mg through a jet nebulizer, delivered by oxygen at a flow rate of 6 liters per minute, four times daily for a total of seven days).

From our contact tracing, we found that the first patients began to have symptoms two days after the index patient's admission. Moreover, all doctors and nurses who participated in the care of the patient, all medical students who had examined him, and the patients around him were the ones who first reported febrile illness, on March 10. We therefore defined all cases that developed in persons who had had direct contact with the index patient or who had been exposed to him in the medical ward as secondary cases. Cases in patients who contracted the disease from these patients (e.g., family members of health care workers or of patients who had stayed in this medical ward) were defined as tertiary cases.

STUDY POPULATION AND DATA ANALYSIS

Our study cohort included all secondary and tertiary cases. Their demographic, clinical, laboratory, and radiologic characteristics were reported and analyzed. The clinical composite end point was the need for care in the ICU, death, or both. Univariate and multivariate analyses of clinical and laboratory data were performed to identify prognostic variables. Statistical analysis was performed with SYSTAT software (version 7.0, SPSS, Chicago). Data are reported as means ±SD unless otherwise specified. Univariate analysis was performed to compare patients who reached the end point and those who did not, with the use of an unpaired Student's t-test or chi-square test, as appropriate. Multivariate logistic-regression analysis was then performed, with backward stepwise analysis, to identify independent predictors of the end point. All comparisons of clinical variables with a P value of less than 0.20 by univariate analysis were entered into the model. A P value of less than 0.05 was considered to indicate statistical significance. All probabilities are two-tailed.

RESULTS

Between March 11 and March 25, 2003, a total of 156 patients were hospitalized with SARS, of whom 138 were identified as having either secondary or tertiary cases as a result of exposure to our index patient. There were 112 patients with secondary cases and 26 with tertiary cases in this cohort, including 69 health care workers (20 doctors, 34 nurses, and 15 allied health workers) and 16 medical students who had worked in the index ward, plus 53 patients who were either in the same medical ward or had visited their relatives there. There were 66 male patients and 72 female patients; their mean age was 39.3±16.8 years. A total of 19 patients had coexisting conditions: cardiovascular disease in 4, the myelodysplastic syndrome in 2, chronic liver disease in 3, diabetes mellitus in 5, chronic renal failure in 2, and chronic pulmonary disease in 3. Most of the health care workers were previously healthy. All patients were ethnic Chinese.

CLINICAL FEATURES

The interval between exposure to the index patient or ward and the onset of fever ranged from 2 to 16 days. The median incubation period was six days. The most common symptoms at presentation were fever (in 100 percent of the patients); chills, rigor, or both (73.2 percent); myalgia (60.9 percent); cough (57.3 percent); headache (55.8 percent); and dizziness (42.8 percent). Less common symptoms included sputum production (in 29.0 percent), sore throat (23.2 percent), coryza (22.5 percent), nausea and vomiting (19.6 percent), and diarrhea (19.6 percent). Physical examination on admission revealed a high body temperature in most patients (median temperature, 38.4°C; range, 35 to 40.3°C). Inspiratory crackles could be heard at the base of the lung. Wheezing was absent except in one patient with a history of asthma. Rash, lymphadenopathy, and purpura were not seen in this cohort.

HEMATOLOGIC FINDINGS

The initial blood count showed leukopenia (total white-cell count, $<3.5\times10^9$ per liter) in 33.9 percent of patients. Whereas the neutrophil count (median, 3500 per cubic millimeter; range, 500 to 11,800) and the monocyte count were normal in most cases, 69.6 percent of the patients had moderate lymphopenia (absolute lymphocyte count, <1000 per cubic millimeter). Thrombocytopenia (platelet count, <150,000 per cubic millimeter) was documented in 44.8 percent of the patients on presentation. The lymphocyte count continued to drop within the first few days after admission (Table 1). A prolonged activated partial-thromboplastin time (>38 seconds) was noted in 42.8 percent of the patients, whereas the prothrombin time remained normal in most cases. In 45.0 percent of the patients, the D-dimer level was also elevated. Reactive lymphocytes were detected in peripheral-blood films in 15.2 percent of cases.

BIOCHEMICAL FINDINGS

Serum chemical values were normal in the majority of cases. There were, however, several abnormalities in a substantial proportion of patients. Serum alanine aminotransferase levels were elevated (>45 IU per milliliter) in 23.4 percent of patients (mean level, 60.4±150.4 IU per milliliter); only two patients had a history of chronic liver disease. Creatine kinase levels were elevated in 32.1 percent of patients (median level, 126 U per liter; range, 29 to 4644). None of the patients with elevated creatine kinase levels had abnormal values for creatine kinase MB or troponin T, indicating that the source of creatine kinase was unlikely to be cardiac muscles. The lactate dehydrogenase level was elevated in 71.0 percent of patients. Hyponatremia (sodium level, <134 mmol per liter) was documented in 20.3 percent of patients, and hypokalemia (potassium level, <3.5 mmol per liter) in 25.2 percent of patients. The results of laboratory tests performed during the first week of hospitalization are listed in Table 1.

MICROBIOLOGIC AND VIROLOGIC FINDINGS

In our cohort of 138 patients, there were five positive sputum cultures; three were positive for *Haemophilus influenzae*, one for *Streptococcus pneumoniae*, and one for *Klebsiella pneumoniae*. None of the blood cultures were positive. Other bacteriologic investigations were unrevealing. Of all the nasopharyngeal aspirates collected, one was positive for influenzavirus A, one was positive for influenzavirus B,

Table 1. Mean (±SD) Laboratory Results in 138 Patients in Our Study Cohort during the First Seven Days of Hospitalization.

Variable*	Day 1	Day 3	Day 5	Day 7
Hemoglobin (g/dl)	13.5±1.7	13.1±1.7	13.0±1.6	12.9±1.7
Platelets ($\times10^{-9}$/liter)	150.2±60.1	153.2±61.3	164.9±70.7	206.3±89.9
White cells ($\times10^{-9}$/liter)	5.1±2.1	5.1±2.7	6.0±3.4	8.3±4.9
Neutrophils ($\times10^{-9}$/liter)	3.9±2.0	4.0±2.7	5.0±3.3	7.2±4.7
Lymphocytes ($\times10^{-9}$/liter)	0.9±0.7	0.8±0.7	0.7±0.4	0.6±0.4
Prothrombin time (sec)	11.2±4.7	12.7±8.6	11.2±4.6	11.3±4.0
Activated partial-thromboplastin time (sec)	41.6±8.9	44.8±12.8	41.2±8.1	36.3±6.9
Sodium (mmol/liter)	135.6±3.4	135.9±3.5	137.0±4.4	139.2±4.9
Potassium (mmol/liter)	3.7±0.4	3.8±0.5	3.8±0.4	3.9±0.4
Urea (mmol/liter)	4.7±5.1	4.5±4.5	4.6±3.8	6.3±7.2
Creatinine (μmol/liter)	99.0±111.8	94.3±100.4	82.8±23.8	82.7±27.2
Bilirubin (mmol/liter)	10.0±19.4	10.7±17.8	12.5±19.3	14.3±16.3
Alanine aminotransferase (IU/liter)	60.4±150.4	67.4±113.7	69.4±72.3	89.8±104.5

* To convert values for creatinine to milligrams per deciliter, divide by 88.4, and to convert values for bilirubin to milligrams per deciliter, divide by 17.1.

and two were positive for respiratory syncytial virus. Microscopical examination of nasopharyngeal aspirates from five patients showed paramyxovirus-like viral particles in one and coronavirus-like viral particles in another. The aspirates from the other three patients were negative. Further virologic studies are in progress.

FINDINGS ON CHEST RADIOGRAPHS

At the onset of fever, 108 of the 138 patients (78.3 percent) had abnormal chest radiographs, all of which showed air-space consolidation. Of these 108 patients, 59 (54.6 percent) had unilateral focal involvement (Fig. 1) and 49 (45.4 percent) had either unilateral multifocal or bilateral involvement. Air-space opacities developed in all patients eventually during the course of the disease.

The initial radiographic changes were indistinguishable from those associated with other causes of bronchopneumonia. Interestingly, peripheral-zone involvement was predominant. Pleural effusion, cavitation, and hilar lymphadenopathy were absent in our cohort. Among patients with clinical deterioration, serial chest radiographs showed progression of pulmonary infiltrates approximately 7 to 10 days after admission. Lung opacities enlarged, and multiple areas of involvement were often seen (Fig. 2A and 2B). A successful response to therapy could be demonstrated by serial chest radiographs showing the resolution of lung opacities (Fig. 2C). In cases in which typical lung opacities could not be found on the initial plain chest radiograph, conventional and high-resolution CT images of the thorax proved to be useful. The typical finding on thoracic CT images, as shown in 25 cases, was ill-defined, ground-glass opacification in the periphery of the affected lung parenchyma, usually in a subpleural location (Fig. 3). The characteristic peripheral alveolar opacities were very similar to those found in bronchiolitis obliterans organizing pneumonia.[6,7] There was no obvious bronchial dilatation.

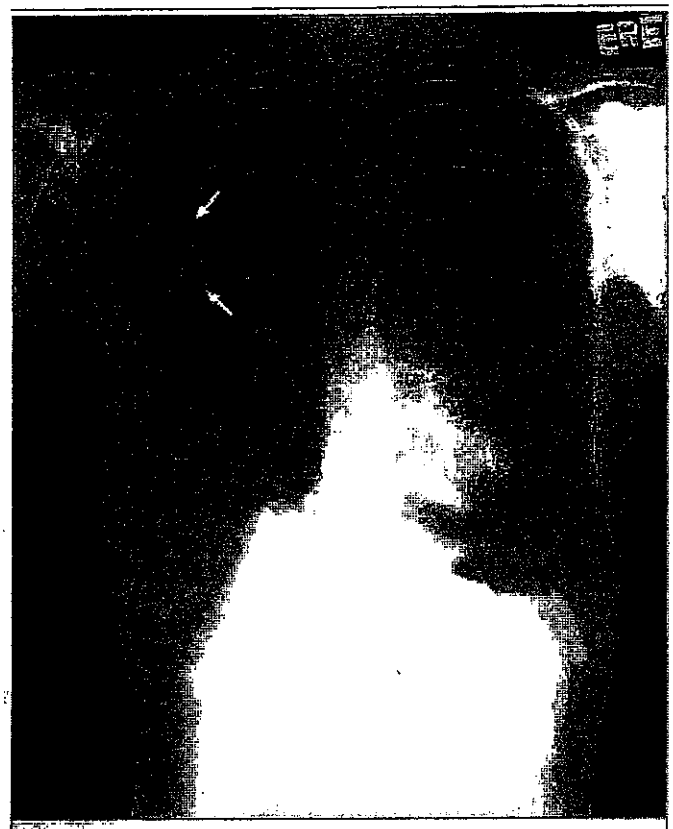

Figure 1. Frontal Chest Radiograph in a 25-Year-Old Woman Showing Ill-Defined Air-Space Shadowing (Arrows).
There is no associated pleural effusion or hilar or mediastinal adenopathy.

CLINICAL OUTCOMES

Of the 138 patients, 32 (23.2 percent) were admitted to the ICU, all because of respiratory failure. Mechanical ventilatory support with positive end-expiratory pressure was required in 19 patients (13.8 percent). Among the 32 patients in the ICU, dramatic increases in lung opacity, shortness of breath, and hypoxemia occurred at a median of 6.5 days (range, 3 to 12) and led to their ICU admission. By day 21 of the outbreak, five patients had died (crude mortality rate, 3.6 percent). All five had originally been admitted because of major medical conditions. Two patients had the myelodysplastic syndrome, one had congestive heart failure, one had alcoholic liver cirrhosis, and one had a reactivation of hepatitis B. None of the health care workers or medical students died. To date, a total of 76 patients (55.1 percent) have been discharged, of whom 44 (31.9 percent) were health care workers. Fitness for discharge was based on defervescence for at least 96 hours, with radiographic evidence of improvement in lung consolidation.

FACTORS PREDICTIVE OF ICU ADMISSION AND DEATH

Univariate analysis showed that advanced age, male sex, a high peak creatine kinase value, a high lactate

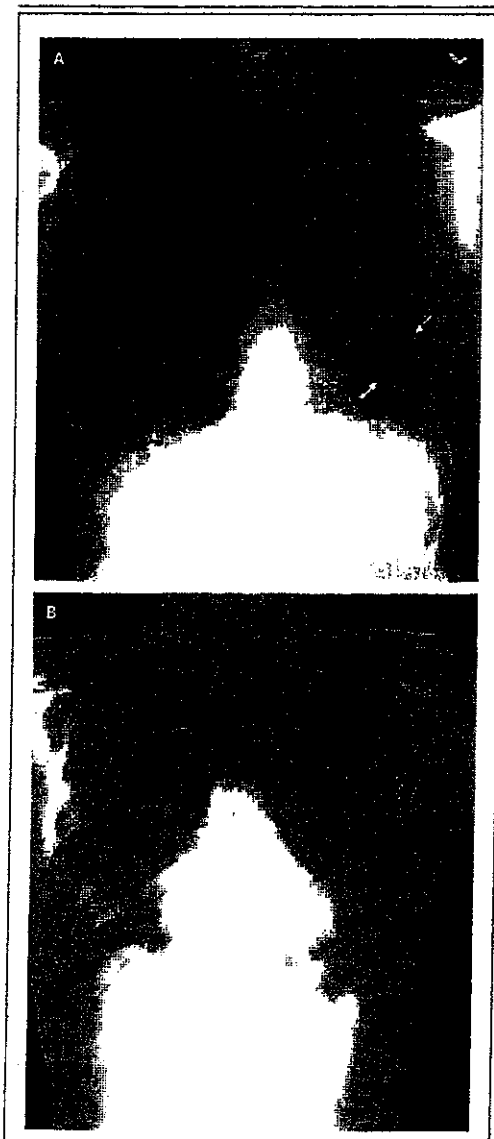

Figure 2. Frontal Chest Radiographs in a 46-Year-Old Man.
Panel A shows an obvious area of air-space shadowing (arrows) on the left side. A follow-up chest radiograph showed progression of the disease, with multiple bilateral areas of involvement (Panel B). A subsequent chest radiograph shows improvement of bilateral lung opacities after therapy (Panel C).

dehydrogenase level on presentation and a high peak value, a high initial absolute neutrophil count, and a low serum sodium level were significant predictive factors for ICU admission and death (Table 2). The presence of coexisting conditions (in 19 patients) did not appear to be associated with a worse clinical outcome (P=0.14). On multivariate analysis, the only factors that were predictive of an adverse outcome were advanced age (odds ratio for every 10 years of age, 1.80; 95 percent confidence interval, 1.16 to 2.81; P=0.009), a high peak lactate dehydrogenase level (odds ratio for every 100 U per liter, 2.09; 95 percent confidence interval, 1.28 to 3.42; P=0.003), and an absolute neutrophil count that exceeded the upper limit of the normal range on presentation (odds ratio, 1.60; 95 percent confidence interval, 1.03 to 2.50; P=0.04).

POSTMORTEM FINDINGS

Postmortem examination in two cases showed gross consolidation of the lungs. Histologic features varied from region to region. The early phase and organizing phase of diffuse alveolar damage were seen in different parts of the lung. The early phase was characterized by pulmonary edema with hyaline membrane formation suggestive of the early phase of ARDS (Fig. 4). Cellular fibromyxoid organizing exudates in air spaces indicated the organizing phase of alveolar damage. There was a scanty lymphocytic inflammatory infiltrate in the interstitium.

Figure 3. A High-Resolution CT Scan Showing the Characteristic Ground-Glass Abnormality in a Subpleural Location.

There is no cavitation. A conventional CT scan did not show pleural effusion or lymphadenopathy.

Vacuolated and multinucleated pneumocytes were also identified. Viral inclusions were not detected. There was no evidence of the involvement of other organs.

DISCUSSION

We report an outbreak in our hospital of a deadly pneumonia, which caused rapid deterioration of pulmonary function requiring ICU admission in 23.2 percent of cases and mechanical ventilation in 13.8 percent. Within a period of less than two months, SARS has become a global health problem, prompting the WHO to issue a global alert for the first time in more than a decade.[1]

SARS developed in 69 health care workers and 16 medical students, all with unremarkable medical histories, after exposure at work in the medical ward for men where our index patient was hospitalized. The high infectivity was also demonstrated by the fact that there were 26 tertiary cases, which included family members of the infected health care workers. We suspected that the infection was transmitted by droplets and possibly by fomites, and we therefore instituted both airborne precautions (e.g., use of the N-95 respirator) and contact precautions (e.g., use of gowns and gloves), as recommended by the CDC.[8] However, the use of a jet nebulizer to administer aerosolized albuterol in the index patient had probably aggravated the spread of the disease by droplet infections.

Table 2. Univariate Analyses of Clinical and Laboratory Variables Associated with the Combined Outcome of ICU Care or Death.*

Variable	No ICU Care	ICU Care or Death	P Value
Age (yr)	36.1±14.6	50.2±18.4	0.007
Male sex (%)	41.9	66.7	0.01
Peak D-dimer (ng/ml)	951.0±1197.9	1686.9±2132.3	0.31
Platelets ($\times 10^{-9}$/liter)	156.8±61.2	131.7±64.9	0.06
Neutrophils ($\times 10^{-9}$/liter)	3.7±1.9	4.6±2.1	0.02
Lymphocytes ($\times 10^{-9}$/liter)	0.9±0.7	0.8±0.5	0.49
Activated partial-thromboplastin time (sec)	41.0±7.5	43.6±11.7	0.23
Sodium (mmol/liter)	136.1±2.7	134.0±4.6	0.02
Urea (mmol/liter)	3.8±1.1	7.3±9.6	0.05
Creatinine (μmol/liter)†	86.1±19.4	135.5±218.0	0.21
Alanine aminotransferase (IU/liter)	46.5±81.4	99.4±262.0	0.27
Creatine kinase (U/liter)			
On presentation	268.5±434.8	609.3±973.2	0.06
Peak	352.7±544.0	697.4±971.1	0.04
Lactate dehydrogenase (U/liter)			
On presentation	287.7±143.3	558.0±258.0	<0.001
Peak	310.0±153.8	629.7±283.5	<0.001

* Plus–minus values are means ±SD.
† To convert values for creatinine to milligrams per deciliter, divide by 88.4.

The clinical presentation and radiologic features of SARS bear some resemblance to the syndrome commonly referred to as "atypical pneumonia"; mycoplasma, chlamydia, and legionella are the usual pathogens implicated in this syndrome. Fever, chills, headache, myalgia, and dry cough are the common features in patients presenting with the syndrome. However, the clinical and radiographic characteristics of atypical pneumonia are not useful in differentiating these pathogens from usual bacterial pathogens such as *S. pneumoniae* and *H. influenzae*. The exclusion of common extracellular pathogens and a response to empirical therapy with macrolides or quinolones are the usual strategy of management. In our cohort, most of the common bacterial pathogens were ruled out, in addition to viral diseases such as influenza and respiratory syncytial virus infection. Moreover, lack of a response to the initial antimicrobial treatment we provided

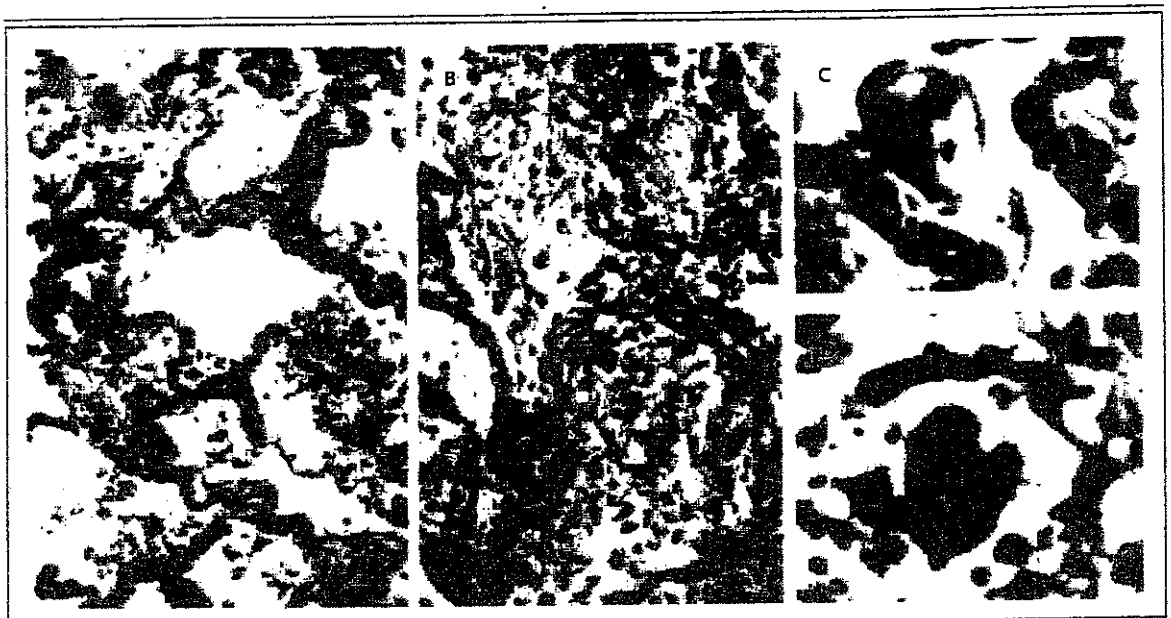

Figure 4. Lung Biopsy Specimen Obtained at Autopsy.

Panel A shows diffuse alveolar damage with pulmonary congestion, edema, and formation of hyaline membrane (hematoxylin and eosin, ×100). Panel B shows the organizing phase of diffuse alveolar damage, with scanty interstitial inflammatory cell infiltrates (hematoxylin and eosin, ×200). Panels C and D show vacuolated and multinucleated pneumocytes (hematoxylin and eosin, ×400).

led to the suspicion that we were dealing with a novel virus that causes lower respiratory tract infection. So far, there have been only preliminary data reported on the causative agent of SARS, and metapneumovirus and coronavirus have been implicated.[5] The relevance of histologic features such as vacuolated and multinucleated pneumocytes in the pathogenesis of SARS remains to be determined. As of this writing, no reliable diagnostic test is available. In the first 138 cases, we have identified several cardinal symptoms of SARS. Besides fever, chills, and rigor, which were present in more than 70 percent of cases, cough was present in more than 50 percent and dizziness in more than 40 percent of cases. Rigor may represent the viremic phase of the disease, which subsided gradually as the illness progressed. In addition, moderate lymphopenia and its subsequent progression, thrombocytopenia, a prolonged activated partial-thromboplastin time, elevated lactate dehydrogenase and creatine kinase levels, and elevated alanine aminotransferase levels were prevalent in the early phase of the illness in our cohort; all these findings are quite different from those associated with pneumonia caused by usual bacterial pathogens. Although these symptoms and laboratory findings are nonspecific, the constellation of these features should alert medical practitioners to the possibility of SARS.[9]

We have also found that the chest radiograph offers an important diagnostic clue to this condition. Typically, our patients presented with unilateral, predominantly peripheral areas of consolidation. After approximately one week, it progressed rapidly to bilateral patchy consolidation, and the extent of the lung opacities was correlated with the deterioration in respiratory function. In cases in which plain chest radiographs appeared normal in the presence of a high spiking fever and lymphopenia, CT of the thorax was a sensitive imaging approach for the diagnosis. The characteristic finding on CT was bilateral peripheral air-space ground-glass consolidation mimicking that in bronchiolitis obliterans organizing pneumonia. In fact, the similarity of this radiographic picture to that of bronchiolitis obliterans organizing pneumonia and the similarity of the histologic features to those of early ARDS in postmortem studies have prompted us to

use corticosteroid in combination with ribavirin for the treatment of SARS. In ARDS and particularly in bronchiolitis obliterans organizing pneumonia, corticosteroid therapy has been used with some success.[7] The majority of our cohort appeared to have a response to corticosteroid therapy, in addition to ribavirin, with resolution of fever and lung opacities within two weeks.

In this study, we were able to identify some clinical and laboratory features on presentation that were associated with the adverse clinical outcome of respiratory failure requiring care in the ICU or death. Univariate analyses showed that advanced age, male sex, a high neutrophil count, a high peak creatine kinase level, high initial and peak lactate dehydrogenase levels, and a low serum sodium level were associated with an adverse outcome. Only advanced age, a high neutrophil count, and a high peak lactate dehydrogenase level were independent predictors. Since high lactate dehydrogenase levels are often seen in association with tissue damage, we propose that this finding indicates more extensive lung injury. The significant association between a high neutrophil count and an adverse outcome remains to be explained. All five patients who died had major coexisting disorders; however, in our analyses, coexisting illness was not correlated with a poor outcome, probably because of the small number of such patients.

SARS has already become a global health hazard, and its high infectivity is alarming. The discovery of the infective agent and studies of its behavior are crucial to an understanding of this new disease. A reliable, rapid diagnostic test, based on blood samples or nasopharyngeal aspirates, is of great importance in the future management of this disease. Until such a diagnostic test is available, a clear picture of its clinical presentation will help physicians be on the alert for this condition. Early recognition, prompt isolation, and appropriate therapy are the keys in combating this deadly infection.

We wish to dedicate this report to the patients we have described, many of whom are our colleagues and their family members, together with medical students from the Faculty of Medicine, Chinese University of Hong Kong. We are also indebted to the many members of the frontline medical and nursing staff who demonstrated selfless and heroic devotion to duty in the face of this outbreak, despite the potential threat to their own lives and those of their families.

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Appendix 2

COMMENTARY

SARS: experience at Prince of Wales Hospital, Hong Kong

The Prince of Wales Hospital (PWH) has been at the forefront of the outbreak of severe acute respiratory syndrome (SARS) in Hong Kong.[1] We relate our experience at this hospital. A working definition of SARS is important,[2] although clinical conditions rarely remain within artificial boundaries. Some patients might not have all features, others may present unusually. Fever is a cardinal symptom but not always so, and is sometimes absent in elderly patients. Some patients have presented with diarrhoea or, in at least two cases, with severe acute abdominal pain requiring exploratory laparotomy. All these patients developed typical SARS. Patients presenting with other respiratory infections must now all be regarded as potential SARS cases until proven otherwise. Contact with a known case is an important discriminator but, if emphasised too strongly in the diagnostic process, may lead to false positives or negatives.

The difficulty of making a firm diagnosis until chest radiographic changes appear has important implications for health-care personnel and for surveillance. Three major reasons for spread of infection to health-care workers have been: failure to apply isolation precautions to cases not yet identified as SARS, breaches of procedure, and inadequate precautions. Every patient must now be assumed to have SARS, which has major long-term implications for the health-care system. Another reason for spread among health-care workers is infected workers continuing to work despite symptoms, such as mild fever. Such individuals must now cease working. However, staying at home can also have disastrous consequences for exposed family members. Potential cases therefore require early isolation from both workplace and household. Extreme measures are required to protect health-care workers, who account for about 20% of cases.

Early diagnosis by virus isolation or serological testing is essential to halt the spread of SARS. Progress has been made with the isolation of the coronavirus.[3–5] A metapneumovirus was also identified in Canada[4] and in many of the cases at PWH. Coronavirus appears to be the main pathogen, but dual infections may be possible. Such situations are uncommon in human disease, apart from HIV-related infections, but in veterinary medicine combined infections with coronavirus and other agents have been described.[6,7]

The first cases probably occurred in Guangdong Province in southern China in November, 2002.[8] The term SARS appears to have been first used for a patient in Hanoi who became ill on Feb 26, 2003, and was evacuated back to Hong Kong where he died on March 12. The physician who raised the alarm in Hanoi, Carlo Urbani, subsequently contracted SARS and died. The first case in Hanoi had stayed at a hotel in Kowloon, Hong Kong, at the same time as a 64-year-old doctor who had been treating pneumonia cases in southern China. This doctor was admitted to hospital on Feb 22, and died from respiratory failure soon afterwards.[9] He was the first known case of SARS in Hong Kong and appears to have been the source of infection for most if not all cases in Hong Kong as well as the cohorts in Canada, Vietnam, Singapore, USA, and Ireland, and subsequently Thailand and Germany.[10]

The index patient at PWH was admitted on March 4, 2003, and had also visited this hotel. He had pneumonia which progressed initially despite antibiotics, but after 7 days he improved without additional treatment.[1] On March 10, 18 health-care workers at PWH were ill and 50 potential cases among staff were identified later that day. Further staff, patients, and visitors became ill over the next few days and there was subsequent spread to their contacts. By March 25, 156 patients had been admitted to PWH with SARS, all traceable to this index case.[1] One important factor in the extensive dissemination of infection appears to have been the use of nebulised bronchodilator, which increased the droplet load surrounding the patient. Overcrowding in the hospital ward and an outdated ventilation system may also have contributed.

The second major epicentre in Hong Kong, accounting for over 300 cases, has been an apartment block called Amoy Gardens. The source has been attributed to a patient with renal failure receiving haemodialysis at PWH who stayed with his brother at Amoy Gardens.[11] He had diarrhoea, and infection may have spread to other residents by a leaking sewage drain allowing an aerosol of virus-containing material to escape into the narrow lightwell between the buildings and spread in rising air-currents. Sewage also backflowed into bathroom floor drains in some apartments. Spread to people in nearby buildings also occurred, probably by person-to-person contact and contamination of public installations.

Although the rapid spread of the disease in some situations may have been explained, many uncertainties remain. Why the disease spread in the Kowloon hotel has not been clarified, and there are many other important issues. "Super-spreaders" may be prone to carry a high viral load because of defects in their

immune system, as could be the case in the patient with end-stage renal failure implicated in the Amoy Gardens outbreak and another with renal failure at the centre of an outbreak in Singapore. Subclinical infections may also occur and will not be recognisable until reliable diagnostic tests are available. Procedures causing high risk to medical personnel include nasopharyngeal aspiration, bronchoscopy, endotracheal intubation, airway suction, cardiopulmonary resuscitation, and non-invasive ventilation procedures. Cleaning the patient and the bedding after faecal incontinence also appears to be a high-risk procedure.

Treatments have been empirical. Initial patients were given broad-spectrum antibiotics but, after failing to respond for 2 days, were given ribavirin and corticosteroids. Patients who continued to deteriorate with progression of chest radiographic changes or oxygen desaturation, or both, were given pulsed methylprednisolone.[1] Steroids were used on the rationale that progression of the pulmonary disease may be mediated by the host inflammatory response, similar to that seen in acute respiratory distress syndrome, and produced by a cytokine or chemokine "storm". The clinical impression is that pulsed steroids sometimes produce a dramatic response. However, apparent benefits of steroid treatment have proven to be incorrect before, as in infection with respiratory syncytial virus.[12]

Lack of knowledge of SARS' natural history adds to the difficulty of determining the effectiveness of therapy. Some patients have a protracted clinical course with potential for relapses continuing into the second or third week, or beyond. Long hospital stays, even in less ill patients, are required, and the high proportion of patients requiring lengthy intensive care, with or without ventilation (23% in the 138 cases from PWH[1]), and the susceptibility of health-care workers bodes ill for the ability of health-care systems to cope. Even when the acute illness has run its course, unknowns remain. Continued viral shedding and the possible development of long-term sequelae, such as pulmonary fibrosis or late post-viral complications, means that patients will require careful surveillance.

This Commentary is dedicated to the frontline health-care staff who have shown courageous devotion to duty throughout this epidemic.

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The dietary fibre debate: more food for thought

See pages 1491 and 1496

This issue of *The Lancet* contains two important papers that associate high intake of dietary fibre with a decreased risk of either colonic adenomas or colorectal cancer. The USA-based study done by the Prostate, Lung, Colorectal, and Ovarian Cancer Screening project team (PLCO) compared the dietary fibre intake of 33 971 people who on sigmoidoscopy showed no polyps with 3591 people who had at least one histologically-verified adenoma in the distal large bowel. The study involved ten different US centres, with very different dietary practices. The European Prospective Investigation into Cancer and Nutrition (EPIC) consortium used a different approach to reach the same conclusion. They prospectively examined the dietary-fibre intake and incidence of colon cancer in 519 978 people recruited from ten European countries. The findings of both research teams contrast with those of at least three other studies that have been published in the past 4 years,[1-3] all of which found no protective effect of dietary-fibre intake on the development of either colonic adenomas or colorectal cancer. The new results give fresh impetus to fundamental research to determine the reasons for the protective action of dietary fibre, or to establish the definitive clinical trial.

The US Nurses Health Study[1] was based on numbers of cases of colorectal cancer as large as in EPIC, and had a considerable impact on thinking. After its publication,[1] doubts were expressed not only about population recommendations for health but even about the need for continued research. For example, Santani-Rim and Dashwood[4] posed the question about whether it was "time to discontinue antigenotoxicity studies of dietary fibre". Of equal concern was the downturn in interest of commercial food companies to do applied research in such areas as high-fibre food products.

Why did these two groups of studies give such different results? Although this question is obviously important, it is very difficult to answer. Random variation is unlikely, given the numbers in the population groups involved. Conflicting studies would be more difficult to explain if dietary fibre was a well-

Research letters

Clinical presentations and outcome of severe acute respiratory syndrome in children

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

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

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

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

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

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

Lymphopenia (0·3–3·0×10⁹/L) was reported in all patients, but the teenagers were generally more severely affected than the younger children. Lymphopenia mostly occurred between days 3 and 7, after the onset of fever. No bacteria, fungi, mycoplasma, chlamydia, or common respiratory viruses were detected by the laboratory investigations. Coronavirus was isolated by viral culture from the nasopharyngeal aspirates of patients 2 and 3. Reverse-transcriptase PCR targeting the novel coronavirus present in the nasopharyngeal aspirate samples was positive in four of six children tested (patients 1, 7, 9, and 10).

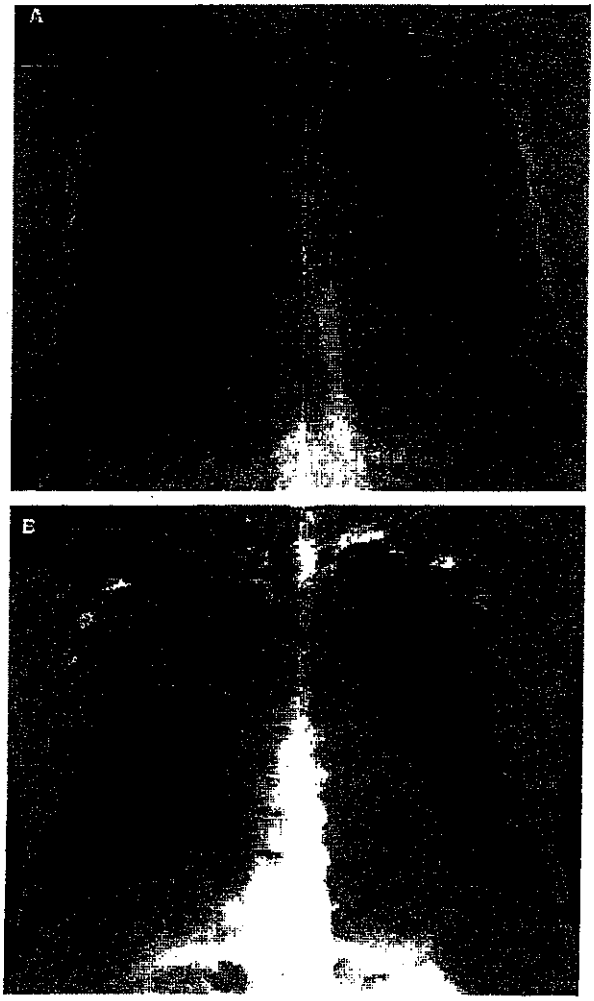
	Patient number									
	1	2	3	4	5	6	7	8	9	10
Age (years)	1·5	2·2	5·1	6·2	7·5	13·2	13·3	15·6	15·6	16·4
Sex (M/F)	F	M	F	F	M	F	F	F	F	F
Clinical features										
Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dyspnoea	No	No	No	No	No	Yes	Yes	Yes	Yes	No
Runny nose	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	No
Cough	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Sore throat	No	No	No	No	No	No	Yes	Yes	Yes	No
Chills/rigors	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Myalgia	No	No	No	No	No	No	Yes	Yes	Yes	Yes
Headache	No	No	No	No	No	No	Yes	Yes	Yes	Yes
Other	..	Febrile convulsion	..	..	Dizziness	Nausea	Abdominal pain	..	Nausea	..
Contact history	Community outbreak	Grandmother	Grandmother	Family doctor	Parents	Health-care worker	Community outbreak	Mother*	Mother*	Health-care worker
Laboratory findings										
Lowest lymphocyte count (×10⁹/L)	3·0 (day 3)	1·1 (day 3)	1·1 (day 4)	1·1 (day 3)	1·2 (day 3)	0·8 (day 6)	0·7 (day 4)	0·4 (day 6)	0·3 (day 11)	0·4 (day 7)
Lowest platelet count (×10⁹/L)	345	216	143	196	131	178	147	136	131	209
Highest serum LDH (U/L)†	376	308	324	273	332	286	676	392	431	208
Highest serum ALT (U/L) ‡	29	35	25	12	38	45	44	95	65	168
Radiological findings										
Initial chest radiograph	Right lower-zone focal	Right perihilar	Left middle-zone consolidation	Left upper-zone consolidation	Right upper-zone consolidation	Right lower-zone consolidation	Left and right lower-zone consolidation	Left lower-zone consolidation	Left lower-zone consolidation	Normal
Progressive changes of chest radiograph	Increased right lower-zone consolidation (day 2)	Progress to involve right upper zone (day 8)	Increased left middle-zone consolidation (day 5)	Increased left upper-zone consolidation (day 4)	Increased right upper-zone consolidation (day 5)	Increased right lower-zone consolidation (day 5)	Increased right and left upper-zone consolidation (day 6)	Diffuse confluence left and right lower zones (day 9)	Diffuse confluence right and left lower zones (day 11)	Normal
Findings on CT of thorax	None	Bilateral multifocal air space consolidations	None	None	None	None	None	None	None	Consolidation at right basal segments
Treatment and outcome										
Oral ribavirin	Prescribed	Prescribed	Prescribed	Prescribed	Prescribed	Prescribed	Not prescribed	Not prescribed	Not prescribed	Prescribed
IV ribavirin	Not prescribed	Prescribed	Not prescribed	Not prescribed	Not prescribed	Prescribed	Prescribed	Prescribed	Prescribed	Not prescribed
Oral prednisolone/IV hydrocortisone	Not prescribed	Prescribed	Prescribed	Not prescribed	Prescribed	Prescribed	Not prescribed	Prescribed	Prescribed	Prescribed
IV pulse methylprednisolone	Not prescribed	Twice (day 10)	Not prescribed	Not prescribed	Not prescribed	Once (day 6)	Three times (days 4–6)	Once (day 6)	Once (day 7)	Not prescribed
Duration of fever (days)	4	6	7	3	6	6	5	10	11	4
Ventilatory support	Not prescribed	Not prescribed	Not prescribed	Not prescribed	Not prescribed	Nasal cannula (days 5–9)	Nasal cannula (days 4–10)	Face mask (days 7–8; 12–15), BiPAP (days 8–12)	Face mask (days 7–10; 13-19), IPPV (days 10–13)	Not prescribed
Maximum oxygen requirement	Air	Air	Air	Air	Air	2 L/min	3 L/min	50%	50%	Air

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

Clinical features and treatment outcomes among SARS children

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

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



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

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

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

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

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Papers

Evaluation of WHO criteria for identifying patients with severe acute respiratory syndrome out of hospital: prospective observational study

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Abstract

Objectives To determine the clinical and radiological features of severe acute respiratory syndrome (SARS) and to evaluate the accuracy of the World Health Organization's guidelines on defining cases of SARS.
Design Prospective observational study.
Setting A newly set up SARS screening clinic in the emergency department of a university hospital in Hong Kong's New Territories.
Participants 556 hospital staff, patients, and relatives who attended the screening clinic and who had had contact with someone with SARS.
Main outcome measure Number of confirmed cases of SARS.
Results Of the 556 people, 141 were admitted to hospital, and 97 had confirmed SARS. Fever, chills, malaise, myalgia, rigor, loss of appetite, vomiting, diarrhoea, and neck pain but not respiratory tract symptoms were significantly more common among the 97 patients than among the other patients. The overall accuracy of the WHO guidelines for identifying suspected SARS was 83% and their negative predictive value was 86% (95% confidence interval 83% to 89%). They had a sensitivity of 26% (17% to 36%) and a specificity of 96% (93% to 97%).
Conclusions Current WHO guidelines for diagnosing suspected SARS may not be sufficiently sensitive in assessing patients before admission to hospital. Daily follow up, evaluation of non-respiratory, systemic symptoms, and chest radiography would be better screening tools.

Introduction

Initial reports on severe acute respiratory syndrome (SARS) described the clinical features of confirmed cases.[1–4] Later reports have described the epidemiology and progression of the illness in greater detail.[5,6] On the basis of early findings in hospitals, the World Health Organization and the Hospital Authority of Hong Kong produced case definitions for suspected and probable cases of SARS that may be used for screening patients before admission to hospital and in non-clinical contexts such as airports.[7,8] The discovery of the virus and the development of rapid serological tests may improve case definition, but the tests are not yet widely available.[9–11]

In the first two weeks of March 2003, 15 doctors, 15 nurses, 17 medical students, and five other staff (auxiliary staff, a clerk, and cleaning staff) associated with ward 8A of the Prince of Wales Hospital were infected with SARS. In response to this outbreak the hospital set up an emergency screening clinic on 12 March to evaluate all staff and their immediate contacts. The clinic gave us the opportunity to study the clinical response to the virus in a high contact environment. We investigated the clinical features of SARS in the early stages of infection to evaluate the WHO criteria for identifying suspected and probable cases of SARS and to report the safety of our current strategies to prevent the spread of SARS among our staff.

Methods

The study was conducted from 12 March to 31 March 2003 in the newly opened SARS clinic in the emergency department of the Prince of Wales Hospital, a 1400 bed university teaching hospital in the New Territories of Hong Kong. Health advice was given to all hospital staff, patients, and relatives who attended the clinic (see bmj.com for details).

Defining cases of SARS

As no diagnostic investigations for SARS were available at the time the clinic opened, we based diagnosis on exclusion of other diseases and on the WHO guidelines (box).[7,12] For suspected cases, we took a broad interpretation of the respiratory symptoms in the WHO criteria to include upper and lower tract clinical features. We confirmed a diagnosis of SARS when a patient was known to have contact with someone with SARS, had documented persistent fever (>38°C), a consistent clinical course of the illness, and evidence of pneumonia.

We used plain radiography or computed tomography to diagnose pneumonia. We diagnosed non-SARS pneumonia if the patient responded well to antibiotics within 48 hours. Final diagnoses were made by a team of general medical, respiratory, and infectious diseases clinicians. The recent discovery of the virus and the development of an immunofluorescence assay based

Details of health advice given to attenders at the screening clinic are on bmj.com

WHO case definitions for suspected and probable SARS

SARS suspected in patient with:
- Fever (>38°C)
- One or more respiratory symptoms (such as cough, shortness of breath, or breathing difficulty), and
- Close contact within previous 10 days with person previously diagnosed with SARS (close contact: family member or healthcare worker in contact with infected patient or patient with SARS)

SARS diagnosed in patient who meets the criteria of suspected SARS and has laboratory evidence of infection with coronavirus (coronavirus reverse transcriptase polymerase chain reaction test)

on vero cells infected with coronavirus have since allowed us to confirm diagnoses by measuring levels of anti-coronavirus IgG antibody in saved serum samples.

Inclusion and exclusion criteria

All hospital staff, patients, and relatives of staff or patients had access to the clinic. People attending the clinic were included in the study if they had had contact with anyone with SARS. We excluded children aged less than 11 years because their laboratory results and the clinical course of the disease are likely to differ from those of adults. Patients admitted to hospital with pneumonia but who had a diagnosis of non-SARS pneumonia were not excluded from the analysis.

Discharge and follow up criteria

Patients were discharged after their first attendance at the clinic if they had vague or no symptoms, no fever, and normal radiological and laboratory test results. These patients were given hygiene advice and told to return if they became feverish. Patients were followed up daily after their first attendance at the clinic if they had had contact with someone with SARS, had one or more symptoms (upper and lower respiratory tract symptoms, gastrointestinal symptoms, or systemic symptoms), were feverish (>38°C) on at least one occasion, and had a normal or indeterminate chest radiograph and if the results of investigations were abnormal (such as leucopenia, lymphopenia, monocytosis, or thrombocytosis). These patients were clinically assessed and had anteroposterior chest radiography daily. Patients were given hygiene advice and a follow up appointment for the next day. Patients who were followed up daily and who were clear of symptoms for 48 hours, with no documented fever and normal chest radiographs and laboratory tests, were discharged.

Data collection and measurement

All patients completed a health questionnaire and saw a doctor. Basic observations were recorded, including pulse, systolic and diastolic blood pressure, respiratory rate, tympanic temperature, and oxygen saturation in room air. All patients had daily frontal, plain chest radiography until either their symptoms subsided or a pneumonic change was seen. Patients whose fever and symptoms persisted for more than two days underwent standard and high resolution computed tomography, even if their chest radiographs were normal, to confirm or exclude occult pneumonia. Chest radiographs were evaluated firstly by a specialist emergency physician with reference to clinical details and then by a radiologist without reference to details. The primary clinical outcome was confirmed cases of SARS.

Statistical analysis

We used the unpaired Student's t test to analyse continuous data and the χ^2 test or Fisher's exact test for categorical data. We used Statview for Windows version 5.0 (Abacus Concepts, SAS Institute, Cary, NC). All analyses were two tailed. P values of <0.05 were considered statistically significant.

Results

Between 11 March and 31 March 2003 a total of 556 people with a history of contact with someone with

Table 1 Characteristics of patients presenting to the SARS screening clinic who had previous contact with someone with SARS. Values are numbers (percentage) unless otherwise stated

Characteristic	All patients (n=556)	Patients without SARS (n=459)	Patients with SARS (n=97)	P value*
Mean (SD) age (years)	35.8 (14.0)	35.6 (13.7)	37.0 (15.4)	0.73
No (%) of men	168 (30)	131 (29)	37 (38)	0.06
Median No of days (interquartile; range) between onset of symptoms and first presentation	3.0 (1.0 to 5.0; 1 to 30)	3.0 (1.0 to 5.0; 1 to 30)	3.0 (1.75 to 4.25; 1 to 15)	0.22
Status:				
Healthcare worker	325 (59)	262 (57)	63 (65)	0.01
Other hospital staff	82 (15)	77 (17)	5 (5)	
Patients and relatives of staff or patients	149 (27)	120 (26)	29 (30)	
Presentation:				
Without symptoms	41 (7)	41 (9)	–	0.0022
With symptoms	515 (93)	418 (91)	97 (100)	
Patients who met WHO definitions for suspected SARS	46 (8)	21 (5)	25 (26)	<0.0001
Disposal:				
Follow up without admission	374 (67)	372 (81)	2 (2)	<0.0001
Admission to hospital	141 (25)	46 (10)	95 (98)	
Admission at first presentation	79 (14)	33 (7)	46 (47)	
Admission during follow up	62 (11)	13 (3)	49 (51)	
Final diagnosis:				
Pneumonia†	114 (21)	17 (4)	97 (100)	<0.0001
Upper respiratory tract infection	81 (15)	81 (18)	–	

*Student's t test or χ^2 test.
†Typical pneumonia was diagnosed in 17 patients who recovered quickly after treatment with antibiotics alone.

Table 2 Clinical characteristics of people presenting to screening clinic with symptoms. Values are numbers (percentage) of patients

Characteristic	Total (n=515)	Patients without SARS (n=418)	Patients with SARS (n=97)	P value*
Clinical features (No (%) of patients)				
Fever	233 (45)	154 (37)	79 (81)	<0.0001
Chills	139 (27)	87 (21)	52 (54)	<0.0001
Malaise	118 (23)	85 (20)	33 (34)	0.004
Myalgia	76 (15)	50 (12)	26 (27)	0.0002
Rigor	27 (5)	15 (4)	12 (12)	0.0005
Neck pain	4 (<1)	1 (0.2)	3 (3)	0.004
Cough	363 (70)	301 (72)	62 (64)	0.12
Sputum	146 (28)	121 (29)	25 (26)	0.52
Sore throat	195 (38)	161 (39)	34 (35)	0.53
Runny nose	161 (31)	136 (33)	25 (26)	0.20
Chest pain	5 (1)	4 (1)	1 (1)	0.95
Shortness of breath	40 (8)	28 (7)	12 (12)	0.04
Loss of appetite	9 (2)	4 (1)	5 (5)	0.005
Vomiting	15 (3)	9 (2)	6 (6)	0.03
Abdominal pain	11 (2)	7 (2)	4 (4)	0.14
Diarrhoea	19 (4)	12 (3)	7 (7)	0.04
Night sweats	3 (<1)	2 (0.5)	1 (1)	0.52
Anorexia	5 (1)	5 (1)	0 (0)	0.28
Headache	110 (21)	85 (20)	25 (26)	0.24
Dizziness	28 (5)	22 (5)	6 (6)	0.72
Rash	0	0	0	
Basic observations (mean (SD))				
Heart rate per minute	95.2 (17.4)	94.0 (17.0)	104.5 (16.8)	<0.0001
Systolic blood pressure (mm Hg)	136.6 (19.5)	137.3 (19.0)	132.8 (20.8)	0.04
Diastolic blood pressure (mm Hg)	75.8 (12.7)	76.1 (12.8)	73.7 (12.4)	0.1
Respiratory rate per minute	18.6 (3.3)	18.7 (3.6)	18.8 (2.0)	0.74
Highest temperature while at clinic	37.0 (0.9)	36.8 (0.8)	37.9 (0.8)	<0.0001

*χ^2 test, Fisher's exact test, or Student's t test.

SARS attended the screening clinic (table 1). We excluded 41 patients who had no symptoms. Table 2 shows the clinical features and observations in the other 515 patients. Symptoms that were more common (though not significantly) among patients who did not develop SARS than in patients with confirmed SARS were cough (72% of patients), sputum production (29%), sore throat (39%), and runny nose (33%). Clinical symptoms that were significantly more common among patients with confirmed SARS were fever, chills, malaise, myalgia, rigor, neck pain, loss of appetite, shortness of breath, vomiting, and diarrhoea. Of the common upper and lower respiratory tract symptoms only shortness of breath was significantly more common among patients with SARS.

Only two patients with obvious radiological evidence of consolidation had chest signs that were detectable on physical examination. Compared with patients who did not develop SARS, patients with confirmed SARS had a significantly higher heart rate, lower mean systolic blood pressure, and higher mean temperature. Respiratory rate did not differ between the groups.

Table 3 Accuracy of WHO criteria for identifying suspected severe acute respiratory syndrome (SARS)

	SARS confirmed (No of patients)		
	No	Yes	Total
Suspected SARS according to WHO criteria			
No	438	72	510
Yes	21	25	46
Total	459	97	556

Sensitivity 25.8% (95% confidence interval 17.4% to 35.7%), specificity 95.4% (93.1% to 97.1%), positive predictive value 54.3% (39.0% to 69.1%), negative predictive value 85.9% (82.6% to 88.8%).

Predictive ability of the WHO criteria for diagnosing suspected SARS

Of the 97 patients with confirmed SARS, 25 met the criteria for suspected SARS in the WHO guidelines (table 3). The criteria had an overall accuracy of 83% (463 of 556 cases correctly identified). They had a negative predictive value of 86% (95% confidence interval 83% to 89%), a positive predictive value of 54% (39% to 69%), a sensitivity of 26% (17% to 36%), and a specificity of 95% (93% to 97%). Applying the WHO criteria for suspected SARS in our group of patients would have missed 72 cases (74%). The odds ratios of predicting SARS for particular symptoms were 12.0 (6.8 to 21.0) for fever, 1.0 (0.6 to 1.7) for cough, and 1.5 (0.7 to 3.5) for shortness of breath.

Radiological changes

All patients had chest radiography. Pneumonic change was evident in 129 patients (23%): 72 (56%) on the first presentation and 57 (44%) on follow up. Chest x ray changes were unifocal (figure 1), bifocal, or diffuse. The odds ratio for radiological findings predicting SARS was 32.1 (18.0 to 57.3).

High resolution computed tomography was requested for 27 patients (5%) who had normal chest radiographs but persistent fever and symptoms. Eighteen of the 27 scans (67%) were positive and one was indeterminate. Figure 2 shows two patients' scans that were taken on the same day: one with a retrocardiac lesion and one with a retrodiaphragmatic lesion. The median time from onset of symptoms to identification

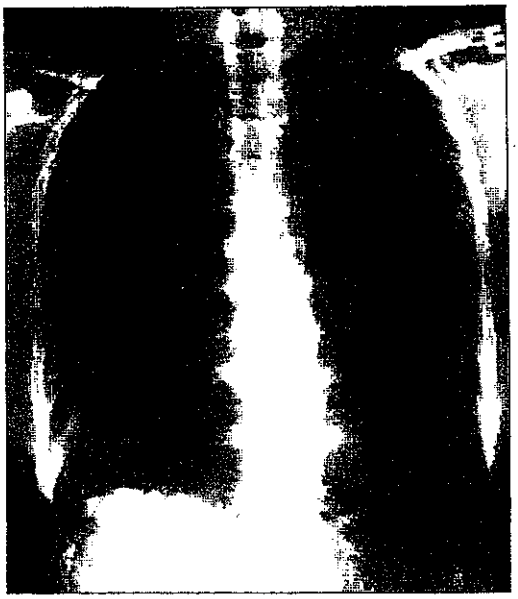

Fig 1 Frontal chest radiograph showing an area of opacification in the right lower zone

of positive radiological changes was four days and to identification of changes in scans was seven days.

Secondary infections and serology

No healthcare workers in the clinic were infected once it was fully operational, and no secondary infections occurred among the patients with suspected SARS. A preliminary serological analysis of samples from 179 patients who have attended the clinic have shown that 98 samples from 99 people with confirmed SARS were positive for coronavirus and that all the samples from 80 people who did not develop SARS were negative.

Discussion

The WHO guidelines on diagnosing SARS emphasise respiratory tract symptoms such as cough, shortness of breath, and breathing difficulty. However, these clinical symptoms in the WHO case definitions do not feature strongly in the early stages of the illness, when patients are highly infectious but before they are hospitalised. In screening patients for SARS systemic symptoms such as fever, chills, malaise, myalgia, and rigors may be better discriminators than the symptoms listed in the WHO guidelines, which were based on study of patients who were already in hospital. The absence of clinical signs in all but a few of our patients when they were screened—even in patients with obvious pneumonic changes in radiographs—means that chest radiography ought to be mandatory for all patients being screened for SARS. Of all the predictors we tested, chest radiological changes had the highest odds ratio. Almost 75% of patients in our study with history of contact with SARS and evidence of pneumonia on radiography did not have a high fever.

One limitation of our study is that it took place in a single centre with a high proportion of healthcare workers and primary contacts, and thus the results may not be generalisable to the wider community. Establishing whether patients have had contact with someone with SARS is difficult and sometimes impractical. However, one advantage of our group was that contact was highly likely and was documented. Screening may be more difficult in situations where a contact history is difficult to establish.

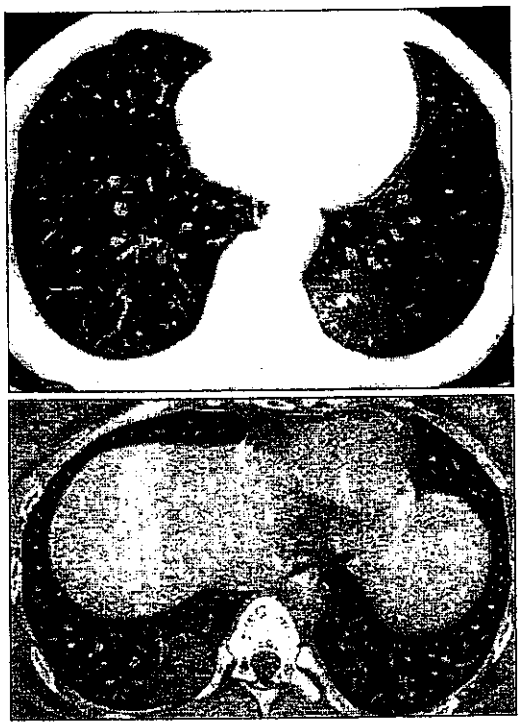

Fig 2 High resolution computed tomograms of two patients whose chest radiographs were normal: (above) ground glass opacification in the posterior segments of the left lower lobe (difficult to identify on a frontal chest radiograph because of location behind the heart); (below) ground glass opacification in the posterior segments of the right lower lobe (difficult to identify on a frontal chest radiograph because of location behind the diaphragm)

Preliminary blood testing for coronavirus indicates that our screening and diagnostic criteria are over 99% accurate. Our patients showed no secondary infection or severe secondary deterioration, prevention of which was the main reason for setting up the screening clinic,

What is already known on this topic

The main criteria in WHO's case definitions for suspected SARS among people who have had close contact are fever (>38°C) and respiratory symptoms such as cough or breathing difficulty

WHO's case definitions, which are based on study of patients in hospital, have not been evaluated in the context of screening patients before admission to hospital

What this study adds

In the early stages of SARS the main discriminating symptoms are not cough and breathing difficulty but fever, chills, malaise, myalgia, rigors, and, possibly, abdominal pain and headache

Documented fever (>38°C) is uncommon in the early stages, and radiological evidence of pneumonic changes often precedes fever

WHO case definitions for suspected SARS have a negative predictive value of 85% and a sensitivity of 26% for detecting SARS in patients who have not been admitted to hospital

and thus our protocols seem to be safe. No healthcare workers in the clinic or close contacts of the patients became infected.

As SARS continues to spread worldwide, other healthcare settings will need to screen staff and patients who have symptoms and who have had close contact with SARS patients after an outbreak.[13] With a sensitivity of 26% and a negative predictive value of 85%, the WHO criteria should be refined to include routine daily follow up, documentation of non-respiratory systemic symptoms, and daily chest radiography until patients have passed at least 48 hours without symptoms.

Contributors: THR had the idea for the study, oversaw its planning and execution and the statistical analysis, and prepared the manuscript. PAC, DS, and KLO participated in the planning, execution, and analysis. ANWH, DCPN, and ATA were responsible for assessment of radiographs and scans. LCYS planned the epidemiological follow up. JJYS supervised the clinical assessment of patients after admission. All authors contributed to the final version of the paper. THR will act as guarantor.

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Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis

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Abstract

Objectives To evaluate the haematological findings of patients with severe acute respiratory syndrome (SARS).

Design Analysis of the demographic, clinical, and laboratory characteristics of patients with SARS.

Setting Prince of Wales Hospital, Hong Kong.

Subjects All patients with a diagnosis of SARS between 11 March and 29 March 2003 who had no pre-existing haematological disorders.

Main outcome measures Clinical end points included the need for intensive care and death. Univariate and multivariate analyses were performed to examine factors associated with adverse outcome.

Results 64 male and 93 female patients were included in this study. The most common findings included lymphopenia in 153 (98%) of the 157 patients, neutrophilia in 129 (82%), thrombocytopenia in 87 patients (55%), followed by thrombocytosis in 77 (49%), and isolated prolonged activated partial thromboplastin time in 96 patients (63%). The haemoglobin count dropped by more than 20 g/l from baseline in 95 (61%) patients. Four patients (2.5%) developed disseminated intravascular coagulation. Lymphopenia was shown in haemato-lymphoid organs at postmortem examination. Multivariate analysis showed that advanced age and a high concentration of lactate dehydrogenase at presentation were independent predictors of an adverse outcome. Subsets of peripheral blood lymphocytes were analysed in 31 patients. The counts of CD4 positive and CD8 positive T cells fell early in the course of illness. Low counts of CD4 and CD8 cells at presentation were associated with adverse outcomes.

Conclusions Abnormal haematological variables were common among patients with SARS. Lymphopenia and the depletion of T lymphocyte subsets may be associated with disease activity.

Introduction

An outbreak of severe acute respiratory syndrome (SARS) has recently been reported from Hong Kong.[1] A novel coronavirus has been identified as the aetiological agent of the syndrome.[2 3] Viral infection may produce various haematological changes. Early studies have shown that lymphopenia and thrombocytopenia are common among patients with SARS.[1 4] This study summarises the haematological findings in patients with SARS who were treated at the Prince of Wales Hospital, Hong Kong.

Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong

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Summary

Background Health authorities worldwide, especially in the Asia Pacific region, are seeking effective public-health interventions in the continuing epidemic of severe acute respiratory syndrome (SARS). We assessed the epidemiology of SARS in Hong Kong.

Methods We included 1425 cases reported up to April 28, 2003. An integrated database was constructed from several sources containing information on epidemiological, demographic, and clinical variables. We estimated the key epidemiological distributions: infection to onset, onset to admission, admission to death, and admission to discharge. We measured associations between the estimated case fatality rate and patients' age and the time from onset to admission.

Findings After the initial phase of exponential growth, the rate of confirmed cases fell to less than 20 per day by April 28. Public-health interventions included encouragement to report to hospital rapidly after the onset of clinical symptoms, contact tracing for confirmed and suspected cases, and quarantining, monitoring, and restricting the travel of contacts. The mean incubation period of the disease is estimated to be 6·4 days (95% CI 5·2–7·7). The mean time from onset of clinical symptoms to admission to hospital varied between 3 and 5 days, with longer times earlier in the epidemic. The estimated case fatality rate was 13·2% (9·8–16·8) for patients younger than 60 years and 43·3% (35·2–52·4) for patients aged 60 years or older assuming a parametric γ distribution. A non-parametric method yielded estimates of 6·8% (4·0–9·6) and 55·0% (45·3–64·7), respectively. Case clusters have played an important part in the course of the epidemic.

Interpretation Patients' age was strongly associated with outcome. The time between onset of symptoms and admission to hospital did not alter outcome, but shorter intervals will be important to the wider population by restricting the infectious period before patients are placed in quarantine.

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Introduction

The rapid worldwide spread of the coronavirus that causes severe acute respiratory syndrome (SARS)[1,2] has led to 28 countries reporting cases as of May 5, 2003. The evolution, spread, and persistence of infectious diseases are facilitated by the mobility of contemporary society, for example through air travel, the continued growth in the world population, and the steady rise in the number of densely populated urban areas, especially in Asia.

The Asia Pacific region, including mainland China, has been badly affected by SARS. The impact on the regional economy and health-care systems led to a meeting of health ministers from 14 Association of South East Asian Nations on April 24–26. Health authorities are urgently seeking guidance on the public-health measures most likely to be effective in controlling the epidemic.

Key epidemiological determinants of the magnitude and timescale of the epidemic (figure 1) include the interval between infection and onset of symptoms and between onset and hospital admission, the degree and duration of the infectiousness of the agent, and the extent of contact and mixing between infectious and susceptible people enabling transmission of the virus. Public-health interventions can affect many of these factors.

The Hong Kong authorities have taken several measures to combat the spread of SARS. Since formal recognition of the outbreak in the Prince of Wales Hospital, Hong Kong, on March 10, these measures have included: public-service announcements about personal protection (March 17); addition of SARS to the list of notifiable diseases and requests for close contacts of cases to attend designated medical centres for screening (March 26) until the later introduction of mandatory home quarantine; a 2-week suspension of schools' (March 26) and universities' (March 29) sessions; introduction of health declarations for all incoming residents and visitors (March 29); isolation of residents of a building in the Amoy Gardens estate, at the centre of a cluster of about 300 cases (March 30) and their subsequent move to rural isolation camps for 10 days (March 31); home quarantining of close contacts and restrictions on their travel out of Hong Kong (April 10); new public announcements urging symptomatic people to seek medical attention (April 15); and body-temperature checks for all air passengers (April 17).

In the global response to SARS, there are three priority tasks: the identification of the causal agent and the

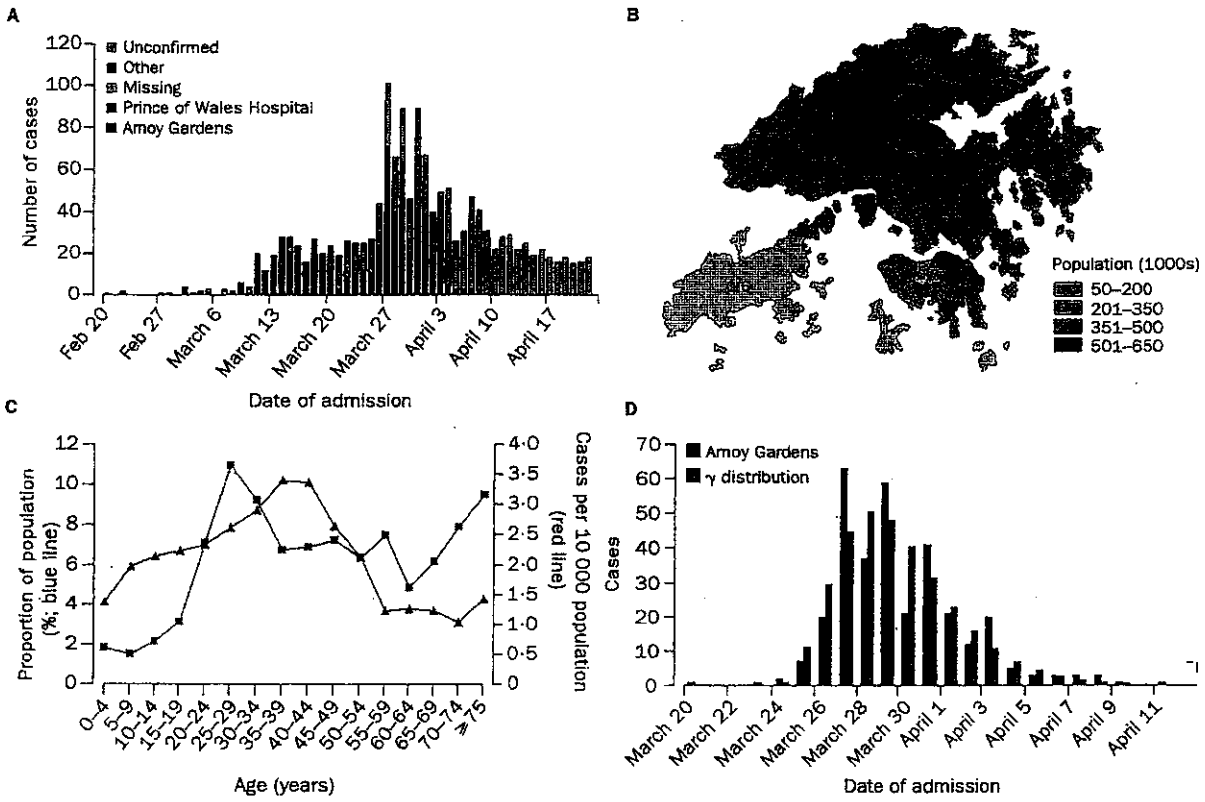

Figure 1: **Epidemiological description of SARS epidemic in Hong Kong**

A: Temporal pattern of SARS epidemic in Hong Kong by cluster of infection. B: Spatial distribution of population of Hong Kong and district-specific incidence (per 10 000 population) over course of epidemic to date. C: Age distribution of residents of Hong Kong and age-specific incidence (per 10 000 population) over course of epidemic to date. D: Detail of temporal pattern for Amoy Gardens cluster, according to day of admission, and fitted γ distribution.

development of tests to detect the virus and allow rapid confirmation of cases; the development and assessment of treatment protocols; and the determination of the key epidemiological processes and parameters that affect the spread and persistence of infection to support the formulation of appropriate public-health interventions. We describe the epidemiology in Hong Kong in the first 9 weeks of the epidemic, during which 1425 cases were confirmed, and 122 deaths from SARS occurred. We focus on the key distributions and parameters that define the observed pattern of the spread of SARS, and their change over time since the introduction of the virus into Hong Kong.

Methods

Data sources

We analysed an integrated database, coordinated by the Department of Community Medicine, University of Hong Kong on behalf of the Health, Welfare and Food Bureau, derived from the Hong Kong Hospital Authority eSARS system, and the Department of Health's Master List, which contains details of all patients with confirmed or suspected SARS admitted to hospitals in Hong Kong since Feb 20, 2003. Primary health care in Hong Kong is provided by private practitioners (80%) and general outpatient departments operated by the public sector. The Hospital Authority also currently provides 95% of total inpatient bed-days.[3] The Department of Health provides the public-health function, including the monitoring and control of communicable diseases.[4] The eSARS system is designed as a registry and monitoring system. All patients admitted for investigation and observation into the SARS cohort wards in all the hospitals under the Hospital Authority of Hong Kong are recruited on entry. The patients on the registry are progressively classified into: patient under observation, patient suspected of SARS, patient with confirmed SARS, and not SARS. The criteria for inclusion in the eSARS register as a patient confirmed with SARS are radiographic evidence of infiltrates consistent with pneumonia, and current fever higher than 38°C or history of such at any time in the past 2 days, and at least two of the following: history of chills in the past 2 days, cough (new or increased) or breathing difficulty, general malaise or myalgia, and known exposure. Patients are listed as suspected of having SARS if they do not fulfil this definition but are still thought to be likely cases of SARS on the basis of the collective evidence and clinical judgment. However, patients are excluded if an alternative diagnosis can fully explain their illness.

A questionnaire was administered to all patients 24 h after confirmation of SARS by the Department of Health, initially by regional community-medicine teams and later by a central interviewing team of nurses, to record symptoms at presentation to hospital and to identify contacts and events of probable relevance to transmission. When possible, patients are classified into infection clusters by location (eg, housing estates), occupation (eg, health-care workers), and workplace (eg, hospitals and other buildings). In addition, we used demographic data on Hong Kong, which has a population size of 6·7 million in 19 districts (figure 1).

Statistical analysis

Time-delay distributions (infection to onset, onset to admission, admission to death, and admission to discharge) were fitted to γ distributions by maximum likelihood estimation methods, with allowance for censoring for incomplete observation of the disease process in all cases. Likelihood ratio statistics were used for tests of significance when comparing distributional parameters and for calculating CI.

While the epidemic is continuing, the estimation of the admission-to-death and admission-to-discharge distributions must be undertaken jointly with the estimation of the case fatality rate, because among patients still recorded as being in hospital it is impossible to ascertain who will eventually die or be discharged. We assume that no confirmed SARS patients who has been discharged from hospital will go on to die of SARS-related causes. If F() and G() are the cumulative distribution functions of the admission-to-death and admission-to-discharge distributions, respectively, and π_F is the case fatality rate—ie, the proportion of SARS patients who will die of the disease—the following likelihood structure is assumed: if a patient died t days after admission, the likelihood is $\pi_F \times [F(t+1)-F(t)]$; if a patient was discharged t days after admission, the likelihood is $(1-\pi_F) \times [G(t+1)-G(t)]$; and if a patient remained in hospital t days after admission, the likelihood is $\pi_F \times [1-F(t)]+(1-\pi_F) \times [1-G(t)]$. The parameters of the F() and G() distributions are thus jointly estimated along with the case fatality rate.

To assess further the case fatality rate, we also used a version of the Kaplan-Meier survival curve, adapted to allow for two types of outcome (death and discharge). Censoring was used to obtain non-parametric estimates of the admission-to-death and admission-to-discharge distributions and the case fatality rate.

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or in the writing of the report.

Results

The development of the epidemic (figure 1) features a period of exponential growth, beginning on March 10, after the formal announcement of the outbreak, followed by a period of comparative stability throughout early to mid April, with evidence of a slight decay over the week April 21–28. The geographical and age distributions of the cases are presented in figure 1. 57% of patients were female and 43% male.

Clinical symptoms at presentation were fully recorded for about 90% of the cases confirmed by the Department of Health. The frequency of self-reported symptoms is similar to that noted in the early cases.[5] The most common reported symptom was fever (94%), with 51–72% of patients reporting general influenza-like symptoms, chills, malaise, loss of appetite, and myalgia. Gastrointestinal symptoms were less common at presentation, including diarrhoea (27%), vomiting (14%), and abdominal pain (13%). 88% reported fever plus any one other symptom, and 79% fever plus one of the five most common symptoms (table).

Infection events cannot be observed, but for patients with short and defined periods of exposure to known SARS cases, data on the timing and duration of exposure can be used to estimate the distribution of the incubation period, the time from infection to the onset of clinical symptoms of SARS. The database contained 57 patients with one exposure to SARS over a limited time scale with recorded start and end dates. The maximum likelihood estimate of the mean and variance of the time from infection to onset was 6·37 days (95 CI 5·29–7·75) and 16·69 days^2, respectively; therefore 95% of patients would experience the onset of symptoms within 14·22 days of infection. The estimated distribution is presented in figure 2. However, this distribution is based on a limited number of observations to date, and has high variance and may reflect biases in reporting, different routes of transmission, or varying infectious doses of the virus.

Onset and admission times are both observable events. However, allowance must be made in the analysis for censoring due to incomplete observation. If censoring is not taken into account, the distribution will be biased towards short onset-to-admission times, because patients are only eligible to be included in the hospital-based database on admission to hospital. Patients with recent onsets and long onset-to-admission times are less likely to have been admitted to hospital and thus be included.

In the analysis, patients were grouped by their week of clinical onset, and seven weekly time periods were analysed (Feb 26 to March 4, March 5–11, March 12–18, March 19–25, March 26 to April 1, April 2–8, and April 9–15). There were too few patients with clinical onset before Feb 26 for robust analysis and too little time has elapsed after onset to allow analysis of those with clinical onset after April 15. We assume that the recorded data are complete up to April 15. Estimated mean onset-to-admission times were obtained for each week, assuming that the times were γ distributed: Feb 26 to March 4, 5·36; March 5–11, 3·21; March 12–18, 5·06; March 19–25, 4·95; March 26 to April 1, 3·83; April 2–8, 3·67; and April 9–15, 3·46. The distributions differed significantly over the 7-week period ($p<0·001$) but not for the first 4 weeks ($p=0·053$) or the last 2 weeks ($p=0·459$). The maximum likelihood means and variances for the resulting three time periods are: Feb 26 to March 25, 48·5 days (95% CI 4·49–5·24) and 12·19 days^2; March 26 to April 1, 3·83 (3·61–4·06) and 5·99 days^2; and April 2–15,

	Overall proportion with specified symptom (%)
Symptom	
Fever	94·0
Influenza-like	72·3
Chills	65·4
Malaise	64·3
Loss of appetite	54·6
Myalgia	50·8
Cough	50·4
Headache	50·1
Rigor	43·7
Dizziness	30·7
Shortness of breath	30·6
Sputum	27·8
Night sweat	27·8
Diarrhoea	27·0
Coryza	24·6
Sore throat	23·1
Nausea	22·2
Vomiting	14·0
Abdominal pain	12·6
Fever+at least 1 other	87·6
Fever+at least 2 other	80·3
Fever+at least 3 other	70·7
Fever+at least 1 of 5 most common*	78·5
Fever+at least 2 of 5 most common*	61·7
Fever+at least 3 of 5 most common*	42·9

*Five most common symptoms (except fever): influenza-like, chills, malaise, loss of appetite, and myalgia.

Prevalence of self-reported clinical symptoms in cases confirmed by Department of Health

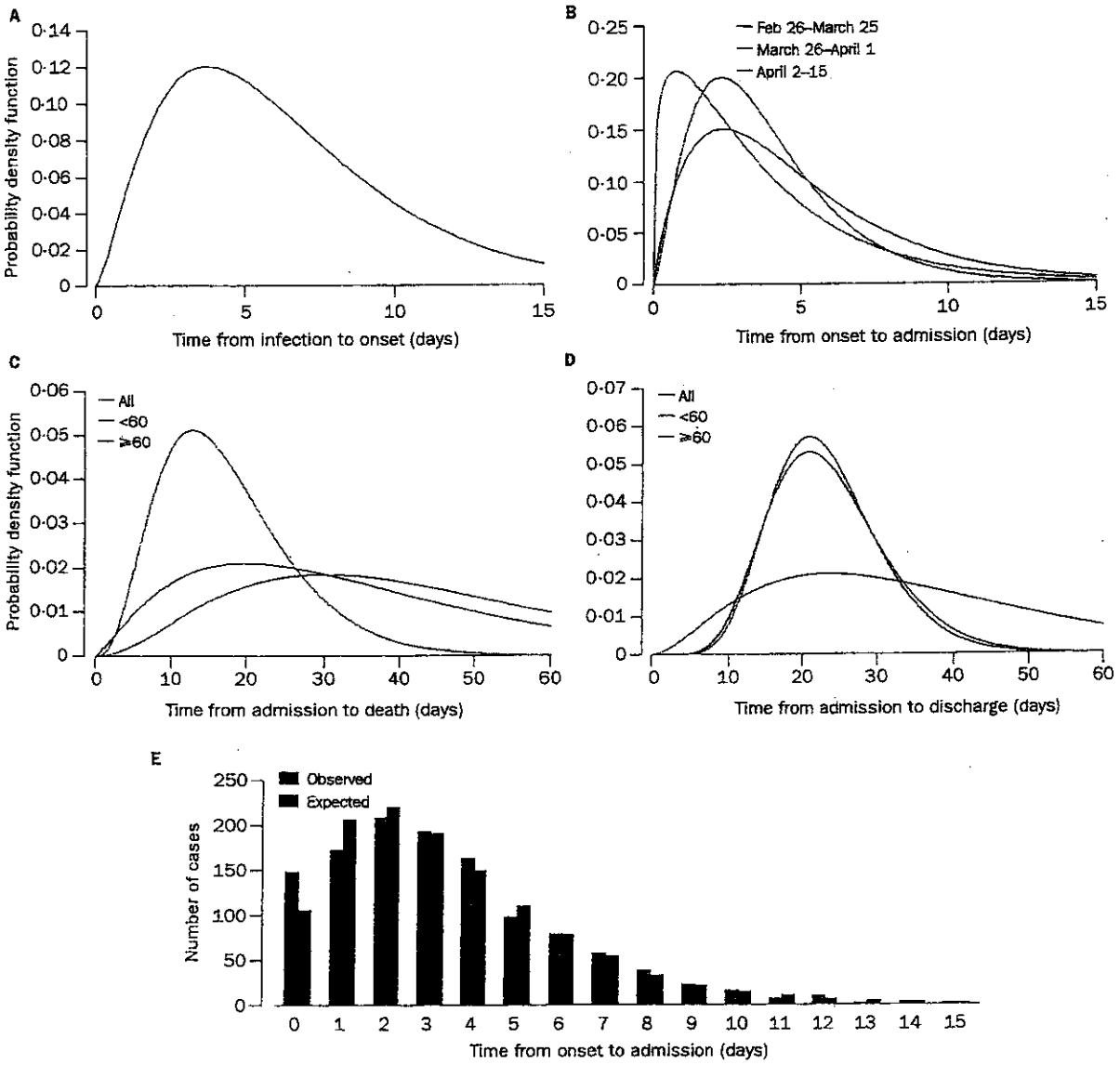

Figure 2: **Maximum likelihood estimates**

A: Infection-to-onset distribution. B: Time-dependent onset-to-admission distribution as a function of time of onset of clinical symptoms. C: Admission-to-death distribution by patients' age. D: Admission-to-discharge distribution by patients' age. E: Observed and maximum likelihood estimated onset-to-admission intervals in presence of censoring.

3·67 days (3·31–4·11) and $10·71^2$ days. The corresponding distributions are presented in figure 2, as well as the qualitatively good fit between the observed and expected values in the presence of censoring.

The estimated mean and variance of the admission-to-death time was 35·9 days and $572·9^2$ days, respectively, and the estimated mean and variance of the time from admission to discharge was 23·5 days and $62·1^2$ days, respectively (figure 2). If γ distribution is assumed, the estimated distributions and case fatality rate varied as a function of patients' age, but not the time from onset to admission (figure 2). The estimated case fatality rate for patients younger than 60 years was 13·2% (9·8–16·8) and 43·3% (35·2–52·4) for patients aged 60 years and older. The adapted Kaplan-Meier-like non-parametric method gave estimates of 6·8% (4·0–9·6) and 55·0% (45·3–64·7), respectively (figure 3). The estimated fatality rates are higher than the estimate obtained from the current cumulative number of deaths divided by the current cumulative number of hospital admissions, because of the incomplete follow-up on patients still in hospital.

A key feature of this epidemic is the clustering of cases in place and time linked to a particular individual (in some cases in a particular setting such as a residence block or health-care setting), where one primary case has led to many secondary and tertiary cases. The Amoy Gardens outbreak is particularly striking, with the onset times of the cases identified as arising from this setting following a γ distribution (figure 1). Work on the clusters is still evolving and will be reported in detail separately.

Discussion

Our findings underline the importance of estimating the key epidemiological determinants of the epidemic, the infection-to-onset and onset-to-admission interval

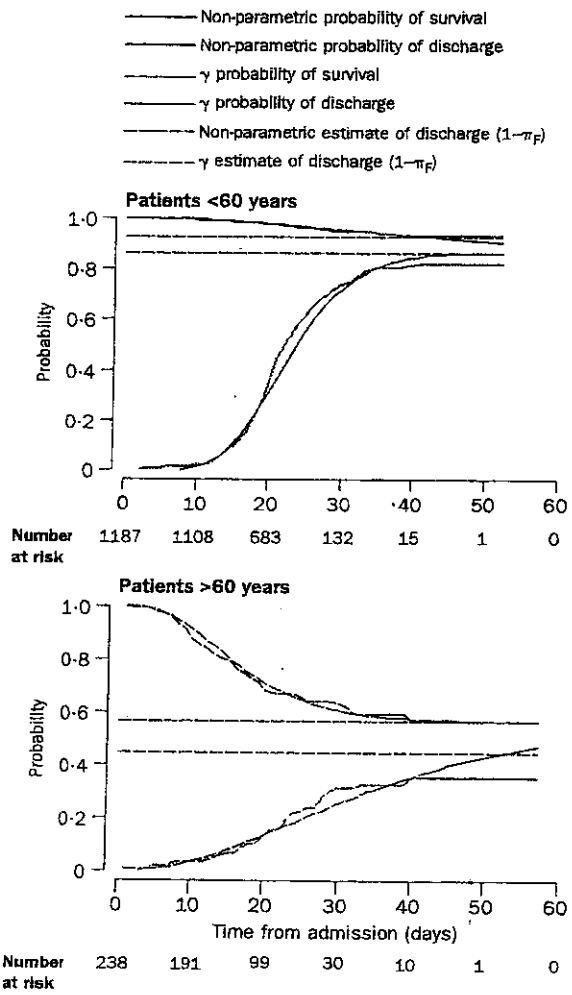

Figure 3: **Non-parametric and maximum-likelihood γ probabilities of survival and discharge**

distributions. The analysis of the onset-to-admission interval shows that over time there has been a progressive shortening of the time from clinical onset of symptoms to presentation at hospital.

The estimation of case fatality rates in the situation of an emerging epidemic is not straightforward. First, our estimates are derived from data on clinical cases that have been admitted to hospital and, hence, estimate the mortality rate only in this population. Second, the temporal evolution of the epidemic complicates analysis. Finally, the estimates of the case fatality may vary dependent on the methods used and their underlying assumptions, although the estimates we present have statistical validity. All these issues require further investigation as the epidemic evolves, and explain partly the wide range of mortality estimates reported to date.

Shortening the time between onset of clinical symptoms and admission to hospital does not seem to affect clinical outcome. However, shortening the time from clinical onset to admission expedites isolation and reduces the effective infectious period and, thus, the risk of onward transmission. Such changes were already evident in late March and early April, but any additional shortening of the time that symptomatic individuals are in the community will lead to further benefits at the population level. The extent to which this time needs to be shortened to reduce the generation of secondary cases from each primary case to less than one (the effective reproductive number, R_e) in Hong Kong is the subject of a continuing analysis.

Given the likely benefits to the wider community from early presentation at hospital after the onset of symptoms, there should now be an intensive assessment of the different public-health interventions, including publicity campaigns in various media, to assess their impact on the early reporting of symptoms. The promotion of early reporting of all symptoms will challenge the health-care system in dealing with those caused by other pathogens and the so-called worried well. However, given the high need for intensive care of patients, the case fatality rate, and public alarm worldwide, use of stringent measures to limit the effective infectious period of probable SARS cases would seem prudent. This approach alone may contribute substantially to the eventual curtailing or even eradication of the epidemic.

The epidemic has shown the need for communication of risk that will inform and warn the public, in a way that will improve personal protection, without inducing raised anxiety and fear, as an essential part of epidemic control. A change in risk perception would potentially lead to an increase in early reporting of symptoms as well as improvements in hygiene and prevention of transmission.

Further data may reveal that the incubation period depends on the route of transmission and on the infectious dose received by an individual. The duration of the infectious period and its relation to the incubation period is uncertain at present (for example, the onset of infectiousness may precede the onset of clinical symptoms). Continuing clinical studies involving quantitative assays of viral load at known times after exposure and after the onset of clinical symptoms should, however, clarify this property of the SARS agent. Critical questions relating to how long patients should remain in isolation are whether and to what extent virus remains in faeces or in aspirate after overt clinical symptoms have stopped.

The occurrence of clusters of cases linked to particular individuals in a particular spatial setting has been an important determinant of the overall magnitude of the epidemic to date. A WHO team has now joined the Hong Kong Government in examining on-site factors that were apparently associated with a possible point-source outbreak in Amoy Gardens.[6] The assessment of whether there is variation in the characteristics of the disease, including presenting symptoms by different clusters, requires further investigation as the definition of clusters improves. The occurrence of clusters is not necessarily a feature that can inform public-health interventions in advance, except within health-care settings in which stringent isolation procedures must be adopted in handling suspected and confirmed cases. Clusters do, however, provide a focus for contact-tracing studies to assess incubation periods and the nature of the contact that resulted in transmission.

The reported cases to date in Hong Kong and elsewhere may simply reflect people with the most severe clinical symptoms of infection with the new SARS virus. We estimated the case fatality rate based on cases in hospital only. If additional infections in the community do not lead to admission to hospital or death, the case fatality rate based on all infections would be lower. Community-based serological surveys to assess infection and recovery rates are a priority once a specific and sensitive serological test is available.

Finally the warm season has begun in Hong Kong, with daily temperatures now at 25–30°C. The seasonal risks of

dengue and influenza will increase, and if serious outbreaks occur, they will complicate the triage of patients with possible symptoms of SARS. Thus, measures that can be taken now to limit further transmission, such as the shortening of the onset-to-admission interval, should be given high priority.

We thank David R Cox for developing a suitable non-parametric method for estimation of the case fatality rate. ACG and NMF receive fellowship support from The Royal Society. SR and NMF receive research funding from the Howard Hughes Medical Institute, CF, LJA-R, and NMF from the Medical Research Council, and RMA from the Wellcome Trust. We thank Tom Johnston for Geographic Information System assistance. We thank all our colleagues in the Department of Health and the Hospital Authority for their work in data collection and processing, and pay tribute to all the front-line health workers who are caring for patients with SARS.

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LETTER FROM HONG KONG

An outbreak of atypical pneumonia among healthcare workers

The recent outbreak of atypical pneumonia, better known as severe acute respiratory syndrome (SARS) underscores the importance of occupational health risk to healthcare workers. Within one week, about 50 healthcare workers have contracted the disease, all traced to one index patient. Nurses, doctors, ward assistants, and medical students alike were infected. Despite the general belief of a person-to-person mode of transmission by droplets, the shape of the epidemic curve in the early phase resembled that of a common source outbreak. From preliminary epidemiological evidence, a suspected source of the infection was the nebuliser used on the patient, the culprit believed to have aerosolised infectious droplets and thus facilitated the spread of the disease. After the patient was isolated and the use of the nebuliser stopped, the rate of infection among healthcare workers has declined considerably. By now, the disease has spread to the community, affecting over 400 victims and showing no signs of abatement. Wherever the disease first originated, it is now clear SARS has become a serious and challenging public health problem of global dimensions. Our virology colleagues have been very efficient in identifying a metapneumovirus (of the paramyxoviridae family) from the nasopharyngeal aspirate shortly after the start of the outbreak, and great efforts are being made to elucidate the aetiology of the disease.

What lessons have we learnt? The safety of certain clinical procedures has to be re-evaluated. An apparently "routine" treatment for a patient with respiratory illness might turn out to be a major health threat not only to healthcare workers, but to other patients and the hospital work environment as well. Infection control practices should be reinforced for all respiratory infections, among primary healthcare providers, hospital workers, and hospital visitors alike. This outbreak also illustrates how easily it is, at a time when air travel is a norm, for a respiratory disease to spread to other cities and develop into a global health threat.

Our war is far from over. All healthcare workers in Hong Kong are working hard to track down the disease contacts. Quarantine measures, not enforced for nearly 40 years, are being implemented. Primary and secondary schools and the universities are closed. Health education is stepped up, and the community has responded by positive actions such as holding community health forums, raising awareness of personal hygiene, and practising personal protective measures, including wearing masks in public places. For all its damages, the outbreak is a sobering reminder to healthcare workers of the importance of infectious diseases and occupational health, and to the general public of the equally important, but sometimes unrecognised role of preventive medicine.

Photographs are of the Prince of Wales Hospital where the outbreak first occurred.

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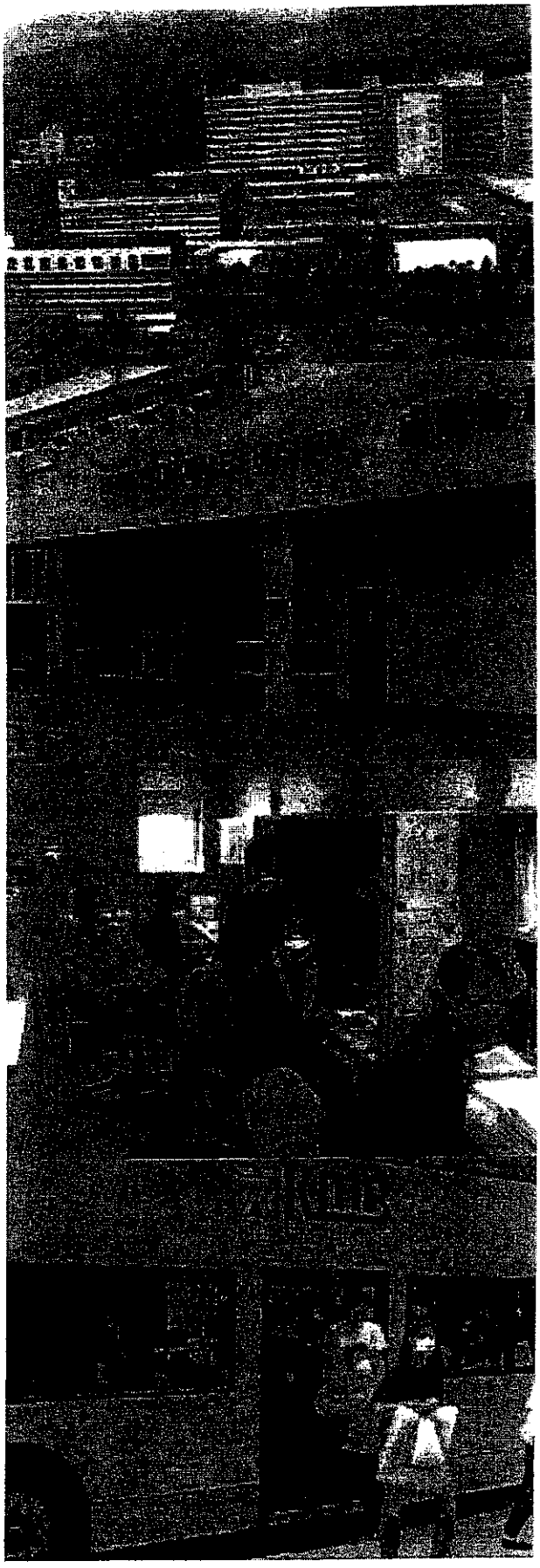

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Thoracic Imaging

Thin-Section CT of Severe Acute Respiratory Syndrome: Evaluation of 73 Patients Exposed to or with the Disease[1]

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ABSTRACT

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PURPOSE: To retrospectively analyze the thin-section computed tomographic (CT) features in patients with severe acute respiratory syndrome (SARS) at the authors' institution.

MATERIALS AND METHODS: From March 11, 2003, to April 2, 2003, 74 patients with symptoms and signs suggestive of SARS underwent CT of the thorax; all underwent thin-section CT except for one patient who

underwent conventional CT. Group 1 (n = 23) patients had symptoms of SARS in keeping with criteria from the Centers for Disease Control and Prevention and a positive chest radiograph. Group 2 (n = 17) patients had a high clinical suspicion of SARS but a normal radiograph. Group 3 (n = 34) patients had minor symptoms and a normal chest radiograph. The thin-section CT images were analyzed for ground-glass opacification or consolidation, lesion size in each lung segment, peripheral or central location, interstitial thickening, and other abnormalities.

RESULTS: Thin-section CT scans were abnormal only for patients in groups 1 and 2. The patient with only conventional CT scans was in group 3; scans for group 3 patients were normal. Affected segments were predominantly in the lower lobes (91 of 149 affected segments). Common findings included ground-glass opacification, sometimes with consolidation, and interlobular septal and intralobular interstitial thickening. The size of each lesion and the total number of segments involved were smaller in group 2 patients. A majority of patients in group 1 (14 of 23) had mixed central and peripheral lesions. In group 2, however, peripheral lesions were more common (10 of 17). In both groups, a purely central lesion was uncommon (one of 23 in group 1 and two of 17 in group 2).

CONCLUSION: Common thin-section CT features of SARS are ground-glass opacification and lower lobe and peripheral distribution.

Index terms: Lung, CT, 69.12118 • Pneumonia, acute interstitial, 69.21 • Severe acute respiratory syndrome

INTRODUCTION

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Editor's Note: Although 25 patients included in this report were also included in a report published online by the New England Journal of Medicine (www.nejm.org; *April 7, 2003), the analysis of the specific thin-section computed tomographic findings for these 25 patients and for all others included in the* Radiology *report has been performed in much greater detail. —Anthony V. Proto, MD, Editor*

In mid-March 2003, there was an outbreak of atypical pneumonia in one of the wards at our institution in Hong Kong, China. The disease initially affected mainly medical personnel, thus raising alarm that this might be an unusual form of infection. Within 1 week, the number of infected individuals soared and included inpatients and patient relatives, in addition to medical personnel. Cases were beginning to appear in other countries in the region, Europe, North America, and Australia. By the end of the 2nd week, quarantine measures and international travel were substantially altered due to the rapidly rising number of cases. This infection was termed *severe acute respiratory syndrome* (SARS) and is of unknown etiology, although a coronavirus has been implicated (1). Clinically, the syndrome is defined by the Centers for Disease Control and Prevention (CDC) by three criteria (2): (*a*) a high fever of more than 38°C *and* (*b*) one or more clinical findings of respiratory illness (eg, cough, shortness of breath, difficulty breathing, hypoxia, or radiographic findings of either pneumonia or acute respiratory distress syndrome) *and* (*c*) travel within 10 days of onset of symptoms to an area with documented or suspected community transmission of SARS, or close contact within 10 days of onset of symptoms with either a person with a respiratory illness who traveled to a SARS area or a person known to be a suspect SARS case (close contact is defined as having cared for, having lived with, or having had direct contact with respiratory secretions and/or body fluids of a patient suspected of having SARS).

Since there is no single test that can be used to diagnose the condition with a reasonable degree of accuracy and reliability, the diagnosis must be based on clinical appearance in combination with imaging features. Chest radiography is one of the major diagnostic components according to World Health Organization and CDC guidelines (3,4). The purpose of our study was to analyze retrospectively the thin-section computed tomographic (CT) features in patients with SARS at our institution.

MATERIALS AND METHODS

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Patients and CT Imaging

Our institutional review board approved this retrospective study; informed consent was not required.

From March 11, 2003, to April 2, 2003, 74 patients underwent CT scanning (Highspeed Advantage; GE

Medical Systems, Milwaukee, Wis) of the thorax. The average age of the 22 male and 52 female patients was 34.7 years (range, 2–82 years). Initially, because we were faced with an unknown disease affecting mainly medical personnel working in the same ward, the first 50 patients underwent both conventional CT of the entire thorax (7-mm section thickness, pitch of 1.5, 120 kV, 180 mA) and thin-section CT of the thorax to better evaluate the lungs (1-mm section thickness with 6-mm gap, supine position, scanning during inspiration, 1 second per scan, 120 kV, 140 mA). On the basis of our findings in these first 50 patients, we performed only thin-section CT in subsequent patients. In one patient (a 2-year-old boy), only conventional CT was performed because the boy was unable to hold his breath.

The patients were sorted into three groups. Group 1 (n = 23) included patients who had symptoms and signs consistent with what is now defined as SARS and abnormalities on their chest radiographs consistent with pneumonia or acute respiratory distress syndrome. Because SARS is a new entity and thus we had no previous literature to refer to for guidance, we performed CT in these patients—despite their positive chest radiographs—to look for any additional findings. CT was performed an average of 3.3 days (range, same day to 13 days) after admission in this group. Group 2 (n = 17) included patients in whom there was a strong suspicion of SARS but who had a normal chest radiograph. All had a history of contact with a person without a respiratory illness who traveled to a SARS area or a person known to be a suspect SARS case, high fever (higher than 38°C), respiratory symptom(s), and leukopenia. CT was performed an average of 0.8 days (range, same day to 5 days) after admission in this group. Group 3 (n = 34) included medical personnel or patients who had minor symptoms such as cough or low-grade fever, a normal chest radiograph, and a low suspicion for SARS. They underwent CT because they had a history of contact with other personnel or patients with a diagnosis of SARS. CT was performed an average of 1.4 days (range, same day to 6 days) after admission in this group.

Review of CT Images

All CT images were reviewed by three radiologists (A.T.A., K.T.W., G.E.A.) using a viewing console. Decisions were reached by consensus. Each segment of the lung was reviewed for opacification, and the lesion size was described as small (diameter, <1 cm), medium (diameter, 1 to <3 cm), large (diameter, 3 cm to <50% of the segment), or segmental (50%–100% of the segment). The location of the lesion was defined as peripheral if it was in the outer one-third of the lung; otherwise, it was

defined as central.

Ground-glass opacification was defined as increased lung parenchymal attenuation that did not obscure the underlying vascular architecture (5). Consolidation was defined as opacification in which the underlying vasculature was obscured (5). Each lesion was magnified and examined for intralobular, interlobular septal, or peribronchovascular interstitial thickening. Attention was also paid to the presence of nodules or masses, cavitation or calcification, bronchiolar or bronchial dilatation, and emphysema. Any other abnormalities seen were noted.

Follow-up Chest Radiography in Group 2

Follow-up chest radiographs, obtained daily in the patients in group 2 (all of whom had normal initial radiographs), were reviewed by three radiologists (K.T.W., E.H.Y.Y., G.E.A.). Decisions were reached by consensus. The radiographs were reviewed separately from the CT scans and were evaluated for development of areas of opacification.

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The 40 patients in groups 1 and 2 (all of whom underwent thin-section CT) consisted of 13 male and 27 female patients. Their ages ranged from 2 to 82 years of age with a mean of 37.2 years (mean of 39.6 years for patients in group 1 and 33.9 years for patients in group 2). The patients in groups 1 and 2 were considered to have SARS or were strongly suspected of having SARS on the basis of CDC criteria. The 34 patients in group 3 were ultimately considered not to have SARS, since they did not fulfill the CDC criteria. The CT scans in these patients were normal, including the scans in one patient who underwent only conventional CT and the 33 patients who underwent thin-section CT.

Sites Involved and Frequency

Although all segments of the lung can be involved, affected segments were predominantly in the lower lobes (91 of 149 affected segments, 61.1%) (Table 1, Fig 1). The number of patients with lower lobe involvement (30 of 40 patients) was also greater than the number with involvement in other lobes (14 of 40 had upper lobe involvement) (Table 2). Patients in group 2 had a higher percentage of lower lobe

involvement than did those in group 1.

View this table: TABLE 1. Number of Segments Affected by Abnormality
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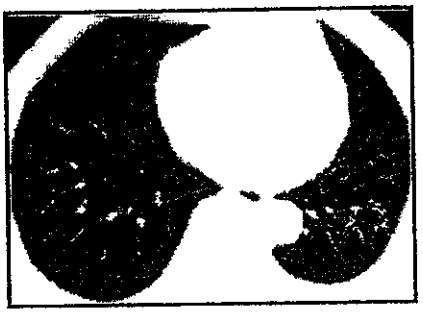

Figure 1. Transverse thin-section CT scan of lower lobes shows involvement in multiple segments. Lesions show opacification, are of various sizes, and are distributed in a peripheral manner.

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View this table: TABLE 2. Number of Patients with Affected Segments in Particular Lung Regions
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The average number of segments involved per patient was 5.0 for the patients in group 1 (range, 1–15) and 2.0 for the patients in group 2 (range, 1–3) (Table 1). Bilateral involvement was present in 14 (61%) of the 23 patients in group 1 and three (18%) of the 17 patients in group 2 (Table 2).

Size of Lesions

There was a difference between the sizes of the lesions in group 1 and those in group 2 (Table 3). A higher proportion of large lesions (>3 cm) was seen in group 1 (68 of 115, 59%) compared with group 2 (eight of 34, 24%).

View this table: TABLE 3. Number of Segments with Lesions of Particular Sizes
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Characteristics of Lesions at Thin-Section CT

In terms of location within a lung segment, the lesions tended to be peripheral (71.8%) or both central and peripheral (19.5%) (Table 4). A purely central location was uncommon (8.7%). The proportion of mixed central and peripheral lesions was greater in group 1 (14 of 23) than it was in group 2 (five of 17); in group 2, peripheral lesions were more common (10 of 17). In both groups, a purely central lesion was uncommon (one of 23 in group 1 and two of 17 in group 2).

View this table: TABLE 4. Number of Patients with Particular Characteristics at Thin-Section CT
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The lesions most often showed ground-glass opacification (68.4%) (Table 4, Fig 2) or mixed ground-glass opacification and consolidation (14.8%) (Fig 3). Consolidation without ground-glass opacification (16.8%) was less common. Ground-glass opacification was present alone or in combination with consolidation in 20 of 23 patients in group 1 and in 16 of 17 patients in group 2. Consolidation alone was uncommon, however, and was seen in only three of 23 patients in group 1 and one of 17 patients in group 2.

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Figure 2. Transverse thin-section CT scan shows ground-glass opacification of lesion. Underlying vascular architecture (arrowhead) is clearly visible. The bronchi are dilated.

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Figure 3. Transverse thin-section CT scan shows mixed ground-glass opacification and consolidation. Air bronchogram (arrow) is present in the center of the consolidation.

Other findings included thickening of interlobular septa (24.2%) and intralobular interstitium (32.2%) (Table 4). These were only seen superimposed on ground-glass opacification to produce a crazy-paving pattern (Fig 4). Bronchiectasis was present in 6.7% of lesions (Table 4) and affected the segmental bronchi supplying the area of parenchymal opacification.

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Figure 4. Transverse thin-section CT scan shows ground-glass opacification and thickened interlobular septa (arrow) and intralobular interstitium (crazy-paving pattern).

Peri-bronchovascular interstitial thickening, masses or nodules, emphysema, cavitation, or calcification was not present.

Two patients had apical fibrosis and a calcified nodule, findings that are suggestive of

old tuberculosis infection. One patient (a 76-year-old man) had bilateral pleural effusions and cardiomegaly, which are suggestive of congestive cardiac failure. One patient (an 82-year-old woman) had enlarged lymph nodes, which appeared matted, and another patient (a 60-year-old woman) had a 1.8-cm irregular nodule in the left upper lobe and a 4-mm nodule in the right upper lobe. These two patients will undergo further evaluation.

Follow-up Chest Radiography in Group 2

Follow-up chest radiography of patients in group 2 showed abnormalities (areas of opacification) in 12 patients (71%) and normal findings in the other five (29%). The radiographic abnormalities developed an average of 2.0 days (range, same day to 5 days) after CT. The five patients with no subsequent radiographic abnormalities were followed up for an average of 3.4 days (range, 2–6 days) after CT.

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SARS is a newly described infection of unknown etiology. A coronavirus has been implicated as the causative agent (4). Our initial experience has shown some frequent findings at thin-section CT. In terms of distribution, the lower lobes are preferentially affected (average of 5.0 segments for group 1 and 2.0 for group 2), especially in the early stages (assuming the group 2 patients to be in an earlier stage of infection than the group 1 patients). The patients with more advanced cases show more bilateral involvement (61% in group 1). The lesions tend to be peripheral and smaller (76% were smaller than 3 cm in group 2) in the less severely affected lungs, also suggesting that we are scanning patients with an earlier stage of the disease. In patients with more advanced cases, there is involvement of the central, perihilar regions by larger (>3 cm) lesions. The majority of the lesions contained an area of ground-glass opacification with or without consolidation. Other findings include intralobular thickening, interlobular septal thickening, a crazy-paving pattern, and bronchiectasis. None of the CT features of this syndrome were themselves specific or diagnostic. The crazy-paving pattern, once thought to be characteristic of alveolar proteinosis, has been shown to occur in many other diseases, such as usual interstitial pneumonia, infection, pulmonary edema, adult respiratory distress syndrome, bronchiolitis obliterans organizing pneumonia (BOOP), and hemorrhage and as a result of irradiation (6). Some of these diagnoses could be

excluded by correlating the clinical history with the distribution of opacification. Thus, our differential diagnosis in terms of CT findings included other causes of atypical pneumonia, BOOP, chronic eosinophilic pneumonia, and acute extrinsic allergic alveolitis.

Atypical pneumonia is frequently caused by *Mycoplasma* species, influenza virus, or *Chlamydia* species. Tanaka et al (7) described a central pattern of ground-glass opacification and consolidation in these types of atypical pneumonia. This appearance may then progress to centrilobular, acinar shadows and air-space consolidation with a lobular distribution. We have not found these to be major features of SARS in our series.

Bronchiolitis obliterans is an inflammatory disease of the bronchioles and alveolar ducts that results in destruction of the airways and scarring. This condition combined with an organizing pneumonia is termed BOOP. The CT findings of BOOP are well recognized (8–10) and are similar to those of SARS. These similarities include the lower lobe and peripheral distribution, a mixture of ground-glass opacification and consolidation, interstitial or septal thickening, and bronchiectasis. Nodules were not present in the patients with SARS in our series but are relatively common (31.6%) in patients with BOOP (11). Patients with BOOP also demonstrate lymphadenopathy (13%) (12) and pleural effusion (20%) (12), of which we saw only one case each in our patients with SARS.

Chronic eosinophilic pneumonia shares many of the features of BOOP and thus SARS. In a recent thin-section CT study of BOOP and chronic eosinophilic pneumonia (11), both diseases showed a high prevalence of consolidation (86.8% and 74.4%, respectively) aside from ground-glass opacification. In a report by Jederlinic et al (13), chronic eosinophilic pneumonia has been shown to have middle and upper zone predominance, which is different from the lower zone predominance in SARS.

Acute allergic extrinsic alveolitis is an abnormal immunologic reaction to inhaled allergens, which produces an alveolar inflammation, ground-glass opacification, and consolidation. However, its distribution is predominantly in the middle zone (sparing the lower lobes), and centrilobular nodules may be present (14).

During this outbreak of SARS, our initial 50 patients underwent both conventional CT (7-mm section thickness, pitch of 1.5) and thin-section CT (1-mm section thickness, 6-mm gap). Both examinations were performed because we were faced with an

unknown disease and we wanted to rule out other findings such as lymphadenopathy and pleural effusion. Because we did not observe these findings in the initial 50 patients, we changed the protocol to include only thin-section CT of the thorax.

In retrospect, the 34 patients in group 3, who had minor symptoms and a normal chest radiograph, would not have been scanned if we strictly adhered to the definition subsequently released by the CDC. These patients—some of whom were inpatients but most of whom were medical personnel and all of whom had a history of contact with a person without a respiratory illness who traveled to a SARS area or a person known to be a suspect SARS case—were scanned at a time when we were faced with an unknown disease and were experiencing a high level of anxiety. Although we now consider CT unnecessary for such patients, these CT findings did help us as we began learning about this disease.

Our current imaging protocol is the following: (*a*) Patients with symptoms and signs consistent with SARS and with abnormalities on chest radiographs are followed up with serial radiography. CT scanning is not required for diagnosis. (*b*) Patients with symptoms and signs consistent with SARS and with a normal chest radiograph undergo thin-section CT to confirm the diagnosis. They subsequently undergo serial radiography for follow-up. (*c*) Patients with minor symptoms and signs that do not match the definition of SARS do not undergo thin-section CT.

There are limitations to our study. First, on the basis of the number of patients studied, the full range of disease distribution and appearance may not have been demonstrated. Second, we have no proof, histologic or biochemical, that the patients had been infected with the same causative agent. At this writing, the causative agent has not been definitively isolated and a definitive test has not yet been developed for diagnosis.

In summary, the CT features of SARS are predominantly ground-glass opacification, lower lobe predominance, and peripheral distribution.

FOOTNOTES

See also the article by Wong et al in this issue.

Abbreviations: BOOP = bronchiolitis obliterans organizing pneumonia, CDC = Centers

for Disease Control and Prevention, SARS = severe acute respiratory syndrome

Author contributions: Guarantor of integrity of entire study, A.T.A.; study concepts, A.T.A., K.T.W., G.E.A.; study design, K.T.W., G.E.A., D.S.C.H., P.C., S.S.C.C.; literature research, K.T.W., G.E.A.; clinical studies, D.S.C.H., N.L., A.W., C.B.L., T.H.R., P.C., S.S.C.C., J.J.Y.S.; data acquisition, A.T.A., K.T.W., G.E.A., N.L., E.H.Y.Y., A.W., T.H.R., C.B.L.; data analysis/interpretation, G.E.A., A.T.A., K.T.W.; statistical analysis, G.E.A., K.T.W.; manuscript preparation and definition of intellectual content, G.E.A., A.T.A., K.T.W.; manuscript editing, A.T.A., K.T.W., J.J.Y.S., S.S.C.C.; manuscript revision/review and final version approval, A.T.A., K.T.W., G.E.A.

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Thoracic Imaging

Severe Acute Respiratory Syndrome: Radiographic Appearances and Pattern of Progression in 138 Patients[1]

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ABSTRACT

PURPOSE: To retrospectively evaluate the radiographic appearances and pattern of progression of severe acute respiratory syndrome (SARS).

MATERIALS AND METHODS: Chest radiographs obtained at clinical presentation and during treatment in 138 patients with confirmed SARS (66 men, 72 women; mean age, 39 years; age range, 20–83 years) were assessed. Radiographic appearances of pulmonary

parenchymal abnormality, distribution, and extent of involvement on initial chest radiographs were documented. Recognizable patterns of radiographic progression were determined by comparing the overall mean percentage of lung involvement for each patient on serial radiographs.

RESULTS: Initial chest radiographs were abnormal in 108 of 138 (78.3%) patients and showed air-space opacity. Lower lung zone (70 of 108, 64.8%) and right lung (82 of 108, 75.9%) were more commonly involved. In most patients, peripheral lung involvement was more common (81 of 108, 75.0%). Unifocal involvement (59 of 108, 54.6%) was more common than multifocal or bilateral involvement. No cavitation, lymphadenopathy, or pleural effusion was demonstrated. Four patterns of radiographic progression were recognized: type 1 (initial radiographic deterioration to peak level followed by radiographic improvement) in 97 of 138 patients (70.3%), type 2 (fluctuating radiographic changes) in 24 patients (17.4%), type 3 (static radiographic appearance) in 10 patients (7.3%), and type 4 (progressive radiographic deterioration) in seven patients (5.1%). Initial focal air-space opacity in 44 of 59 patients (74.6%) progressed to unilateral multifocal or bilateral involvement during treatment.

CONCLUSION: Predominant peripheral location; common progression pattern from unilateral focal air-space opacity to unilateral multifocal or bilateral involvement during treatment; and lack of cavitation, lymphadenopathy, and pleural effusion are the more distinctive radiographic findings of SARS.

Index terms: Lung, radiography, 68.11 • Pneumonia, acute interstitial, 68.21 • Severe acute respiratory syndrome

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Editor's Note: Although the 138 patients described in this report were also included in a report published online by the New England Journal of Medicine (www.nejm.org; *April 7, 2003), the analysis of the radiographic findings for these patients in the* Radiology *report has been performed in much greater detail.*

—Anthony V. Proto, MD, Editor

In early March 2003, there was an outbreak of atypical pneumonia in Hong Kong. The World Health Organization (WHO) defined the illness as severe acute respiratory syndrome (SARS). At the time of writing this article, there have been 1,059 reported cases in Hong Kong and more than 2,890 cases worldwide (1), including 32 deaths in Hong Kong related to the illness.

At our institution, over 200 confirmed cases of SARS have been treated (2). Imaging plays a crucial role in diagnosis and in monitoring of disease progress during medical treatment. From our experience, the radiographic appearances of SARS at the time of initial presentation are variable, ranging from normal to widespread opacification. In addition, patients show different radiologic progression during treatment.

Because the role of imaging is central to the diagnosis and the care of the patients, radiographers and radiologists should be aware of the radiographic appearances of this disease and the infection-control guidelines to prevent transmission of the disease. The purpose of our study was to retrospectively evaluate the radiographic appearances and patterns of progression in patients with SARS.

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Subjects

Between March 11 and 25, 2003, 138 subjects (66 men, 72 women; mean age, 39 years; age range 20–83 years) were identified as being secondary (history of direct contact with index case at our institution) or tertiary (history of direct contact with secondary cases) cases of SARS at our institution. There were 66 men and 72 women, with a mean age of 39 years, age range of 20–83 years. Sixty-nine of the 138 were health care workers and an additional 16 were medical students who were present for clinical teaching in the index ward (Table 1). The remaining 53 were inpatients in the same medical ward or those who had visited their relatives in that ward. The diagnosis of SARS was based on WHO diagnostic criteria (3). This retrospective study was approved by our Institutional Review Board; patient informed consent was not required.

View this table: TABLE 1. Profile of 138 Subjects with SARS
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Chest Radiography and Evaluation

Frontal chest radiographs were obtained at initial clinical presentation and during treatment. The initial chest radiograph was obtained an average of 2.5 days (range, 0–10 days) after onset of fever. Only frontal chest radiographs were obtained (posteroanterior for subjects who could stand, anteroposterior for those who could not). All radiographic examinations were performed with computed radiography equipment (Mobilett Plus; Siemens, Erlangen, Germany) by using a standardized technique (75 kV, 4 mAs, 180-cm film-focus distance for posteroanterior; 70 kV, 4 mAs, 100-cm film-focus distance for anteroposterior; broad tube focus for both). The images were assessed by using a picture archiving and communication system viewer with a 2,048 x 2,048-pixel monitor (Magicview version VA22E; Siemens).

The frontal chest radiographs obtained at clinical presentation and at follow-up during treatment were retrospectively reviewed in consensus by three radiologists (K.T.W., G.E.A., H.Y.Y.) who were unaware of the clinical progress of the subjects. Each lung was divided into three zones: upper, middle, and lower. Each zone spanned one-third of the craniocaudal distance of the lung on the frontal radiograph and was evaluated separately.

The observers assessed the presence, appearances, distribution, and size of lung parenchymal abnormalities on each chest radiograph in all subjects. The appearances were categorized as follows: air-space shadow, reticular shadow, nodular shadow, or mass. The anatomic distribution was noted to be central if the abnormality predominantly involved the medial half of the zone and peripheral if it predominantly involved the lateral half. The size of the lesion was assessed by visually estimating the percentage area occupied in each zone on each side to determine the overall mean percentage of involvement by averaging the percentage involvement of the six lung zones. Associated findings, in particular the presence of cavitation, lymphadenopathy, and pleural effusion, were also assessed.

Serial frontal chest radiographs obtained during treatment were also retrospectively reviewed by the same radiologists in consensus. All subjects included in this study underwent serial follow-up chest radiography for at least 14 days (unless deceased).

For each follow-up radiograph, the extent of lung parenchymal involvement was assessed by using the same method as for the radiograph obtained at initial clinical presentation. Follow-up radiographs were obtained daily during the hospital stay. All subjects were given a combination of ribavirin (Derbin BLC, United Kingdom) (an antiviral agent, administered orally; initial dose of 2.4 g followed by 1.2 g three times daily) and corticosteroid (prednisolone; Clonmel Healthcare, Ireland) (0.5–1.0 mg per kilogram of body weight per day;) for treatment. The steroid methylprednisolone (Solu-medrol; Pharmacia Upjohn, Belgium) was administered intravenously in pulsed fashion (0.5 g for three consecutive days) to 107 subjects whose clinical condition so indicated.

Data Analysis

The radiographic patterns at the time of clinical presentation in all 138 subjects, as assessed on initial chest radiographs, were analyzed and categorized as normal or unifocal, unilateral multifocal, or bilateral multifocal abnormalities. The distribution of lung parenchymal involvement in terms of central or peripheral involvement and the zones involved were noted. We determined if there were recognizable patterns of radiographic progression by comparing the overall percentage of lung involvement for each subject on serial radiographs.

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Appearances of Abnormalities at Presentation

Chest radiographs obtained at presentation were abnormal in 108 of 138 subjects (78.3%). The radiographic pattern observed in all 108 subjects was air-space opacities with ill-defined margins. None of these lesions showed a reticular or nodular pattern or a mass. There was no evidence of cavitation in the area of air-space consolidation, lymphadenopathy, or pleural effusion (except in one subject with concomitant congestive cardiac failure who had a small pleural effusion) on any chest radiograph at initial presentation. Chest radiographs obtained at presentation were normal in 30 of 138 subjects (21.7%).

Distribution of Abnormalities at Presentation

The location and appearance of lung opacities on initial radiographs are shown in Tables 2 and 3, respectively. The right lung (82 of 108 subjects, 75.9%) was involved in more subjects than the left (67 of 108, 62.0%). The disease showed a predilection

for the lower zone (70 of 108, 64.8%). Involvement of peripheral lung parenchyma (81 of 108, 75.0%) (Fig 1) was more common than a mixed peripheral and central pattern (14 of 108, 13.0%) or a central pattern (13 of 108, 12.0%) at the time of presentation. Unifocal involvement (59 of 108, 54.6%) was slightly more common than multifocal involvement (49 of 108, 45.4%). Bilateral disease was present in 41 (38.0%) subjects. At presentation, the overall mean lung involvement was 4.7% (range, 0.8%–63.3%).

View this table: TABLE 2. Location of Lung Opacities on Initial Radiographs in
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View this table: TABLE 3. Appearance of Lung Opacities on Initial
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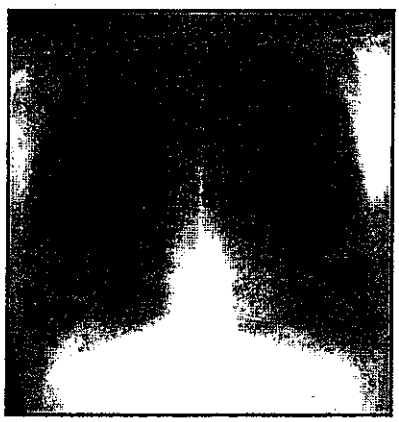

Figure 1. Frontal chest radiograph in a 23-year-old man with SARS shows a focal ill-defined air-space opacity predominantly involving the periphery of right lower zone. Note lack of cavitation, lymphadenopathy, and pleural effusion.

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Radiographic Progression

Of the 30 subjects with an initial normal chest radiograph, 29 showed evidence of air-space opacities on subsequent follow-up chest radiographs after an average of 3.1 days (range, 1–7 days). The remaining subject had normal-appearing follow-up radiographs, but signs and symptoms were strongly suggestive of SARS and the

diagnosis was made with the aid of thin-section computed tomography (CT) of thorax. Thus, of the total of 138 subjects, all but one showed air-space opacity, either initially (n = 108) or subsequently (n = 29) on radiographs.

At review of follow-up radiographs, we were able to identify four patterns of radiographic progression (Table 4, Fig 2): type 1, initial radiographic deterioration to peak level, followed by radiographic improvement, with maximum difference in overall mean lung involvement greater than 25%; type 2, fluctuating radiographic changes with at least two radiographic peaks and an intervening trough, which differed by more than 25% for overall mean lung involvement; type 3, static radiographic changes with no discernible radiographic peak or change in overall mean lung involvement of less than 25% for more than 10 days; and type 4, progressive radiographic deterioration.

View this table: TABLE 4. Patterns of Radiographic Progression of SARS in
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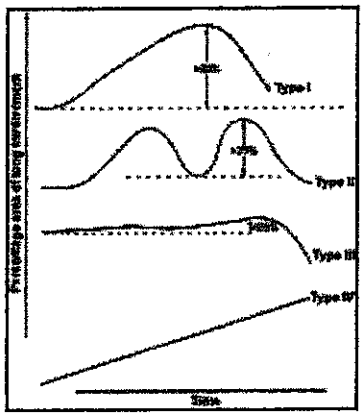

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Figure 2. Schematic depicts the four patterns of radiographic progression determined from serial chest radiographs. See Table 4 for time to peak(s).

The type 1 pattern was the most commonly observed (97 of 138, 70.3%), with radiographic deterioration to a peak (mean time from onset of fever to peak, 8.6 days ± 3.1 [SD]; range, 2–17 days) followed by radiographic improvement (Fig 3). Twenty-four of 138 subjects (17.4%) had the type 2 pattern, with two distinct radiographic

peaks at 6.3 days ± 3.0 and 13.5 days ± 3.7. Ten subjects (7.3%) had the static type 3 radiographic appearances for most of the time during treatment. Among seven subjects with Type 4 pattern, radiographs showed progressive deterioration until the lungs became completely consolidated or the subject died. Six died during the study period, and one remains critically ill at the time of this writing, requiring intensive care and assisted ventilation.

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Figure 3a. Serial radiographic appearances in a 23-year-old woman with SARS, type 1 pattern. **(a)** Frontal chest radiograph obtained at clinical presentation shows unilateral focal air-space opacity in the right middle zone. **(b)** Follow-up frontal chest radiograph obtained 5 days later shows progression of radiographic changes, with multifocal bilateral air-space opacities in both lungs. **(c)** Subsequent follow-up chest radiograph obtained after another 7 days shows radiographic improvement in extent of pulmonary parenchymal air-space opacities after successful medical therapy with a combination of oral ribavirin and corticosteroids.

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Figure 3b. Serial radiographic appearances in a 23-year-old woman with SARS, type 1 pattern. **(a)** Frontal chest radiograph obtained at clinical presentation shows unilateral focal air-space opacity in the right middle zone. **(b)** Follow-up frontal chest radiograph obtained 5 days later shows progression of radiographic changes, with multifocal bilateral air-space opacities in both lungs. **(c)** Subsequent follow-up chest radiograph obtained after another 7 days shows radiographic improvement in extent of pulmonary parenchymal air-space opacities after successful medical therapy with a combination of oral ribavirin and corticosteroids.

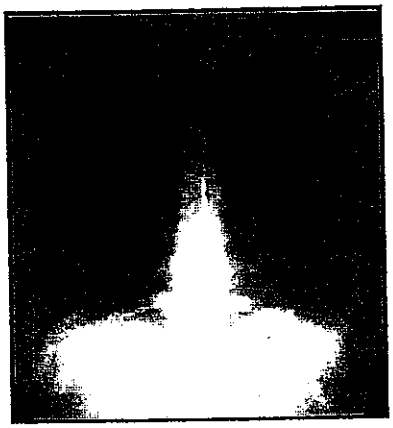

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Figure 3c. Serial radiographic appearances in a 23-year-old woman with SARS, type 1 pattern. **(a)** Frontal chest radiograph obtained at clinical presentation shows unilateral focal air-space opacity in the right middle zone. **(b)** Follow-up frontal chest radiograph obtained 5 days later shows progression of radiographic changes, with multifocal bilateral air-space opacities in both lungs. **(c)** Subsequent follow-up chest radiograph obtained after another 7 days shows radiographic improvement in extent of pulmonary parenchymal air-space opacities after successful medical therapy with a combination of oral ribavirin and corticosteroids.

Of the 59 subjects with unilateral focal air-space opacity on initial radiographs, 44 (74.6%) progressed to unilateral multifocal ($n = 10$) or bilateral multifocal ($n = 34$) air-space opacities during hospitalization. In fifteen (25.4%), the opacity remained unilateral focal in terms of lung involvement.

Confluent air-space opacities diffusely involving both lungs, compatible with acute respiratory distress syndrome, were observed in 11 of 138 subjects (8.0%) during the course of the disease (Fig 4); this occurred almost exclusively in subjects with poor clinical outcome (six died and five required prolonged assisted ventilation at the end of the study period).

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Figure 4. Frontal chest radiograph in a 76-year-old man with SARS who was undergoing medical treatment shows diffuse confluent air-space opacities involving both lungs and normal heart size. These findings are compatible with radiologic features of acute respiratory distress syndrome.

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SARS was recognized as a global health hazard in March 2003. At our institution it initially affected mainly health care professionals but soon spread to involve inpatients, outpatients and their contacts. With the convenience of air travel, the disease has now spread to all parts of the world, with patients appearing in other parts of Asia, Europe, North America, and Australia. In view of the worldwide increase in number of confirmed cases, the WHO issued a global alert for the first time in more than a decade (1). The disease is highly infectious and, at the time of this writing, only preliminary data have been reported on the causative agent of SARS. A coronavirus has been implicated as the causative agent (4). It is suspected that infection is transmitted by means of droplets and, possibly, fomites; hence, both respiratory and contact infection-control precautions are important for the protection of health care workers, as recommended by the Centers for Disease Control and Prevention (5).

On the basis of our results, air-space opacification is the pattern seen on chest radiographs in patients with SARS. All but one of 138 subjects showed air-space opacification of varying extent and distribution at some stage of the disease. In one subject, the initial and early-progress radiographs were normal and the diagnosis was made with the aid of thin-section CT of thorax. The CT scans in this subject showed a small (approximately 2-cm) area of ground-glass opacification with intralobular interstitial and interlobular septal thickening in the posterior costophrenic recess of the right lung. We have recently reported the thin-section CT findings in patients with SARS (6).

The peripheral location of air-space opacification was another common radiographic feature of SARS in our study. The opacities occupied a peripheral or mixed peripheral and central location in 88% of subjects. Important absent findings included the lack of cavitation, lymphadenopathy, or pleural effusion.

The radiographic appearance of peripheral air-space opacities in SARS is indistinguishable from other causes of atypical pneumonia, such as *Mycoplasma,*

Chlamydia, and *Legionella* (7,8), and overlap with other types of viral pneumonia in adults (9). Since imaging alone cannot help differentiate SARS from other diseases, the clinical manifestation is indispensable for diagnosis. The presence of characteristic clinical features, including high fever (temperature > 38°C), chills, rigor, myalgia, and laboratory findings such as leukopenia and thrombocytopenia in patients with recent exposure, are very suggestive of SARS. The presence of an air-space opacity on chest radiographs has been as helpful in confirmation of the diagnosis.

Radiographic progression to unilateral multifocal or bilateral involvement occurred in most subjects with unilateral focal air-space opacity on the initial chest radiograph obtained during treatment with a combination of an antiviral agent and corticosteroids. We found that only a small percentage (7.2%) of subjects with SARS showed a static radiographic appearance (type 3 pattern) for most of the time during treatment. On the other hand, progressive radiographic deterioration despite medical treatment seems to be associated with poor prognosis, with all deaths in our series occurring in patients with the type 4 pattern.

There are some limitations to our early study: *(a)* The subjects in this study were a heterogeneous group, and we have not taken into account the severity of clinical symptoms and clinical outcome. *(b)* Visual estimation of the percentage of lung involvement may appear to be subjective; however, in our opinion this appears to be the most practical method in real life, in an epidemic crisis in which it is not possible to design detailed computer-based models at short notice. *(c)* A frontal radiograph alone may not be accurate in helping identify central versus peripheral lesions; however, in patients who underwent thin-section CT, this localization proved to be accurate (6). *(d)* This report does not deal with clinical and radiologic comparison, particularly the timing and type of treatment regimen and the timing of the radiographic response. It also does not include evaluation of any outcome indicators. Such an evaluation requires detailed clinical, immunologic, and statistical analyses, which may be possible when more data and experience become available.

In conclusion, SARS has become a global health hazard and its high infectivity is alarming. Imaging plays an important role in the diagnosis and monitoring of response to therapy. The predominant peripheral location; common progression pattern from unilateral focal air-space opacity to unilateral multifocal or bilateral involvement during treatment; and lack of cavitation, lymphadenopathy, and pleural effusion are the more distinctive radiographic findings of this potentially lethal

disease.

FOOTNOTES

See also the other article by Wong et al in this issue.

Abbreviations: SARS = severe acute respiratory syndrome, WHO = World Health Organization

Author contributions: Guarantor of integrity of entire study, A.T.A.; study concepts, A.T.A., K.T.W., G.E.A., S.S.C.C., J.J.Y.S.; study design, A.T.A., K.T.W., G.E.A.; literature research, A.T.A., K.T.W., G.E.A.; experimental studies, K.T.W., D.S.C.H., N.L., A.W., C.B.L., T.H.R., P.C., J.J.Y.S., S.S.C.C.; data acquisition, K.T.W., G.E.A., D.S.C.H., N.L., E.H.Y.Y., A.W., C.B.L., T.H.R., P.C.; data analysis/interpretation, K.T.W., G.E.A., A.T.A.; manuscript preparation and editing, K.T.W., G.E.A., A.T.A., D.S.C.H.; manuscript definition of intellectual content, K.T.W., G.E.A., A.T.A., J.J.Y.S., D.S.C.H., P.C.; manuscript revision/review, K.T.W., A.T.A., G.E.A., D.S.C.H., P.C.; manuscript final version approval, K.T.W., A.T.A., D.S.C.H., J.J.Y.S.

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Radiology

Appendix 9

Published online before print June 12, 2003
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Thoracic Imaging

Thin-Section CT in Patients with Severe Acute Respiratory Syndrome Following Hospital Discharge: Preliminary Experience[1]

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ABSTRACT

PURPOSE: To report the initial experience regarding thin-section computed tomographic (CT) findings in patients with severe acute respiratory syndrome (SARS) who improved clinically after treatment.

MATERIALS AND METHODS: Twenty-four patients (10 men, 14 women; mean age, 39 years; age range, 23–70 years) with confirmed SARS underwent follow-up thin-section CT of the thorax. The scans were obtained on

average 36.5 days after hospital admission and were analyzed for parenchymal abnormality (ground-glass opacification, consolidation, or interstitial thickening) and evidence of fibrosis (parenchymal band, traction bronchiectasis, irregular interfaces). Patients were assigned to group 1 (with CT evidence of fibrosis) and group 2 (without CT evidence of fibrosis) for analysis. Patient demographics, length of hospital stay, rate of intensive care unit admission, peak lactate dehydrogenase level, pulsed intravenous methylprednisolone therapy, and peak opacification on chest radiographs were compared between the two groups.

RESULTS: Parenchymal abnormality was found in 96% (23 of 24) of patients and ranged from residual ground-glass opacification and interstitial thickening in group 2 (nine of 24, 38%) to fibrosis in group 1 (15 of 24, 62%). Patients in group 1 were older (mean age, 45 vs 30.3 years), had a higher rate of intensive care unit admissio (27% [four of 15] vs 11% [one of nine]), more requirement for pulsed intravenous methylprednisolone (87%, [13 of 15] vs 67% [six of nine]), higher peak lactate dehydrogenase level (438.9 vs 355.6 U/L), and higher peak opacification on chest radiographs (estimated area, 14% vs 11%) than patients in group 2.

CONCLUSION: Pulmonary fibrosis may develop early in patients with SARS who have been discharged after treatment. Patients who are older and have more severe disease during treatment are more likely to develop thin-section CT findings of fibrosis.

Index terms: Lung, CT, 69.12118 • Pneumonia, acute interstitial, 69.21 • Severe acute respiratory syndrome

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Severe acute respiratory syndrome (SARS) is thought to be caused by a mutated coronavirus (1). Imaging plays an important role in the diagnosis and treatment of patients with SARS. Chest radiography is one of the major diagnostic components according to the World Health Organization and Centers for Disease Control and Prevention guidelines (2,3). Chest radiography helps in the diagnosis by depicting lung opacities and also helps in

the evaluation of the progress of disease and response to treatment (4). The role of thin-section computed tomography (CT) is particularly important in early diagnosis in patients with a high clinical suspicion of disease and a negative chest radiograph (5).

In view of the role of imaging in the diagnosis and management of SARS, we were interested in determining its role, if any, in the evaluation of patients after they have responded to treatment and have been discharged from the hospital. We were particularly interested in determining if thin-section CT demonstrates any residual parenchymal abnormalities or scarring in the early postdischarge period, as this may have implications for future treatment. Thus, the purpose of this study was to report our initial experience regarding the thin-section CT findings in patients with SARS who improved clinically after treatment.

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This study and the use of patient case files were approved by the review board of our institution. Informed consent was waived by the review board.

Patients and CT Imaging

Our study extended from April 7, 2003, to May 6, 2003, and included 24 patients who had been discharged from the hospital after treatment for SARS as inpatients at our institution. Their diagnosis was based on World Health Organization criteria (2). All patients also met specified discharge criteria that included *(a)* being afebrile for at least 96 hours after the last dose of steroid, *(b)* resolving respiratory symptoms and oxygen independence, *(c)* radiologic improvement (based on serial chest radiographs) (4), and *(d)* improving laboratory parameters. If the patients met the discharge criteria and the date of hospital discharge was less than 21 days since the day of the onset of fever, they were discharged from the SARS hospital ward to a step-down convalescent facility. If the date of the hospital discharge was beyond 21 days since the day of the onset of fever, the patients were discharged home. Infection control protection maneuvers to be followed at home were explained to them. The 24 patients included 10 men and 14 women (age range, 23–70 years; mean age, 39 years).

Although these patients met the discharge criteria and were otherwise well enough to perform their daily activities, they complained of exertional dyspnea and/or reduced

exercise tolerance at clinical follow-up. Because this was a new entity with no previous literature about disease progression for guidance, we performed follow-up thin-section CT (in addition to conventional chest radiography) in the patients to document any residual lung abnormalities. An additional 19 patients met our criteria but were not included in our study since thin-section CT, which had been scheduled, had not yet been performed.

Thin-section CT (HiSpeed Advantage; GE Medical Systems, Milwaukee, Wis) was performed (1-mm section thickness with 6-mm gap, supine position, scanning during inspiration, 1 second per scan, 120 kV, 140 mA). The scans were obtained on average 36.5 days (range, 16–56 days) after the initial hospital admission and 17.8 days after discharge (range, 1–33 days).

Review of CT Images

All CT images were reviewed by three radiologists (A.T.A., K.T.W., G.E.A.) using a viewing console, and findings were established by consensus. Each segment of the lung was reviewed for ground-glass opacification, airspace consolidation, interstitial thickening, bronchiectasis, and architectural distortion. Ground-glass opacification was defined as increased lung parenchymal attenuation that did not obscure the underlying vascular architecture (6). Consolidation was defined as opacification in which the underlying vasculature was obscured (6). Abnormalities were magnified by using a zoom function and were examined for intralobular interstitial, interlobular septal, or peribronchovascular interstitial thickening. Attention was also paid to the presence of nodules or masses, cavitation or calcification, and emphysema. The presence of parenchymal bands, irregular interfaces (bronchovascular, pleural, or mediastinal), and traction bronchiectasis were considered as evidence of fibrosis (7–9). Thickened interstitium could not be used as evidence of fibrosis since it may also be present during the acute illness (5).

For patients who underwent an initial examination (conventional or thin-section CT) for diagnosis, the abnormalities were compared with those seen on the follow-up thin-section CT scans.

Chest Radiography and Evaluation

Frontal chest radiographs were obtained during the hospital stay, at discharge, and at follow-up. All radiographic examinations were performed with CT equipment by using standardized techniques, as previously reported (4). The images were assessed by using a picture archiving and communication system viewer with a 2,048 x 2,048-pixel

monitor (Magicview version VA22E; Siemens, Erlangen, Germany).

The chest radiographs were retrospectively reviewed by three radiologists (A.T.A., K.T.W., G.E.A.) in consensus by using a method identical to that used in a previous study (4).

Clinical Comparison and Data Analysis

Patients with evidence of pulmonary fibrosis at thin-section CT were designated as group 1, and patients without evidence of fibrosis at thin-section CT were designated as group 2.

Patient age, sex, average hospital stay, rate of intensive care unit admission, peak lactate dehydrogenase level, and the presence and number of doses of pulsed intravenous methylprednisolone were compared between the two groups. The peak opacification on chest radiographs during the hospital stay and the number of abnormal lung segments (showing any form of opacification or evidence of fibrosis) for each patient on follow-up thin-section CT scans were also compared between the two groups.

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Fifteen patients (eight men, seven women; mean age, 45 years; age range, 23–70 years) were designated as group 1 (62%); nine patients (two men, seven women; mean age, 30.3 years; age range, 23–50 years), as group 2 (38%).

Chest Radiography at Discharge and Follow-up

At discharge, 20 of the 24 patients still had residual abnormalities on the chest radiographs. These abnormalities included patchy areas of opacification (20 of 24 patients) and signs of volume loss (five of 24 patients). At follow-up (in the review clinic, average of 18 days after discharge), 15 of 24 patients had an abnormal chest radiograph, and nine patients had a normal chest radiograph. Of the 15 patients, 10 showed improvement in the air-space opacification between discharge and follow-up, whereas abnormalities (airspace opacification or volume loss) on the chest radiographs remained static in the other five patients.

Thin-Section CT Abnormalities

The thin-section CT scan was abnormal in 23 (96%) of 24 patients. In all 23 patients, the images showed areas of ground-glass opacification of various sizes, along with thickening of interlobular septa and intralobular interstitium. The mean number of segments showing these abnormalities was 8.7 (range, 1–17). The thin-section CT scan was normal in one patient. There were no masses or nodules, emphysema, cavitation, or calcification.

In nine patients (eight underwent thin-section CT; one, conventional CT) who underwent CT at initial presentation, there was improvement in all patients, with residual ground-glass opacification and thickened interlobular septa in eight of the nine patients (Fig 1). The mean interval between the two CT scans was 23.3 days (range, 14–41 days). In one of the nine patients, there was complete resolution of the lung abnormalities.

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Figure 1a. (a) Transverse thin-section CT scan of right lower lobe in a 25-year-old woman with SARS (obtained at day 3 after admission) shows two areas of ground-glass opacification, with thickened interlobular septa giving crazy-paving appearance. **(b)** Follow-up CT scan after discharge (obtained at day 27 after admission) shows almost complete resolution of lung abnormalities. Small patches of residual ground-glass opacification and septal thickening are still present.

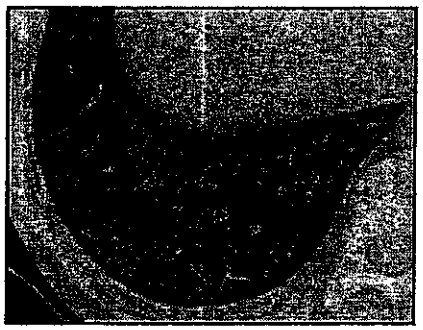

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Figure 1b. (a) Transverse thin-section CT scan of right lower lobe in a 25-year-old woman with SARS (obtained at day 3 after admission) shows two areas of ground-glass opacification, with thickened interlobular septa giving crazy-paving appearance. **(b)** Follow-up CT scan after discharge (obtained at day 27 after admission) shows almost complete resolution of lung abnormalities. Small patches of residual ground-glass opacification and septal thickening are still present.

There were signs of fibrosis (parenchymal band, irregular interfaces, and traction bronchiectasis) and peribronchovascular interstitial thickening (Figs 2, 3) in 15 (62%) of 24 patients. These were associated with architectural distortion that resulted in movement of the fissures and bronchovascular bundles. The ground-glass opacification in these 15 patients surrounded the areas of fibrosis. There were also small patches of consolidation in the center of the fibrotic areas, adjacent to the bronchi.

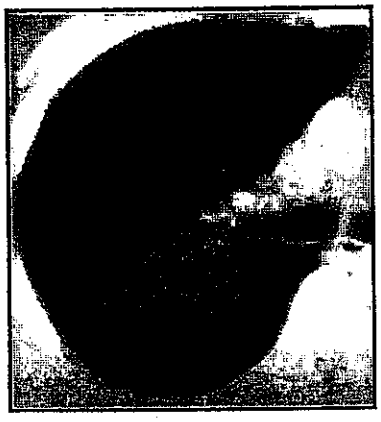

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Figure 2a. (a) Transverse conventional CT scan in 33-year-old man with SARS (obtained at day 4 after admission) shows ground-glass opacification. **(b)** Follow-up thin-section CT scan (obtained at day 46 after admission, 29 days since discharge) of the corresponding area shows evidence of fibrosis, such as parenchymal bands, irregular interface, and traction bronchiectasis.

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Figure 2b. (a) Transverse conventional CT scan in 33-year-old man with SARS (obtained at day 4 after admission) shows ground-glass opacification. **(b)** Follow-up thin-section CT scan (obtained at day 46 after admission, 29 days since discharge) of the corresponding area shows evidence of fibrosis, such as parenchymal bands, irregular interface, and traction bronchiectasis.

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Figure 3. Transverse thin-section CT scan in 36-year-old man at follow-up (obtained at day 43 after admission, 26 days since discharge) shows evidence of fibrosis. Large areas of ground-glass opacification are still present, both surrounding the areas of fibrosis and in other regions.

Comparison between Groups

Patients in group 1 were older than those in group 2 (mean age, 45 vs 30.3 years). The majority of male patients (eight of 10) were in group 1 (Table).

View this table: Comparison between SARS Patients with and Those without
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Group 1 patients stayed in the hospital for a slightly longer period of time than did patients in group 2 (22.3 vs 16.4 days). The intensive care unit admission rate was higher in group 1 patients (27% [four of 15] vs 11% [one of nine]) than in group 2 patients. The peak lactate dehydrogenase level was also higher in group 1 (438.9 vs 355.6 U/L) than in group 2 patients. The normal range of lactate dehydrogenase level at our institution is 87–213 U/L.

During their hospital stay, more patients in group 1 had received pulsed intravenous methylprednisolone (in addition to oral ribavirin and oral corticosteroid) than did patients in group 2 (87% [13 of 15] vs 67% [six of nine]). Group 1 patients also received a higher number of doses of pulsed intravenous methylprednisolone (average dose, 3.9; range, 1–8) than did group 2 patients (average dose, 3.0; range, 2–4).

The peak opacification on chest radiographs was slightly worse in group 1 patients, showing an average of 14% (range, 1.7%–33%) of the total area of opacification compared with that in group 2 patients (11%; range, 1.7%–28%). More lung segments were abnormal on the follow-up thin-section CT scans in group 1 patients

(mean, 10.8; range, three to 17) than in group 2 patients (4.7; range, zero to 11).

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To date, 317 patients have been treated at our hospital for SARS (SARS diagnosis based on World Health Organization criteria). Of these, 55 patients are still in the hospital, 35 have died, and 227 have been discharged. Patient follow-up has only just begun, and 94 patients have been seen at the follow-up clinic. Of these, 43 patients have exertional dyspnea or reduced exercise tolerance. Our study population of 24 of these 43 patients represented those patients in whom thin-section CT had already been performed. The other 19 patients had been scheduled to undergo thin-section CT, but it had not yet been performed.

In our study, follow-up thin-section CT scans obtained in discharged patients have shown that fibrosis occurred in more than half (62%) of the patients. Findings of this study have also revealed how rapidly (mean follow-up, 36.5 days after hospital admission and 17.8 days after discharge) fibrosis may begin in patients with SARS. Viral pneumonia usually resolves without any clinical and radiologic sequelae (10). There have been reports of influenza pneumonia causing pulmonary fibrosis (11) and adenovirus pneumonia causing bronchiolitis obliterans (12). SARS may more commonly cause severe parenchymal damage, with imaging changes appearing early. How many of these changes will resolve in the future is unknown, although it is unlikely that the areas of severe architectural distortion will resolve. This damage may be related to the proposed pathogenesis of lung damage by exaggerated cell-mediated host immune response elicited by a viral antigen (13). We believe the presence of pulmonary fibrosis would at least partially account for the patients' symptoms.

Of the nine patients with both predischarge and follow-up thin-section CT scans, all showed improvement after a mean of 23 days, with residual ground-glass opacification and thickened septa in eight patients and a complete resolution in one patient. Although the number of patients is small, this observation suggests that initial lung parenchymal changes are of an inflammatory nature and improve after successful therapy. In patients with evidence of fibrosis at thin-section CT, the

importance of concomitant presence of ground-glass opacification is not clear. If bronchiolitis obliterans organizing pneumonia, or BOOP, or forms of idiopathic interstitial pneumonia are used as a frame of reference (14,15), these changes may represent persistent inflammation that is potentially reversible at treatment. Currently, treatment with corticosteroids or other steroid-sparing immunomodulating agents (such as cyclophosphamide) has been used in BOOP (16,17). These are being tried in our institution for SARS-induced fibrosis. Hence, we believe the role of thin-section CT in follow-up of patients with SARS is to assess the extent of long-term lung parenchymal injury and/or fibrosis and to identify these potentially reversible components early so that appropriate treatment may be instituted to prevent further lung damage.

Comparison of the follow-up thin-section CT findings with clinical data has revealed differences between patients with thin-section CT evidence of fibrosis and those without in terms of age, sex distribution, intensive care unit admission rate, peak lactate dehydrogenase level, doses of pulsed intravenous methylprednisolone, and peak opacification on chest radiographs during treatment. There is a predominance of men and older patients with evidence of fibrosis. The higher intensive care unit admission rate and the peak extent of changes on chest radiographs during treatment in patients with evidence of fibrosis are most likely a reflection of the severity of disease experienced by these patients.

Patients with evidence of fibrosis at thin-section CT also had a higher requirement of pulsed intravenous methylprednisolone during treatment. Nearly all patients with a clinical diagnosis of SARS were treated initially with a combination of orally administered ribavirin and corticosteroid. In patients not responsive to initial treatment, high-dose corticosteroid in the form of pulsed therapy was administered. In our initial cohort, 107 of 138 patients had received pulsed steroid therapy (13). The need for pulsed steroid therapy may reflect the magnitude of the cytokine "storm" elicited by the viral antigen, which in fact may be the underlying pathogenesis of lung damage and subsequent development of fibrosis.

The peak lactate dehydrogenase level is higher in patients with evidence of fibrosis. Lactate dehydrogenase is an indicator of tissue destruction (presumably lung tissue in SARS) and has been shown to be a good independent predictor of worse clinical outcome (13). This parameter may be helpful in predicting which patients have a higher risk of developing pulmonary fibrosis after discharge so that early appropriate

therapy and the follow-up protocol can be tailored accordingly. As this is a new entity, much is still to be learned about this potentially fatal, highly infectious disease.

There are limitations to our study. First, on the basis of the number of patients and the relatively short follow-up period, the full spectrum of disease appearance has likely not been demonstrated. These patients have not been followed up for a long period of time, and it is possible that many of the clinical and thin-section CT findings may still be reversible. Second, there is no histologic confirmation of fibrosis in any of the patients, although the signs on thin-section CT scans are convincing. Third, there is no comparison with clinical information, such as results from lung function tests and objective assessment of exercise tolerance. Fourth, no thin-section CT was performed in treated patients who were asymptomatic, and, thus, residual abnormalities in these patients cannot be excluded.

In conclusion, on thin-section CT scans, fibrosis was seen in 62% of the 24 symptomatic patients with SARS after treatment, with symptoms of exertional shortness of breath and reduced exercise tolerance. There is a difference between patients with evidence of fibrosis at thin-section CT and those without in terms of intensive care unit admission rate, peak lactate dehydrogenase level, number of doses of pulsed intravenous methylprednisolone, and peak opacification on chest radiographs during treatment, which suggests that fibrosis is more likely to develop in patients with more severe disease. However, we wish to clearly state that our findings are only preliminary, and larger studies with longer follow-up will be necessary to better determine the long-term outcome for patients with SARS.

FOOTNOTES

Abbreviation: SARS = severe acute respiratory syndrome

Author contributions: Guarantor of integrity of entire study, A.T.A.; study concepts, A.T.A., G.E.A., K.T.W., J.J.Y.S.; study design, A.T.A., G.E.A., K.T.W.; literature research, G.E.A., K.T.W.; clinical studies, D.S.C.H., A.W., N.L., C.B.L., T.H.R., P.C., S.S.C.C., J.J.Y.S.; data acquisition, A.T.A., K.T.W., G.E.A., E.H.Y.Y.; data analysis/interpretation, K.T.W., G.E.A.; statistical analysis, K.T.W., G.E.A.; manuscript editing, K.T.W., G.E.A., A.T.A., J.J.Y.S., D.S.C.H.; manuscript preparation, definition of intellectual content, revision/review, and final version approval, K.T.W., G.E.A., A.T.A.

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Appendix 10

THE CHINESE UNIVERSITY
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Your Ref:

Our Ref:

CLO/0303/09

19th March 2003

Dr. Margaret Chan, JP
Director of Health
21/F, Wu Chung House
213 Queen's Road East
Wan Chai
Hong Kong

FAXED
DATE: 19 MAR 2003
Sent out on 20/3/03

Dear Dr. Chan,

Re: SARS

Amongst the more than 100 cases admitted I am particularly worried that we are seeing the infection in contacts that have never been to the hospital. For example:

1. Dr KK Tse had symptoms but stayed at home from 11-3-03 to 19-3-03. Both his mother (Yeung Tan Chin [redacted]) and brother Chia Kian Kok ([redacted]) were admitted with pneumonia on 19-3-03. Dr KK Tse was admitted on 19-3-03 as well and was transferred to the ICU straight away.

2. Cheng Hoi Wa ([redacted]) a five year old girl developed fever on 13-3-03, attended school for 2 days before admission on 16-3-03. There were typical chest x-ray changes. Both parents have been admitted with pneumonia, the mother is in the ICU.

3. Ko Yuk Lung [redacted] is the nephew of the index case. He has consolidation on CT scan. Five other members of the family are admitted with pneumonia.

This condition is posing a severe threat to our community. I urge you to urgently consider all possible measures including quarantine of patients and contacts to contain this outbreak before it is too late.

Yours sincerely,

SC Sydney Chung
Dean

SC/cm

醫院管理局
HOSPITAL
AUTHORITY

何兆煒醫生 行政總裁
Dr William HO, JP
Chief Executive

各位同事：

想不到自從非典型肺炎爆發以來，我寫給大家的第三封信會是在病榻上進行。我入院至今已五天，外面最新情況還不及你們知得多，倒不如談談個人經歷。

目前我的病況穩定，與其他非典型肺炎病人的病徵差不多，時燒時退，X-光片顯示病毒正侵襲我的右肺中葉，幾日來醫生注射特效藥控制著，沒有擴大也不見縮少，好像跟我拉鋸著，第一回合未立刻完全定勝負。不過這個病是要經過一段時間才復元的，急也急不來，醫生說走勢不錯，只是要多住兩星期醫院，這也沒法。我的靜脈對藥比較敏感，已報銷了幾條，現在主要靠頸上「中央線」輸藥。同事們悉心的照顧、超卓的技術，我十分放心，更使我感受到我們醫管局的服務世界一流。我亦肯定其他病人一定也享有如此優良服務，否則何以每日收到病人及家屬的讚揚信，總是如雪片飛來。加上這次肺炎事件，全局各醫院所有同事表現出高度專業、捨己精神，獲得各界日夜公開讚賞、贏盡全港市民的愛戴，在此再一次向各同事致敬。

不知道這是否天意逼我暫停下來。自從大半個月前，威爾斯親王醫院出現醫護人員相繼病倒，引致院內外一片恐慌以來，我就不得不連續多天工作至深夜。眼看著前線同事因公惹病，面對生命危險，我作為大家的上司，感到極之難過。對於同事們一個一個的倒下去，而初期又未找到有效應付方法之時，我感到心急如焚，對於前線人手日漸緊絀、士氣大受打擊，我就覺得職責所在，一定要盡力支持他們、幫助他們。

回想三月十三日，我和梁智鴻主席夜探廣華醫院得病的三位同事，及威院的近二十位同事。翌日，我再到東區醫院探望七位染病同事。此後，我差不多每天都有到威院，有時是探患病同事，有時是與管理層開會，又或與專家教授們研究數據、追蹤線索。當然，我一直都有做足防禦措施，每次探望病人都有洗手，但想不到還是防不勝防。

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究竟自己如何染病，以我多次出入高危地帶，尤其是威院的"O"房、ICU 等，已很難準確估計。或許有人會問，為何我一定要身先士卒？但在當時，我深深感到威院同事的徬徨，甚至有一種被遺棄、困獸鬥的感覺。我希望我的出現，會為他們打打氣。更重要的，就是讓我直接感覺到同事的情緒變化，掌握下一步應如何應變。患病員工並不只是一系列數目字，士氣也沒有量度單位。但從一位同事口中說出：「我想看著我的兒子出世！」可以想像這怪病帶給他的極度恐懼，聞者無不動容。另一位醫科生屢次拔喉不成又屢次插喉，看著她的眼神由充滿希望至極度沮喪、怨憤，令人心酸（幸好她現已痊癒）。我最後到威院 ICU 的一天，看到個別仍在上班的同事儘管仍忙碌地盡著本分，但連多談一句的力氣都沒有了，乾澀的眼睛流不出淚水，倒是由別處到來的生力軍還帶來多少生氣。

三月十六日星期天晚上，我們在威院舉行緊急會議，決定把急症室的內科入院病人轉送別院，這點我上封信已提及。但兩天之後，形勢再度惡化，我們決定全面暫停急症服務，讓威院上下得以喘喘氣。二十日晚十時，接到馮醫生來電請我馬上到威院，發覺整個中大醫學院的教授都差不多到齊，院方管理層更不在話下。原來當天收了兩名社區家庭醫生，都是從 8A 病人的親屬到他們診所看病時感染。另一方面，他們對百多人的追蹤分析又有新線索，因此大家非常恐懼病毒真的已在社區蔓延，認為有關方面從這些資料再去徹查實刻不容緩。我對他們日夜思念公眾安危的精神感到由衷敬佩。在了解情況及掌握了一切來龍去脈後，我立刻在零晨時分聯絡衛生署，而翌日有關人員根據線索立即出動跟進，這是後話。

事不湊巧，就在為肺炎事件不停頻撲，同時又要應付日常大小會議之餘，還碰上我們社會醫學學院的大會。二十一日，各界貴賓開始到來。當晚，準確點應該是二十二日凌晨，我才撐著疲倦的身軀趕好關於 SARS 的講稿（就是大家現在於醫管局網頁看到的那篇），數小時後就已在早上的大會上作為首份文章發表。其後少不免又是一整天的活動至深夜，而午間我還偷了點時間再一次去威院探同事。當然，翌日我就病倒入院了。

事後看來，這一鼓蠻勁真的累事，還令家人和其他接觸過我的人受到威脅。幸好至今為止，他們都安好。但至少令大家擔心，為總部及醫院各同事帶來額外工作，百上加斤，在此十分抱歉。對各位的關懷問候，更加感激不盡。

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我在醫院與疾病周旋，但從電話、電視中知道肺炎仍有不斷蔓延跡象，大家必定忙得不可開交，但務必以我為鑑，先不要累壞自己。我在這裏眼巴巴看著，又幫不上忙，惟有從心底裡祝願大家保重身體，同心協力，互相支持，準備以堅毅的耐力，清醒的頭腦，沉著地去打這場硬仗。況且病毒原兇既已現形，快速測試法又及時趕到，治療成效獲得可喜成功，離開勝利之門還會遠嗎？望繼續努力、加油！

何兆煒

醫院管理局行政總裁
何兆煒醫生

二零零三年三月二十八日

[後按: 擱筆時驚聞馮康總監也不幸罹病，悵甚，與我豈不共同進退！惟望他能暫時拋開一切，專心養病，早日痊癒。]

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THE CHINESE UNIVERSITY OF HONG KONG

FACULTY OF MEDICINE

Executive Committee

Minutes of the Special Meeting (through video conferencing) of the Faculty Executive Committee held on Friday, 21 March 2003 at 10:15 a.m. in the Multi-function Room, 1/F, Postgraduate Education Centre, PWH and concurrently in Room 103, 1/F, Basic Medical Sciences Building, CUHK

Postgraduate Education Centre

Present	:	Professor S.C. Sydney Chung	(Chairman)
		Professor T.F. Fok	
		Professor Joseph Sung	
		Professor Tony Chung	
		Professor Dennis Lo	
		Professor Anil Ahuja	
		Professor P.A. Cameron	
		Professor Anthony Chan	
		Professor Augustine Cheng	
		Professor Helen Chiu	
		Professor Tony Gin	
		Professor Christopher Lam	
		Professor Dennis Lam	
		Professor K.S. Leung	
		Professor H.K. Ng	
		Professor C.A. van Hasselt	
		Professor Jean Woo	
By invitation	:	Dr. Fung Hong	
		Dr. S.F. Lui	
		Professor T.W. Wong	
In Attendance	:	Ms Jenny Jiang	
		Ms Louisa Lam	

Basic Medical Sciences Building

Present	:	Professor C.Y. Lee	
		Professor Moses Chow	
		Professor Walter K.K. Ho	
		Professor John Yeung	(vice Professor R.L. Jones)
		Professor Michael S.C. Tam	
		Professor D.R. Thompson	
		Professor Patricia Chow	(vice Professor David T. Yew for the first hour)
		Professor David T. Yew	
Joint Secretaries	:	Mrs. Alison Lee	
		Mr. Andrew Chan	
In Attendance	:	Ms Janet Chow	
		Ms Senia Ho	

1. Purpose of the Special Meeting

The Dean welcomed Dr. Fung Hong, NTE Cluster Chief Executive of the HA, Dr. S.F. Lui, Co-ordinator of Clinical Services of the PWH, and Professor T.W. Wong of our Department of Community and Family Medicine to this Special Meeting of the Executive Committee. He explained that this Special Meeting had to be called at short notice because the situation regarding SARS infection in Hong Kong had become very serious. Dr. Fung and Dr. Lui would be able to provide an update on the outbreak and in return they would have an opportunity to hear and share the Faculty's concern in this connection. Professor Wong had been invited to attend this meeting because he was among the handful of qualified epidemiologists in the territory. The purpose of the meeting was to ascertain (i) whether there was common understanding among the Faculty regarding the severity of the outbreak; and (ii) if it were generally recognized by Faculty members that the situation was indeed alarming, how best the Faculty should move forward to keep the public informed without at the same time giving rise to panic within the community or to other undesirable repercussions.

2. Situation Update

An update on the SARS situation was given by the Dean and Dr. Lui, as follows:

(i) Figures released by the Government were:

Infected : 165 (96 health workers, including medical students, and 69 others)
Deaths : 6

(ii) The patient who first brought SARS to Hong Kong was, as reported by the Department of Health, the professor from the Sun Yat-sen University of Medical Sciences, Guangzhou, who died in Kwong Wah Hospital on 4 March.

(iii) The index patient who contracted the virus and spread the first layer of SARS infection to PWH hospital staff and our own medical students, was identified as a 26-year-old who visited the Guangzhou professor during the latter's stay at the hotel in Mongkok. His mother and other relatives were also infected.

(iv) SARS was a very virulent and highly contagious disease. Anyone who came into close contact with the infected would get it quite easily. In all, 7 cardiologists, 10 MED 3 and 7 MED 5 students and 18 out of the 20 nurses who tended Ward 8A at PWH or visited there had been infected. Of the 100 or so cases admitted to PWH, 2 who had had other chronic illnesses passed away.

(v) As some of those infected had at some time attended the clinics of general practitioners outside of the hospital setting, some private doctors also contracted the disease. It was known that 4 GP's had been admitted to hospital for treatment of SARS.

(vi) It was most probable that the disease had spread to the community, judging from hospital admission statistics. Infection had not been restricted to the health workers at PWH who tended Ward 8A, but had spread to include lay persons of all walks of life and residing in different localities. This was probably due to the fact that the incubation period of SARS was long, lasting between 3 to 7 days; and people who were infected were not aware of it or did not

show any symptoms or suffer significant discomfort to warrant investigation or treatment, but continued to go about their everyday activity, thus further spreading the disease. Also, there were some cases where the patients' circumstances of infection could not be traced. This suggested that there could be more than one index patient or one source of origin of infection.

3. Treatment for SARS

Professor Sung reported on the SARS cases under the care of his team at PWH. He informed the meeting on the trauma and frustration experienced by the patients and on their chest x-ray findings generally. Although there was still no known or effective drug or medication for management or treatment of the disease, a very high percentage of the cases showed improvement on being given both Ribavirin and steroids. Some patients were already well on the path to recovery.

4. The General Concern

The Dean expressed his grave concern about the situation of SARS in Hong Kong. In his view, the disease had broken out to the community and if the public were not alerted of this, the battle to combat the disease in the community could be long drawn out and difficult as there was no quick method of detection of SARS and no easy cure as yet. The cost could be tremendous.

The meeting generally shared the Dean's concern and some members echoed the Dean's fear over the public being misled by recent official statements to the effect that the SARS situation could be contained within two weeks. Professor Jean Woo believed the disease was still quite prevalent in Guangdong where the first case was first reported in November 2002. So far, a report of 306 cases with 5 deaths had been made officially by the central government, but these figures could well be an understatement. Professor T.W. Wong also expressed the view that SARS seemed to be still going on in Guangzhou after two or three rounds. It was therefore most unlikely that SARS could be cleaned up in Hong Kong in two weeks.

5. An Epidemiologist's View

Professor T.W. Wong further explained to the meeting why in his view the situation was really bad. He said that if no proper advice was given and the public was left to draw its own conclusions, further and rapid transmission within the community was very likely. To protect the public, strict measures needed to be taken, such as:

(i) Quarantine

To restrict the contact of those infected with the general healthy public. This would be a very drastic measure. Hong Kong's only experiences of quarantine had been during the plague in the 1910's and the cholera outbreak in 1960's.

(ii) Very vigilant surveillance of the disease

Public health staff to monitor cases on a daily basis and take appropriate action.

(iii) Passive surveillance

Public health staff to give advice and ask people to come forward if anything wrong were detected. This was what the Government Department of Health was doing at the moment,

which in his view, was not sufficient.

Professor C.Y. Lee was concerned about the free and busy traffic between China and Hong Kong. There could easily be new index cases from across the open border unless the flow could be curbed at an early stage. He would be inclined to quarantine families with known infected cases. He further remarked that when one student in a United College hostel became infected, the Student Union asked for the entire College premises to be sterilized against infection.

6. Actions Taken by the Dean

Contrary to assertions made by health officials in the past several days, the Dean was convinced that SARS had spread through the first layer. Through attendance at private clinics, infected patients had unwittingly carried the virus to the community. He deeply believed that the health of Hong Kong people was in danger.

The Dean called the Director of Health two nights before the date of this meeting and intimated to her his worst worries. He had also sent a letter to her by fax and mail to convey his concerns. In a TV appearance on 17 March, he also hinted at the possibility of an outbreak and informed the public of his fears. But it seemed that his efforts had been futile, and that none of the official actions in the past two days showed any sign of the Administration heeding his advice. He remarked that being a surgeon and not an epidemiologist, he could not claim to be an authority on public health or the outbreak of diseases. When the Director said that there was no outbreak in the community, he had no reason not to believe her, although deep down inside, he strongly suspected that she was wrong.

At a meeting held the day before, the Dean took the opportunity of voicing his view and worries, which were shared and supported by the senior clinicians attending. He therefore considered it necessary to bring his thoughts to the collective wisdom of the Faculty Executive Committee. Hence this Special Meeting.

7. The Faculty's View on Outbreak

Having heard the update of the SARS situation by the Dean and Dr. Lui, the Dean's account of the series of events which led to the Special Meeting, Professor T.W. Wong's view as an epidemiologist, and the report by Professor Sung and other clinicians who were in or close to the frontline combating the disease, members of the Faculty Executive Committee present at the meeting supported the Dean's view that an outbreak of SARS to the community was at the doorsteps, if not already there. As a medical school, the Faculty would have the responsibility of informing the profession and the community of this imminent disaster.

Expressing his strong support for the Faculty's view, Professor Sung proposed the following for the meeting's consideration:

(i) It was indeed obligatory to tell all professionals, via all available channels, what the conditions looked like and ask them to protect themselves and their patients.

(ii) Even if the Department of Health was not seen to be doing its work properly or fast enough, it might be counter-productive to contradict the Department or slight its work. Recognition must be given for the good intentions behind the actions.

(iii) According to Professor Yuen Kwok Yung of HKU who was also working on the microbiology of the virus and in some ways collaborated with the Faculty on this, the Secretary for Health and Welfare, Dr. E.K. Yeoh, had discussed with him the Government's sensitivity on the issue of a possible community outbreak. However, any message or information from PWH would take at least 48 hours before it could be validated and passed on to Dr. Yeoh. This was the way the Government handled things. The Faculty might have to organize its data and wait for the Government to react, which would take time.

In connection with (iii) above, the Dean reported that he understood that the HA Chief Executive, Dr. William Ho, had also spoken to Dr. C.H. Leong, Chairman of HA, who agreed to keep the matter under close scrutiny and to increase places in Princess Margaret Hospital to accommodate infected patients.

(Dr. S.F. Lui and Dr. Fung Hong left the meeting at this juncture.)

8. The Faculty's View on Action

Members then aired their views on the course of action to be taken, the gist of which were summarized as follows:

(i) Professor T.W. Wong proposed the following:

(a) As experts and responsible doctors, the Faculty could issue serious warning to the community.

(b) To warn the medical profession.

(c) To suggest to the Department of Health to step up control measures and surveillance.

(ii) Professor Dennis Lam asked if Dr. E.K. Yeoh could not see the imminent danger to the community, what other channels the Faculty could take to warn the public. One possibility was to work through the Honourable C.H. Tung, the Chief Executive of HKSAR, which would be the final try to reach the Administration. If this failed, the Faculty could then approach the community but a timeframe would be needed. If the Government could be convinced, the course of action could follow a different route.

(iii) Professor Walter Ho and Professor T.F. Fok considered that the Faculty needed more time and should not seem to be riding on its moral high horse if the Faculty wanted to get things done, and done properly. The Faculty had to understand why China had not taken action. What if the Faculty's action resulted in a big panic in the community? What if the Government would not heed the Faculty's advice but turn its back to discredit us? How could the public and the Chinese University be protected in the best way?

(iv) Professor Andrew van Hasselt would like to see a common, crystallized presentation with information which would be the Faculty's prioritized and easy to understand. The presentation should be for shorter than 15 minutes for the public to easily comprehend.

(v) Mr. Andrew Chan urged the Faculty not to take any action which could be looked upon by the HA and the Department of Health as being hostile. The Faculty could send emails with hard

data to all GP's to show the Faculty's concern. The Faculty needed to educate patients and the GP's to take precautions without offending Dr. E.K. Yeoh and Dr. Margaret Chan as far as possible.

Members in general agreed on the need for a strategy to talk to the Administration and convince them, and not to antagonize them, to do something to contain the outbreak.

The Dean would talk with the Vice Chancellor and draft a statement listing out the concrete steps. Dr. C.H. Leong would be approached for a joint statement with HA as necessary.

The Dean agreed with Professor Peter Cameron that he should act fast; if not, he would be negligent. However, Professor Tony Chung advised that perhaps the Faculty should proceed with prudence for the purpose of doing well, rather than rushing into issuing a statement and then facing total confusion.

9. Conclusion

After deliberation, the meeting agreed on the following:

(i) To get data from infection control personnel for Professor T.W. Wong to check.
(ii) To inform the GP's and professional bodies of the necessary precautions to take.
(iii) Professor T.F. Fok, Professor Tony Chung and Professor Peter Cameron to request a meeting with Dr. C.H. Leong (if possible by 3:00 pm) and to present to him the Faculty's concern and advice. If the advice was not heeded, the Faculty would then proceed to discuss further action at a meeting to be held on the next day.

(Post meeting note: Professor Fok and company reported of a very satisfactory meeting with Dr. Leong. Dr. Leong was very receptive and shared his concern for an outbreak of the disease to the community. He agreed to issue warnings to the public in general and the medical profession in particular, with advice and instruction on how best to protect against infection.)

There being no other business, the meeting was adjourned at 11:30 a.m.

Minutes confirmed on April 16, 2003.

Professor S.C. Sydney Chung
Chairman

16.4.2003

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Your Ref:

Our Ref:

21st March 2003

Dear Colleagues,

The dreaded SARS is causing an unprecedented threat to our community. It is heartbreaking to see our fellow colleagues, in private practice as well as in public hospitals, falling ill one by one. It is particularly distressing to see their family members also coming down with the disease.

I would like to share with you some lessons we learned at the Prince of Wales Hospital in the last few days. I hope these points are useful to you.

1. The disease is highly infectious, please be VERY VIGILENT AND METICULOUS in your infection control procedures.
2. Available data suggest the mode of spread is by droplets and possibly formites.
3. Five doctors and 2 infection control nurses at the Prince of Wales Hospital took nasopharyngeal aspirates from some 75 patients on 10th March when the outbreak was first detected. They wore surgical masks and gloves. All 7 staff remain asymptomatic up to now.
4. N95 masks need to be worn close to the face with no leak. It is quite uncomfortable if worn for a long time. Some colleagues wear a paper mask underneath. This completely destroys the purpose of the mask as air can leak through.
5. RSV, which is a similar virus, can survive for up to 6 hours on surfaces. To avoid possible spread via formites disposable gloves should be worn and changed between patients.
6. Hand washing before and after examining patients.
7. Surfaces should be cleaned daily with 1000ppm hypochlorite solution or 70% alcohol for metallic surfaces.
8. I would suggest you to offer surgical masks to your patients in your clinic for the protection of your staff and other patients.

Stay well, live long and prosper!

Sydney Chung

faxed to HKMA on 21/3/03