FACULTY OF MEDICINE • THE CHINESE UNIVERSITY OF HONG KONG
香港中文大學 • 醫學院
Department of Medicine & Therapeutics 內科及藥物治療學系

Prince of Wales Hospital
Shatin, New Territories, Hong Kong
Tel: (852) 2632 3128 / 2632 3174
Fax: (852) 2637 3852 / (852) 2637 5396

香港新界沙田
威爾斯親王醫院
電話：(852) 2632 3128 / 2632 3174
圖文傳真：(852) 2637 3852 / 2637 5396

17th May 2004

Dr Hon LAW Chi-Kwong, JP
Chairman
SARS Select Committee
Legislative Council Building,
8 Jackson Rd.,
Central, HK.

Dear Dr Law,

My colleagues and I were astounded by the alleged accusations, leaked out to the media on 5th May 2004, against Professor Joseph Sung and the handling of the major outbreak of SARS at the Prince of Wales Hospital (PWH) in 2003.

During my participation at the LegCo SARS hearing on 20th Jan 2004, I tried my best to provide members of the Select Committee with clinical information about the management of SARS, including the case of YY, during Mar 2003 with key references. Without sound medical knowledge in the interpretation of basic investigations such as the chest radiographs of YY and clinical experience in the handling of SARS, it would be exceedingly difficult for the Select Committee to come up with impartial judgement about PWH management of the disease during the major outbreak. In contrast, the SARS Expert Committee had the advantage of including 2 medical experts from the mainland. They were able to interpret the clinical events and radiographic changes of SARS (including the case of YY) in the light of their practical experience in the management of the disease. In addition, there were among the panel a number of world-class experts with strong background knowledge in Public Health and Epidemiology of Infectious Diseases.

With retrospective medical knowledge and analysis, the symptom onset of YY on 14th Mar 2003 (Day 1), the right lower lobe infiltrate on 15th Mar 2003, the development of bilateral lung disease on 22nd Mar 2003 (second week of disease), and further deterioration requiring intubation and intensive care support on 23rd Mar 2003 were consistent with progression of SARS from onset of phase 1 to phase 2 of the disease.[1] Similar rates of progression have been observed in our patients at the PWH cohort,[2,3] the Amoy Gardens cohort,[4] and other patients with renal failure on haemodialysis.[5,6] It is important to note that SARS patients with background renal failure have similar radiographic progression to other patients at the initial clinical phases although the renal patients do have a stormy clinical course with prolonged shedding of virus in their excreta.[1,5,6] In a report published by the Kwong Wah Hospital, all 4 dialysis

patients who had contracted SARS developed respiratory failure requiring mechanical ventilation on days 9 through 12.[6] **Together with a mean incubation period between 4 to 7 days before his onset of symptoms, the data would indicate that YY had acquired SARS well before his presentation to PWH on 15th Mar 2003.**

While I support the LegCo's independent investigation on the handling of SARS, I strongly urge the Select Committee to seek independent external opinion from experts, either locally or from overseas, who have had practical experience in the management of SARS, to review the case management of YY during the period 15th to 19th Mar 2003. It must be stressed that the aetiology of SARS (SARS CoV) was only announced on 22nd Mar 2003 and the first generation diagnostic tests for SARS such as PCR and serology were only available on 1st and 23rd April 2003 at PWH respectively.

I have enclosed 6 references for your information. I sincerely hope that the Select Committee members can give frontline health care workers a fair and unbiased verdict.

Yours sincerely,

David Hui

David SC Hui
Associate Professor & Head of Division of Respiratory Medicine
MBBS, MD, FRACP, FRCP (Lond, Edin, Glasg), FCCP, FHKCP, FHKAM(Med)
Department of Medicine & Therapeutics

References:

1) Kwan BC, Leung CB, Szeto CC, et al. Severe acute respiratory syndrome in a hemodialysis patient. Am J Kidney Dis 2003;42:1069-1074.
2) Hui DS, Sung JJ. Editorial: Severe acute respiratory syndrome. Chest 2003;124:12-15.
3) Sung JJ, Wu A, Joynt GM, et al. Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. Thorax 2004;59:414-420.
4) Peiris JS, Chu CM, Cheng VC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361:1767-1772.
5) Tang HL, Cheuk A, Chu KH, et al. Severe acute respiratory syndrome in haemodialysis patients: a report of two cases. Nephrol Dial Transplant 2003;18:2187-2181.
6) Wong PN, Mak SK, Lo KY, et al. Clinical presentation and outcome of severe acute respiratory syndrome in dialysis patients. Am J Kidney Dis 2003;42:1075-1081.

CASE REPORTS

Severe Acute Respiratory Syndrome in a Hemodialysis Patient

Bonnie Ching-Ha Kwan, MBBS, MRCP(UK), Chi-Bon Leung, MBChB, FRCP(EDIN), Cheuk-Chun Szeto, MD, MRCP(UK), Angela Yee-Moon Wang, MBBS, MRCP(UK), and Philip Kam-Tao Li, FACP, FRCP

• **Severe acute respiratory syndrome (SARS) is a highly infective disease caused by a newly identified coronavirus. We described the clinical course of the first long-term hemodialysis patient who developed SARS in the literature, and our experience in performing hemodialysis for this patient. Such patients may present with a less typical clinical picture, making diagnosis difficult. In this patient, the course of disease and duration of viral shedding was apparently prolonged, thus highlighting the need for increased infection control. Despite worsening the anemia in renal failure patients by causing hemolysis, ribavirin is well tolerated after dosage adjustment. Difficulties of diagnosis, infection control, and treatment of SARS in renal failure patients are discussed in this report.** ***Am J Kidney Dis*** **42:1069-1074.**

INDEX WORDS: Severe acute respiratory syndrome (SARS); atypical pneumonia; coronavirus; renal failure.

SINCE MARCH 2003, there have been cases of severe acute respiratory syndrome (SARS) reported in over 30 countries around the world, including China, Vietnam, Singapore, Taiwan, Germany, France, Italy, Thailand, United Kingdom, the United States, and Canada.[1-5] In Hong Kong, over 1,500 cases have been reported to date, with more than 200 deaths. Since SARS is highly contagious by close contact,[1] infection control in dialysis units is a topic of utmost importance for practicing nephrologists in epidemic areas. We hereby describe our experience in the management of a long-term hemodialysis patient who developed SARS.

CASE REPORT

A 33-year-old man was diagnosed with systemic lupus erythematosus (SLE) in 1987. He progressed to end-stage renal disease and was started on maintenance hemodialysis via a left forearm arteriovenous fistula in 1997. His medications include labetalol, nifedipine retard, calcium carbonate, erythropoietin-β, ferrous sulphate, and folic acid supplements. His lupus has been quiescent since dialysis and he does not receive maintenance steroid or other immunosuppressive therapy. Apart from tertiary hyperparathyroidism awaiting parathyroidectomy (parathyroid hormone of 105 pmol/L) and anemia requiring 5,000 U erythropoietin weekly intravenously and occasional transfusion, he remained stable on dialysis.

On the day of his first presentation in March 2003, he was noted to have a fever of 38°C on arrival for a routine hemodialysis session. He also had chills and rigors, but there was no cough, sputum, dyspnea, or diarrhea. On examination, there were some crepitations in the right lung base. Because of his occupation, he made frequent travels to and stayed in southern China. There was no definite history of contact with SARS patients. He was admitted to the hospital after dialysis for the investigation of fever. Chest radiograph on admission showed right lower lobe consolidation (Fig 1A). His peripheral white cell count was $7 \times 10^3/\mu L$ (7×10^9/L) (normal range [NR], 4.0 to $10.8 \times 10^3/\mu L$ [4.0 to 10.8×10^9/L]), and his absolute lymphocyte count was $0.5 \times 10^3/\mu L$ (0.5×10^9/L) (NR, 1.3 to $3.6 \times 10^3/\mu L$ [1.3 to 3.6×10^9/L]). The platelet count was $113 \times 10^3/\mu L$ (113×10^9/L) (NR, 140 to $380 \times 10^3/\mu L$ [140 to 380×10^9/L]). Serum creatinine kinase (CK) level was 144 IU/L (NR, 42 to 218 IU/L). He was initially suspected to have SARS because there was a cluster of cases in the territory and because of his contact in southern China. However, the rapid antigen test of his nasopharyngeal aspirate later revealed influenza A virus. Thus, the subsequent working diagnosis at that time was influenza, with possible superimposed bacterial pneumonia. He became afebrile with improving chest radiograph within 48 hours after treatment with cefotaxime, levofloxacin, and oseltamivir. He was discharged with a course of oral medication 4 days later.

Our patient noticed a dry cough and dyspnea subsequently after discharge. When he came back for his hemodialysis session 3 days after his discharge, he was again noticed to have a fever and was admitted. His peripheral white cell count was $8.0 \times 10^3/\mu L$ (8.0×10^9/L), lymphocyte count $0.6 \times 10^3/\mu L$ (0.6×10^9/L), and platelet count declined to $70 \times 10^3/\mu L$ (70×10^9/L). His activated partial-thromboplastin time was prolonged at 59.7 seconds (NR, 24.8 to 38.0

From from Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, China.

Received May 29, 2003; accepted in revised form July 30, 2003.

Address reprint requests to Philip Kam-Tao Li, FACP, FRCP, Consultant and Chief of Nephrology, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong. E-mail: philipli@cuhk.edu.hk

0272-6386/03/4205-0028$30.00/0
doi:10.1053/S0272-6386(03)01083-7

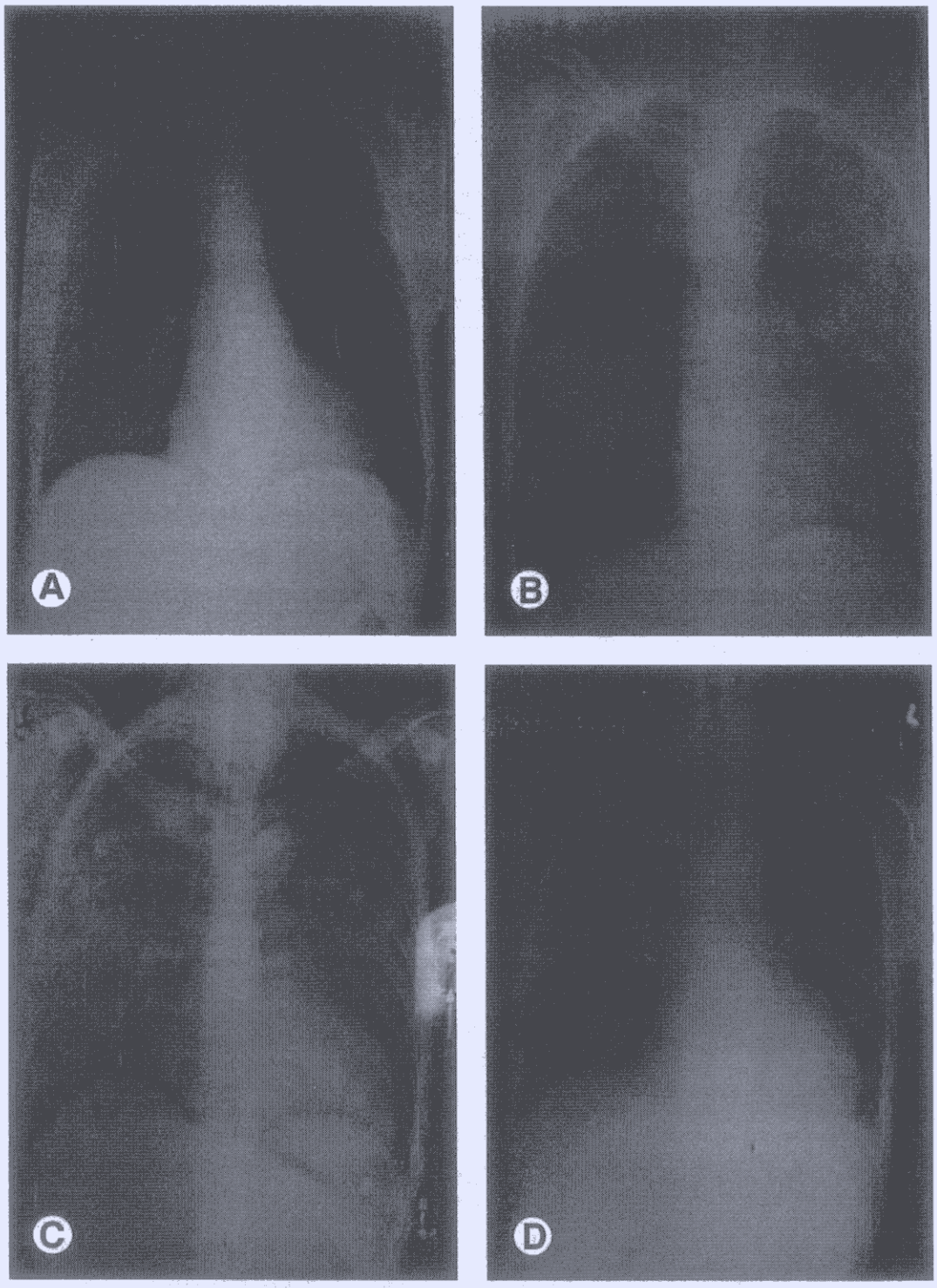


Fig 1. Serial chest radiograph: (A) on initial presentation; (B) 8 days after initial presentation, immediately before the first admission to intensive care unit; (C) 5 weeks after initial presentation, showing persistent bilateral pulmonary infiltrate despite ribavirin and corticosteroid; and (D) 8 weeks after initial presentation, showing slowly resolving pulmonary infiltrate.

seconds), and his D-dimer was elevated at 1,483 ng/mL (NR, <500 ng/mL). The serum CK level rose to 903 IU/L and the lactate dehydrogenase (LDH) level was 351 IU/L (NR, 87 to 213 IU/L). Alanine aminotransferase (ALT) was normal at 14 IU/L (NR, <58 IU/L). A repeated chest radiograph showed increasing right lower lobe consolidation. Based on his clinical features and history of travel, he was considered to fulfill the case definition of SARS given by the World Health Organization (WHO).[6]

Levofloxacin and cefotaxime were continued. He was put on 600 mg oral ribavirin thrice daily (30 mg/kg/day). However, his condition worsened rapidly and he was transferred to the intensive care unit the next day. He required endotracheal intubation and mechanical ventilation. A repeat chest radiograph showed bilateral pulmonary infiltrate (Fig 1B). Polymerase chain reaction (PCR) of a later stool sample identified the presence of SARS-associated coronavirus RNA. Paired serum subsequently also confirmed a 4-fold increase in the immunoglobulin G (IgG) titer of SARS-associated coronavirus. In view of the rapid deterioration and the possibility of a hyperactive immune system contributing to the disease process,[1,7] he was also treated with 500 mg intravenous methylprednisolone daily for 3 days, followed by 60 mg oral prednisolone daily (1 mg/kg/day). His condition improved and he became afebrile after methylprednisolone. He was extubated and discharged to a general ward designated for SARS patients 4 days later.

Hemodialysis Management

As soon as SARS was suspected during the second hospital admission, our patient received hemodialysis in a room with isolation facilities designated for SARS patients. Infection control measures of the dialysis unit staff followed the recommendation by the WHO,[8] with waterproof disposable gown, cap, gloves, face shield, and N95 facemask. A designated Gambro AK100 dialysis machine (Gambro, Lund, Sweden) was used with ordinary tap water supply passing through the Purtrex model PX10-9-7/8 filter (10-μm polypropylene; Osmonics Inc, Minnetonka, MN) without reverse osmosis or other water treatment. We used Fresenius F7 polysulfone dialyzer (Fresenius Medical Care, Bad Hamburg, Germany) without reuse. Spent dialysate was drained directly to the ward washbasin, which was connected to the main sewage drain by a U-trap. After a session of hemodialysis, the dialyzer and all blood tubings were discarded as infectious waste. Unspent dialysate concentrate and sodium bicarbonate cartridge were also discarded. The dialysis machine was disinfected by sodium hypochlorite solution according to the manufacturer's instruction. The dialysis machine was kept in a room in the SARS isolation ward between dialysis sessions and was only used for patients who had contracted SARS and required dialysis. Spent hypochlorite solution and rinse water were drained to the same washbasin, which did not receive additional disinfection.

Clinical Course

The subsequent clinical course and treatment are summarized in Fig 2. Despite some clinical improvement, our patient had intermittent fever, and the pulmonary infiltrate in his chest radiograph waxed and waned. The treatment was changed to 200 mg intravenous ribavirin every 8 hours for 1 week, followed by 600 mg oral ribavirin thrice daily. He received a further course of 500 mg intravenous methylprednisolone daily for 3 days on day 24 since fever onset. However, his oxygen requirement worsened, and there was a progression in the pulmonary infiltrate of his chest radiograph. Although he did not require endotracheal intubation, he was readmitted to the intensive care unit for close monitoring on day 28 (since fever onset).

In view of the protracted disease course and lack of radiographic improvement with ribavirin and corticosteroid (Fig 1C), he was further treated with 200 mL of convalescence plasma from a recovered SARS patient, and 5 mL/kg IgM-enriched human immunoglobulin (Pentaglobulin; Biotest, Dreieich, Germany) for 3 days on day 38 of his illness. He gradually improved, and his oxygen requirement was gradually reduced. Towards the end of the recovery phase, his oxygen saturation on room air remained above 96%. Since the patient became asymptomatic, a formal pulmonary function test was not performed to avoid inadvertent spreading of residual coronavirus during the forced expiration of spirometry. Chest radiograph improved slowly and continued to show bilateral basal infiltrate 8 weeks after the initial presentation (Fig 1D). A high-resolution computed tomography of thorax showed diffuse ground glass opacification, bilateral patchy consolidation, and fibrosis, features compatible with recovery phase of acute respiratory distress syndrome (ARDS) (Fig 3). He was given a total 4-week course of ribavirin and was put on 0.5 mg/kg/day oral prednisolone as maintenance to cover the ongoing pulmonary inflammation.

Despite adjustment in the dosage of ribavirin, he still experienced worsening of his anemia, requiring supportive transfusion. He received transfusions of a total of 20 U during his admission for about 3 months, compared to 10 U in the preceding 6 months (Fig 4).

PCR for RNA of SARS-associated coronavirus in the stool specimen performed on day 53 was still positive, and then 3 consecutive stool specimens were negative for viral culture starting from day 64 to day 75 (Fig 2). The patient recovered and was considered to be no longer infectious.

DISCUSSION

In this report, we described the clinical course of the first long-term hemodialysis patient reported in the literature who developed SARS and our experience in performing hemodialysis for him.

The initial clinical presentation of our patient was similar to that of other SARS patients. In the case series of our hospital ,[1] most patients present with fever, rigor, myalgia, dizziness, and diarrhea. The majority had lymphopenia, thrombocytopenia, prolonged activated partial-thromboplastin time, elevated D-dimer, CK, LDH, and ALT.[1] In general, our patient followed the typical 3-phase course of the illness: viral replicative phase, immune hyperactive phase, and then pulmonary destructive phase.[9] In the first phase, symptoms are similar to upper

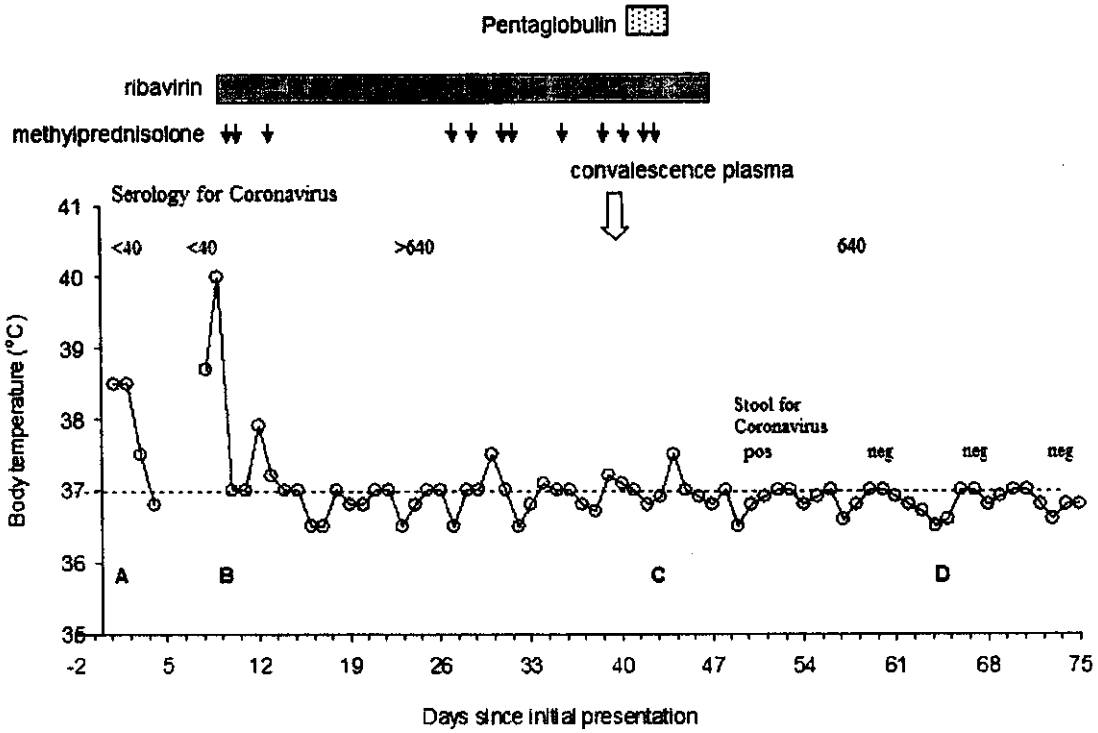


Fig 2. Fluctuation of body temperature. Bold letters along the X-axis indicate the time at which the corresponding chest radiograph in Fig 1 was performed. Note the temporal relationship between fever, radiographic change, and treatments given. Virology results including serology and stool specimen for coronavirus isolation are also shown.

respiratory infection with fever and myalgia. The second phase, due to immune response, causes febrile illness and rapidly increasing pulmonary inflammation with dyspnea. Postinflammatory fibrosis occurs in the third phase. However, our patient had an unexpectedly prolonged course of illness. He required hospitalization for more than 2 months, as compared to the average hospital stay of 14 to 25 days for other SARS patients.[1] The pulmonary infiltrate in his chest radiograph resolved only slowly and remained obvious almost 2 months after his initial presentation (see Fig 1D). Furthermore, PCR for SARS-associated coronavirus RNA was positive in his stool sample for almost 2 months. In other patients, the virus usually becomes undetectable in stool by week 5. It is postulated that renal failure patients cannot eliminate the SARS-associated coronavirus effectively because of their relatively depressed immunity. Similar observation has been described in other chronic viral infections of renal failure patients.[10]

We believe our patient probably contracted the SARS coronavirus during his travel to and stay in mainland China. Retrospectively, he fulfilled the WHO case definition of SARS[6] during his first presentation. The influenza A virus isolated from nasopharyngeal aspirate probably represented either a false-positive result or a genuine concomitant influenza A infection, which was endemic during that season in Hong Kong. It is important to note that neither serologic test nor PCR for SARS-associated coronavirus RNA was available when the patient was first admitted. Our patient highlights the difficulty in the diagnosis of SARS, as well as the need to consider double pathology when the circumstances are suspicious.

Our patient received dialysis in the renal unit along with the other patients during his hemodialysis on the day of his first admission, where patients were normally placed more than 3 feet from each other, and none of the other hemodialy-

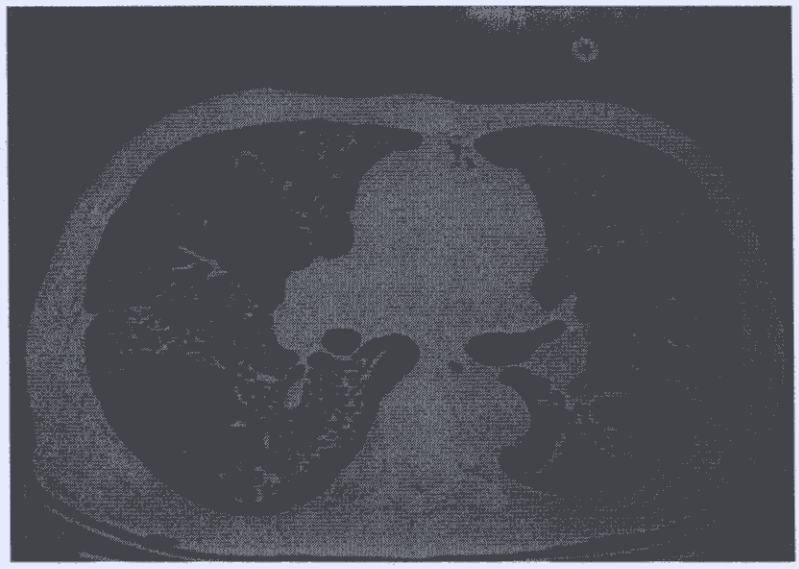


Fig 3. High resolution computed tomography of thorax 8 weeks after initial presentation. There is diffuse ground glass opacification, bilateral patchy consolidation, and fibrosis, features compatible with recovery phase of ARDS.

sis patients of the same session contracted the disease. Unfortunately, 2 dialysis nurses who took care of our patient during his early presentations developed SARS later. Fortunately, both of our nurses improved after treatment with ribavirin and corticosteroid. His subsequent hemodialysis was performed in isolation as described above.

Once the diagnosis of SARS was suspected in our patient, we worked closely with the hospital Infection Control Unit to enforce all the infection control measures (see above), and no more staff or other patients in the hemodialysis unit became infected. It is important to note that we allowed drainage of the spent dialysate through ordinary washbasin. We have not tested for the presence of SARS-associated coronavirus in spent dialysate of our patient. Since coronavirus is approximately 50 nm in diameter, it should not pass

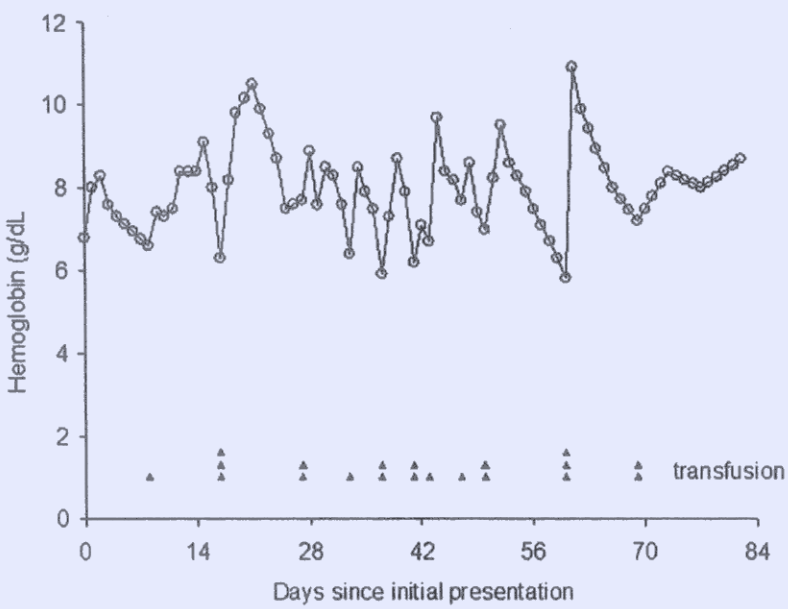


Fig 4. Time course of hemoglobin values and transfusions. Each triangle represents a unit of packed cell transfused. To convert hemoglobin in g/dL to g/L, multiply by 10.

through the conventional low-flux polysulfone membrane. However, the modern high-flux polysulfone dialyzer has a much larger pore size (for example, over 50% of the β2 microglobulin can be removed during a single session of dialysis[15]), and its use should be under great caution.

It is noted that the efficacy of the treatment regimen was not universally agreed.[11] Our patient was treated with ribavirin and steroid according to local experience.[1,7] Ribavirin is eliminated both by hepatic metabolism and renal excretion. There are few studies on the pharmacokinetics of ribavirin in patients with renal dysfunction. It is generally recommended that the dosage of ribavirin should be halved in patients with a glomerular filtration rate below 10 mL/min, and a supplemental dose should be administered after hemodialysis.[12] In fact, some studies found that it was necessary to reduce the dosage in order to maintain its plasma level[16] and to avoid significant hemolysis.[13,14] We followed the recommended dosage regimen adjustment in our patient.

In view of the resistant nature of the disease course in our patient, he was also given convalescence plasma and pentaglobulin. Both are being used as experimental treatments for SARS. Convalescence plasma contains neutralizing antibodies against coronavirus, and pentaglobulin has immunomodulating effects.[17] Both are used to halt the progression to pulmonary destructive phase.

In summary, we described a hemodialysis patient who contracted SARS with prolonged shedding of virus. With appropriate infection control measures, the staff with protective gear who were taking care of the patient were not infected. The use of ribavirin with appropriate dosage reduction was feasible in his treatment. Nephrologists need to be aware of the prolonged viral shedding and the possible infectivity of renal failure patients who have contracted SARS.

ACKNOWLEGMENT

We thank all the medical, nursing, and technical staff from the Renal Unit, Prince of Wales Hospital, Shatin, Hong Kong, for their dedicated care of our dialysis patient during the SARS epidemic.

REFERENCES

1. Lee NL, Hui DS, Wu AK, et al: A major outbreak of severe respiratory syndrome in Hong Kong. N Engl J Med 348:1986-1994, 2003

2. Tsang KW, Ho PL, Ooi GC, et al: A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med 348:1977-1985, 2003

3. Poutanen SM, Low DE, Henry B, et al: Identification of severe acute respiratory syndrome in Canada. N Engl J Med 348:1995-2005, 2003

4. Drosten C, Gunther S, Preiser W, et al: Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 348:1967-1976, 2003

5. Ksiazek TG, Erdman D, Goldsmith CS, et al: A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 348:1953-1966, 2003

6. World Health Organization: Case definitions for surveillance of severe acute respiratory syndrome (SARS). May 1, 2003. (http://www.who.int/csr/sars/casedefinition/en/) Accessed: May 20, 2003

7. So LK, Lau AC, Yam LY, et al: Development of a standard treatment protocol for severe acute respiratory syndrome. Lancet 361:1615-1617, 2003

8. World Health Organization: Hospital infection control guidance for severe acute respiratory syndrome (SARS). April 24, 2003. (http://www.who.int/csr/sars/infectioncontrol/en/) Accessed: May 20, 2003

9. Health, Welfare & Food Bureau, Hong Kong Government: SARS bulletin. May 12, 2003. (http://www.info.gov.hk/dh/diseases/ap/eng/bulletin0512.pdf) Accessed: May 20, 2003

10. Okuda K, Hayashi H, Yokozeki K, Kobayashi S, Kashima T, Irie Y: Acute hepatitis C among renal failure patients on chronic haemodialysis. J Gastroenterol Hepatol 13:62-67, 1998

11. World Health Organization: Management of severe acute respiratory syndrome (SARS). April 11, 2003. (http://www.who.int/csr/sars/management/en/) Accessed: May 20, 2003

12. Aronoff GR, Brier M, Erbeck KM, Ouseph R: Drug dosing in dialysis patients, in Owen WF, Pereira BJ, Sayegh MH (eds): Dialysis and Transplantation—A companion to Brenner & Rector's The Kidney. Philadelphia, PA, Saunders, 2000, pp 358-372

13. Bruchfeld A, Stahle L, Andersson J, Schvarcz R: Ribavirin treatment in dialysis patients with chronic hepatitis C virus infection—A pilot study. J Viral Hepatol 8:287-292, 2001

14. Kramer TH, Gaar GG, Ray CG, Minnich L, Copeland JG, Connor JD: Hemodialysis clearance of intravenously administered Ribavirin. Antimicrob Agents Chemother 34: 489-490, 1990

15. Hoenich NA, Katopodis KP: Clinical characterization of a new polymeric membrane for use in renal replacement therapy. Biomaterials 23:3853-3858, 2002

16. Svensson JO, Bruchfeld A, Schvarcz R, Stahle L: Determination of Ribavirin in serum using highly selective solid-phase extraction and high-performance liquid chromatography. Ther Drug Monit 22:215-218, 2000

17. Peiris JS, Chu CM, Cheng VCC, et al: Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: A prospective study. Lancet 361:1767-1772, 2003

pneumonia had not been the "friend of the aged." Nuland observed, "By and large dying is a messy business."

The stark contrast between the findings of the study by Heyland et al and the SUPPORT studies is troublesome. Is that difference due to cultural, attitudinal, and organizational differences for the delivery of critical care in Canada and America? The easy explanation that American patients want more treatment even at the risk of discomfort may or may not be true. After years of public and often acrimonious debate, á la Quinlan and Cruzan, physicians may feel unsettled with the following question. Are our medical practices regarding the dying more humane than they were 30 or 40 years ago?

Legally and ethically, a lot of ground has been covered. The death-with-dignity movement, living wills, durable power of attorney, and even assisted suicide (in Oregon) are society's attempts to deal with difficult bioethical issues. Yet why do most family members feel betrayed and burdened when their next of kin die in the ICU? The vigorous ethical debates do nothing for the anguish of surrogates caught in the maze of "full code" and "DNR" designations in the hospital. Practically, who decides the question of whether to institute mechanical ventilation or artificial feeding becomes more important than the essential goodness of the decisions.

Although the current study did not report too many out-of-control treatments, many families are fearful. Callahan[3] has referred to the illusion that we could master our medical choices: "Yet there is hardly below the surface, a remarkable and rising anxiety about dying—not necessarily death as such but the combination of an extended critical illness gradually transformed into an extended dying." His personal considerations border on accepting decline and death in an almost fatalistic manner, which is unusual in Western thought.

In an ever-shrinking world, we should not underestimate the effect of life-support technology and medical know-how in societies in which ethical and legal constraints are weak or nonexistent. One often hears of the "illegality" of discontinuing mechanical ventilation in dying patients! Yet, with few support systems, these interventions may be stopped abruptly after the financial ruin of the families. Unfortunately, the immorality of such practices is rarely questioned. Decision making in these highly paternalistic medical systems requires some scrutiny. I feel that we have an obligation to our colleagues in less affluent societies. A universal ethical code for the use of life-support technology in this young century is a laudable goal.

Vinod K. Puri, MD, FCCP
Southfield, MI

Dr. Puri is Medical Director, Critical Care Services, Providence Hospital & Medical Center.

Correspondence to: Vinod K. Puri, MD, FCCP, Medical Director, Critical Care Services, Providence Hospital & Medical Center, PO Box 2043, 16001 W 9 Mile Rd, Southfield, MI 48037-2043; e-mail: vpuri@ix.netcom.com

REFERENCES

1 Lynn J, Teno JM, Phillips RS, et al. Perspectives by family members of the dying experience of older and seriously ill patients. Ann Intern Med 1997; 126:97–106
2 Nuland SB. How we die: reflections on life's final chapter. New York, NY: Vintage Books, 1993; 141–142
3 Callahan D. The troubled dream of life: living with mortality. New York, NY: Simon & Schuster, 1993; 23

Severe Acute Respiratory Syndrome

Severe acute respiratory syndrome (SARS) is an emerging infectious disease with a formidable morbidity and mortality. In March 2003, there was a serious outbreak of SARS in Hong Kong.[1] Within a month, the disease also spread to Singapore,[2] Vietnam, Taiwan, Germany, Canada,[3] and the United States. As of May 10, 2003, 7,296 cases have been reported in 30 countries, with a death toll of 526.[4]

EPIDEMIOLOGY

The early cases of SARS probably occurred in southern China. In November 2002, there were many cases of severe pneumonia of unknown etiology in Guangdong Province in southern China, with a high rate of transmission to healthcare workers.[5] A 64-year-old physician from southern China, who visited Hong Kong on February 21, 2003, and died 10 days later of severe pneumonia, is believed to have been the source of infection, causing subsequent outbreaks of SARS in Hong Kong,[1,6] Vietnam, Singapore,[2] and Canada.[3] The index patients of these cities had been exposed to the Guangdong physician while they were visiting China or had been staying on the same floor of the same hotel. While investigating the outbreak of SARS in Hanoi, Dr. Carlo Urbani unfortunately contracted the disease and died.

SARS appears to spread by close person-to-

person contact via droplet transmission or fomite.[7] The high level of infectivity of this viral illness is highlighted by the fact that 158 patients were hospitalized with SARS within 2 weeks as a result of exposure to one single patient on a general medical ward in Hong Kong. The use of a jet nebulizer for administering bronchodilators to the index case, who presented clinically with community-acquired pneumonia, could increase the droplet load around the patient and, together with the overcrowding condition on the hospital ward, had contributed to this major hospital outbreak.[1] A novel coronavirus (CoV) is now identified as the main pathogen responsible for SARS,[8–11] although the presence of a metapneumovirus also was inferred in studies from Canada[11] and Hong Kong.[1] Several laboratories have recently completed the sequencing of the genome of the CoV that has led to the global epidemic of SARS, and they have noted that the SARS-CoV is not closely related to any of the previously characterized CoVs.[12–14]

Clinical and Laboratory Features

The mean incubation period of SARS is estimated to be 6.4 days (95% confidence interval, 5.2 to 7.7), and the mean time from onset of clinical symptoms to hospital admission varied between 3 and 5 days.[15] The major clinical features on presentation include persistent fever, chills/rigor, myalgia, dry cough, headache, and dizziness. Less common symptoms include sputum production, sore throat, coryza, nausea and vomiting, and diarrhea.[1–3] Watery diarrhea has been reported in a subgroup of patients 1 week down the clinical course. This was reported in a cohort infected in a community outbreak that has been linked to a faulty sewage system, presumably due to involvement of the GI tract via the fecal-oral route.[16]

Lymphopenia (*ie*, the destruction of both CD4 and CD8 lymphocytes), features of low-grade disseminated intravascular coagulation (*ie*, thrombocytopenia, prolonged activated partial thromboplastin time, and elevated d-dimer levels), and elevated lactate dehydrogenase levels (reflecting lung injury) and creatinine kinase levels (reflecting myositis) are common laboratory features of SARS.[1–3,8,11]

The clinical course of SARS appears to follow a triphasic pattern. Phase 1 (viral replication) is associated with increasing viral load and is clinically characterized by fever, myalgia, and other systemic symptoms that generally improve after a few days. Phase 2 (immunopathologic damage) is characterized by the recurrence of fever, oxygen desaturation, and radiologic progression of pneumonia with falls in viral load. The majority of patients will respond to treatment with a combination of ribavirin and IV steroids, but 20% of patients may progress into the phase 3, which is characterized by ARDS necessitating ventilatory support.[16] Compared with adults and teenagers, SARS seems to run a less aggressive clinical course in younger children, with no children in one case series[17] requiring supplementary oxygen.

Pulmonary Features

The radiographic appearances of SARS share features in common with other causes of pneumonia. At fever onset, almost 80% of patients with SARS have abnormal chest radiographs, all of which show airspace consolidation. All patients will eventually develop airway opacities during the course of the disease. In our study, the opacities occupy a peripheral or mixed peripheral and axial location in 88% of patients.[18] The predominant involvement of the lung periphery and the lower zone, in addition to the absence of cavitation, hilar lymphadenopathy, or pleural effusion, are the more distinctive radiographic features of SARS.[1,18] Radiographic progression from unilateral focal airspace opacity to either multifocal or bilateral involvement during the second week of the disease course, followed by radiographic improvement with treatment, is commonly encountered.[1,18] In one case series,[16] 12% of patients developed spontaneous pneumomediastinum and 20% of patients developed evidence of ARDS over a period of 3 weeks. In general, the incidence of barotrauma in ICU admissions seems higher than expected despite treatment with low-volume and low-pressure mechanical ventilation. Chest radiographs and CT scans have not demonstrated excessive hyperinflation or bullous lung disease, and it is difficult to explain this observation.[19]

High-resolution CT scanning of the thorax is useful in detecting lung opacities in patients with unremarkable chest radiograph findings. Common findings include ground-glass opacification, sometimes with consolidation, and interlobular septal and intralobular interstitial thickening, with predominantly peripheral and lower lobe involvement. The characteristic peripheral alveolar opacities are very similar to those found in patients with bronchiolitis obliterans-organizing pneumonia.[1,19]

The postmortem examination of lung tissues in SARS patients has shown various levels of disease severity. Changes include gross consolidation of the lungs, the presence of interstitial mononuclear inflammatory infiltrates, desquamation of pneumocytes in alveolar spaces, pulmonary edema with hyaline membrane formation, and cellular fibromyxoid-orga-

nizing exudates in airspaces, indicating the organizing phase of alveolar damage. Viral inclusions were not detected.[1,10]

Diagnostic Criteria

The diagnosis of SARS is based on clinical, epidemiologic, and laboratory criteria that have been laid down by the Centers for Disease Control and Prevention.[20] The clinical criteria include the following: (1) asymptomatic or mild respiratory illness; (2) moderate respiratory illness (*ie*, temperature, > 100.4°F or 38°C) and at least one respiratory feature (*ie*, cough, dyspnea, difficulty breathing, or hypoxia); (3) severe respiratory illness (features of the second criterion and radiographic evidence of pneumonia, the presence of respiratory distress syndrome, autopsy findings consistent with pneumonia, or the presence of respiratory distress syndrome without an identifiable cause). The epidemiologic criteria include travel (including transit in an airport) within 10 days of the onset of symptoms to an area with current, recently documented, or suspected community transmission of SARS, or close contact within 10 days of the onset of symptoms with a person known or suspected to have SARS infection. Laboratory criteria include the following: (1) the detection of an antibody to SARS-CoV in specimens obtained during acute illness or 21 days after illness onset; (2) the detection SARS-CoV RNA by reverse-transcriptase polymerase chain reaction (PCR) that was confirmed by a second PCR assay by using a second aliquot of the specimen and a different set of PCR primers; or (3) the isolation of SARS-CoV. A case of *probable SARS* is defined as having met the clinical criteria for severe respiratory illness of unknown etiology with onset since February 1, 2003, and epidemiologic criteria, irrespective of the laboratory result. A case of *suspect SARS* is defined as having met the clinical criteria for moderate respiratory illness of unknown etiology with onset since February 1, 2003, and epidemiologic criteria, irrespective of the laboratory result.[20]

Treatment

The treatment of SARS has been empirical during the recent outbreak. Anecdotal experience using a combination of ribavirin and steroids has been described by two studies in Hong Kong.[1,21] Oral ribavirin (1.2 g tid orally or 400 mg q8h IV) and corticosteroids (*ie*, prednisolone, 1 mg/kg/d) were prescribed as combination therapy.[1] During phase 2, when there was radiologic progression of pneumonia and/or hypoxemia, IV high-dose methylprednisolone, 0.5 g daily for up to 6 doses in most cases, is administered to prevent immunopathologic lung injury, with the rationale that progression of the pulmonary disease may be mediated by the host inflammatory response.[16] The majority of our cohort (90% of 138 patients) appeared to have a favorable response to the combination treatment with resolution of fever and lung opacities within 2 weeks, whereas about 23% and 14%, respectively, of the same cohort required ICU admission and invasive ventilatory support.[1] The use of ribavirin therapy in SARS patients is associated with significant toxicity, including hemolysis (76% of patients) and a decrease in hemoglobin of 2 g/dL (49% of patients), elevated transaminase levels (40% of patients), and bradycardia (14% of patients).[3] Any treatment regimen for SARS needs to be tested with a randomized placebo-controlled design. New antiviral agents and immunomodulating agents are also under investigation.

Noninvasive positive-pressure ventilation has been used for treatment with some success in a small number of SARS patients with respiratory failure.[21] However, therapy with noninvasive positive-pressure ventilation should be carried out only if there is adequate protection for the health-care workers (*eg*, an isolation room with adequate air exchange) because of the potential risk of viral transmission via mask leakage and flow compensation causing the dispersion of a contaminated aerosol.

Prognosis/Outcome

The calculation of case fatality rates in the situation of an emerging epidemic is difficult, but it has been estimated to be 13.2% (95% CI, 9.8 to 16.8%) for patients < 60 years of age and 43.3% (95% CI, 35.2 to 52.4%) for those ≥ 60 years of age.[15] The prognostic factors associated with a poor outcome (*ie*, ICU admission or death) include age,[1,15,16] chronic hepatitis B treated with lamivudine,[16] high peak lactate dehydrogenase,[1] high neutrophil count on presentation,[1] or presence of diabetes mellitus or other comorbid conditions.[3]

In conclusion, with the recent onset of the SARS epidemic worldwide, research on the development diagnostic tests and an effective treatment is urgently needed. We hope that the availability of the genome sequence of the SARS-CoV[12–14] will facilitate efforts to develop new and rapid diagnostic tests, antiviral agents, and vaccines in the long run. SARS patients who have recovered from the acute illness should be monitored carefully for the possibility of continued viral shedding[16] and the potential development of pulmonary fibrosis or late postviral complications. The prevention of spread is most important for this highly infectious disease. Isolation facilities, strict precautions against droplet exposure (*ie*, hand hy-

giene, and the wearing of gowns, gloves, N95 masks, and eye protection) among health-care workers managing SARS patients,[22] the avoidance of the use of nebulizers on a general medical ward,[1] contact tracing, and quarantine isolation for close contacts are all important measures.

David S.C. Hui, MD, FCCP
Joseph J.Y. Sung, MD, PhD
Hong Kong

Drs. Hui and Sung are affiliated with the Department of Medicine & Therapeutics, Chinese University of Hong Kong, Prince of Wales Hospital.

Correspondence to: David S.C. Hui, MD, FCCP, Department of Medicine & Therapeutics, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong; e-mail: dschui@cuhk.edu.hk

References

1 Lee N, Hui DS, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003; 348:1986–1994
2 Hsu LY, Lee CC, Green JA, et al. Severe acute respiratory syndrome in Singapore: clinical features of index patient and initial contacts. Emerg Infect Dis [serial online]. Available at: http://www.cdc.gov/ncidod/EID/vol9no6/03-0264.htm. Accessed May 23, 2003
3 Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA epub, posted May 6, 2003. Available at: http://jama.ama-assn.org/cgi/content/full/289.21.JOC30885v1. Accessed May 23, 2003
4 World Health Organization. Cumulative number of reported cases (SARS) from Nov 1 2002 to May 10 2003. Available at: http://www.who.int/csr/sarscountry/2003_05_10/en/. Accessed May 23, 2003
5 World Health Organization. Severe acute respiratory syndrome (SARS): multi-country outbreak update, March 16, 2003. Available at: http://www.who.int/csr/don/2003_03_16/en. Accessed May 23, 2003
6 Tsang KW, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003; 348:1977–1985
7 Centers for Disease Control and Prevention. Severe acute respiratory syndrome: fact sheet; basic information about SARS, May 8, 2003. Available at: http://www.cdc.gov/ncidod/sars/factsheet.htm. Accessed May 23, 2003
8 Peiris JS, Lai ST, Poon LL, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003; 361:1319–1325
9 Drosten C, Gunther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 2003; 348:1967–1976
10 Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003; 348:1953–1966
11 Poutanen SM, Low DE, Henry B, et al. Identification of severe acute respiratory syndrome in Canada. N Engl J Med 2003; 348:1995–2005
12 Rota PA, Oberste MS, Monroe SS, et al. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. Available at: http://www.sciencemag.org/cgi/rapidpdf/1085952v1. Accessed May 23, 2003
13 Marra AM, Jones SJ, Astell CR, et al. The genome sequence of the SARS-associated coronavirus. Available at: http://www.sciencemag.org/cgi/rapidpdf/1085953v1. Accessed May 23, 2003
14 Ruan YJ, Wei CL, Ee LA, et al. Comparative full-length genome sequence analysis of 14 SARS coronavirus isolates and common mutations associated with putative origins of infection. Available at: http://image.thelancet.com/extras/03art4454web.pdf. Accessed May 23, 2003
15 Donnelly CA, Ghani AV, Leung GM, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Available at: http://image.thelancet.com/extras/03art4453web.pdf. Accessed May 23, 2003
16 Peiris JS, Chu CM, Cheng VC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Available at: http://image.thelancet.com/extras/03art4432web.pdf. Accessed May 23, 2003
17 Hon KL, Leung CW, Cheng WT, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. Available at: http://image.thelancet.com/extras/031et4127web.pdf. Accessed May 23, 2003
18 Wong KT, Antonio GE, Hui DS, et al. Severe acute respiratory syndrome: radiographic appearances and pattern of progression in 138 patients. Radiology 2003. http://radiology.rsnajnls.org/cgi/content/full/2282030593v1. Accessed May 29, 2003
19 Wong KT, Antonio GE, Hui DS, et al. Thin-section CT of severe acute respiratory syndrome: evaluation of 73 patients exposed to or with the disease. Available at: http://radiology.rsnajnls.org/cgi/content/full/2283030541v1. Accessed May 23, 2003
20 Centers for Disease Control and Prevention. Updated interim domestic infection control guidance in the health-care and community setting for cases with suspected SARS (May 1, 2003). Available at: http://www.cdc.gov/ncidod/sars/infectioncontrol.pdf. Accessed May 23, 2003
21 So LK, Lau AC, Yam LY, et al. Development of a standard treatment protocol for severe acute respiratory syndrome. Lancet 2003; 361:1615–1617
22 Centers for Disease Control and Prevention. Interim domestic guidance on the use of respirators to prevent transmission of SARS (May 6, 2003). Available at: http://www.cdc.gov/ncidod/sars/pdf/respirators-sars.pdf. Accessed May 23, 2003

RESPIRATORY INFECTION

Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak

J J Y Sung, A Wu, G M Joynt, K Y Yuen, N Lee, P K S Chan, C S Cockram, A T Ahuja, L M Yu, V W Wong, D S C Hui

Thorax 2004;**59**:414–420. doi: 10.1136/thx.2003.014076

See end of article for authors' affiliations

Correspondence to: Dr D S C Hui, Department of Medicine and Therapeutics, Prince of Wales Hospital, Shatin, NT, Hong Kong; dschui@cuhk.edu.hk

Received 5 August 2003
Accepted
26 November 2003

Background: The outcome is reported of a prospective uncontrolled study based on a stepwise treatment protocol during an outbreak of severe acute respiratory syndrome (SARS) in Hong Kong.
Method: One hundred and thirty eight patients were treated with broad spectrum antibiotics, a combination of ribavirin and low dose corticosteroid, and then intravenous high dose methylprednisolone according to responses. Sustained response to treatment was defined as (1) defervescence for ≥4 consecutive days, (2) resolution of lung consolidation by >25%, and (3) oxygen independence by the fourth day without fever. Patients with defervescence who achieved either criterion 2 or 3 were classified as partial responders. Patients who fell short of criteria 2 and 3 were non-responders.
Results: Laboratory confirmation of SARS coronavirus infection was established in 132 (95.7%). None responded to antibiotics but 25 (18.1%) responded to ribavirin + low dose corticosteroid. Methylprednisolone was used in 107 patients, of whom 95 (88.8%) responded favourably. Evidence of haemolytic anaemia was observed in 49 (36%). A high level of C-reactive protein at presentation was the only independent predictor for use of methylprednisolone (odds ratio 2.18 per 10 mg/dl increase, 95% confidence interval 1.12 to 4.25, p=0.02). Thirty seven patients (26.8%) required admission to the intensive care unit and 21 (15.2%) required invasive mechanical ventilation. There were 15 deaths (mortality rate 10.9%), most with significant co-morbidities, whereas 122 (88.4%) had been discharged home 4 months after the outbreak onset.
Conclusion: The use of high dose pulse methylprednisolone during the clinical course of a SARS outbreak was associated with clinical improvement, but randomised controlled trials are needed to ascertain its efficacy in this condition.

In March 2003 there was a serious outbreak of severe acute respiratory syndrome (SARS) in Hong Kong. One hundred and thirty eight patients and healthcare workers contracted the disease from a single index patient on a medical ward at the Prince of Wales Hospital.[1] Patients in this cohort had a very similar presentation with fever, chills and rigor, myalgia, and progression to respiratory failure within 1–2 weeks. Within a month the disease had spread to Singapore, Vietnam, Taiwan, Germany, Canada, and the United States.[2]

SARS is caused by a novel coronavirus (CoV),[3–5] probably originating from an animal reservoir. Without knowledge of the underlying cause of the disease during the outbreak, treatment of this newly emerging disease was empirical. A team of physicians from the Department of Medicine and Therapeutics (infectious disease, respiratory medicine and general medicine) and the intensive care unit was formed to manage the patients. A treatment protocol was developed in response to the demands of the event. The results are reported here.

METHODS

The data of our previously reported cohort[1] recruited during the 2 week period from 11 March to 25 March 2003 were analysed. Because of the unexpected acute medical crisis with many healthcare workers becoming infected, a blind control study was not considered feasible. Instead, a stepwise management algorithm was developed through observation and discussion of the progress of the patients' clinical condition on a day-to-day basis. All data were prospectively collected to assist future clinical management decisions. The final clinical outcome is reported up to 28 July 2003.

Diagnosis and monitoring of progress

The CDC criteria for diagnosis of SARS were applied.[6] Our case definitions were: (1) fever (temperature >38°C), (2) chest radiograph (plain radiograph and/or CT thorax) showing evidence of consolidation with or without respiratory symptoms such as cough or shortness of breath, and (3) history of exposure to an index case suspected of having SARS or direct contact with a person who fell ill following exposure to the index case.

Initial investigations included complete blood count (including differential count), clotting profile (PT, APTT, INR, D-dimer), C-reactive protein (CRP), and serum biochemistry (including electrolytes, urea and creatinine levels, serum alanine aminotransferase, creatine phosphokinase (CPK), lactate dehydrogenase (LDH)). These parameters, together with chest radiography and vital signs (blood pressure, pulse, respiratory rate), were monitored regularly.

Serological examination for SARS CoV infection was performed for all patients. The level of SARS CoV IgG antibody was measured by an immunofluorescence assay based on Vero cells infected with CoV isolated from a patient with SARS. Paired serum samples were tested at serial twofold dilutions starting from 1:40. The tests were regarded as indicating SARS CoV infection if a seroconversion or fourfold rise in antibody titre was detected. Viral isolation using Vero cell culture has been previously described.[1]

Treatment protocol

Patients were treated for the first 2 days with broad spectrum antibiotics for community acquired pneumonia according to the American Thoracic Society guidelines.[7] Initial treatment

consisted of intravenous cefotaxime 1 g every 6 hours with either oral levofloxacin 500 mg daily or clarithromycin 500 mg twice daily. Oseltamivir was also given to the initial patients to treat possible influenza infection (fig 1). Clinical symptoms, blood oxygen saturation, and the chest radiograph were assessed daily. If fever persisted after 48 hours, patients were given a combination of ribavirin and "low dose" corticosteroid therapy commencing on day 3–4 (oral ribavirin as a loading dose of 2.4 g stat followed by 1.2 g three times daily and prednisolone 0.5–1 mg/kg body weight per day), whereas those with dyspnoea were treated with intravenous ribavirin (400 mg every 8 hours) combined with hydrocortisone (100 mg every 8 hours). Pulses of high dose methylprednisolone (0.5 g intravenous infusion for three consecutive days) were given as a response to persistence or recurrence of fever and radiographic progression of lung opacity with or without hypoxaemia despite initial combination therapy. Further pulses of methylprednisolone were given if there was no clinical or radiological improvement, up to a total of 3 g. The intention was to continue with the combination of ribavirin and "low dose" corticosteroid for up to 12 days when there was complete resolution of lung opacity. Those who became afebrile but with incomplete radiological resolution were given oral ribavirin 600 mg three times daily and prednisolone 0.5 mg/kg body weight per day for at least one further week.

Intensive care and mechanical ventilation

Patients who developed hypoxaemia were given supplemental oxygen. Patients were admitted to the intensive care unit (ICU) when severe respiratory failure developed as evidenced by (1) failure to maintain an arterial oxygen saturation of at least 90% while receiving supplemental oxygen of 50% and/or (2) respiratory rate >35 breaths/min. Non-invasive positive pressure ventilation was avoided because of the risk of viral transmission from mask leakage and flow compensation,

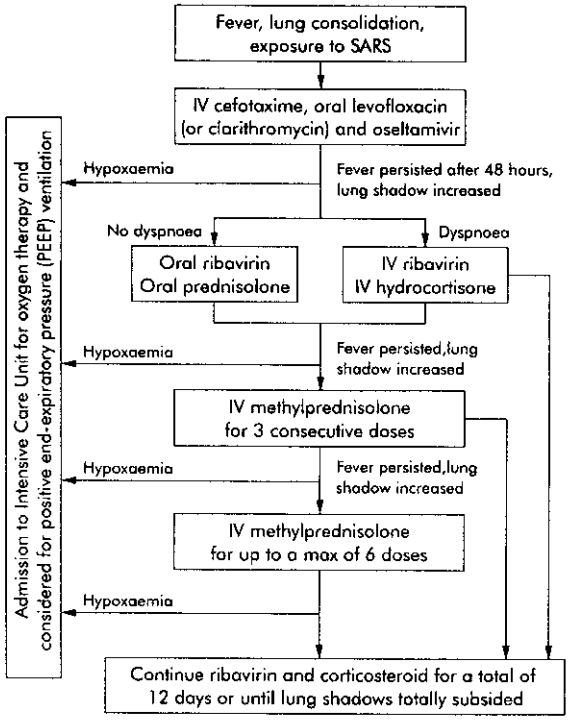


Figure 1 Treatment protocol for SARS.

possibly causing wide dispersion of contaminated aerosol. Criteria for intubation and positive pressure ventilation were (1) persistent failure to achieve arterial oxygen saturation of 90% while receiving 100% oxygen via a non-rebreathing mask and/or (2) onset of respiratory muscle fatigue as evidenced by an increase in $Paco_2$, sweating, tachycardia, and/or a subjective feeling of exhaustion. Mechanical ventilation with synchronised intermittent mandatory ventilation or pressure control ventilation was instituted. Positive end expiratory pressure and inspired oxygen concentration were titrated to achieve an arterial saturation of 90–95%. Tidal volume was maintained at 6–8 ml/kg estimated body weight and plateau pressure maintained at 30 cm H_2O or less. $Paco_2$ was allowed to rise provided the pH was >7.15.[8] Patients unable to meet the above parameters were ventilated in the prone position.

Definitions of clinical outcome

Sustained response (SR) to treatment was defined as (1) defervescence (daily peak temperature ≤ 37.5°C) for at least four consecutive days; (2) radiological improvement as assessed by three radiologists who were blind to the clinical data of more than 25%; and (3) oxygen independence as assessed by pulse oximetry ($Sao_2 \geq 95\%$ on room air) on the fourth afebrile day. Patients with defervescence who achieved either resolution of lung consolidation or oxygen independence, but not both, were classified as showing a partial response (PR). Patients who fell short of criteria 2 and 3 above were classified as non-responders to treatment (NR).

Statistical analysis

Demographic, clinical, laboratory and radiological features of the patients were reported and analysed. Statistical analysis was performed by SAS software version 8.0 (SAS Inc, Cary, NC, USA). Data are presented as mean (SD) unless otherwise specified. The association between baseline parameters and response to a combination of ribavirin and hydrocortisone treatment was analysed by simple logistic regression. Parameters measured during treatment were analysed using either *t* test or Mann-Whitney test, depending on their distribution. A stepwise multiple logistic regression analysis was then performed to identify independent predictors for failure to respond to ribavirin and low dose steroid, which would lead to the subsequent use of pulse methylprednisolone in accordance with our treatment protocol. All clinical parameters with a p value of <0.20 by univariate analysis were entered into the model. A p value of <0.05 was considered statistically significant.

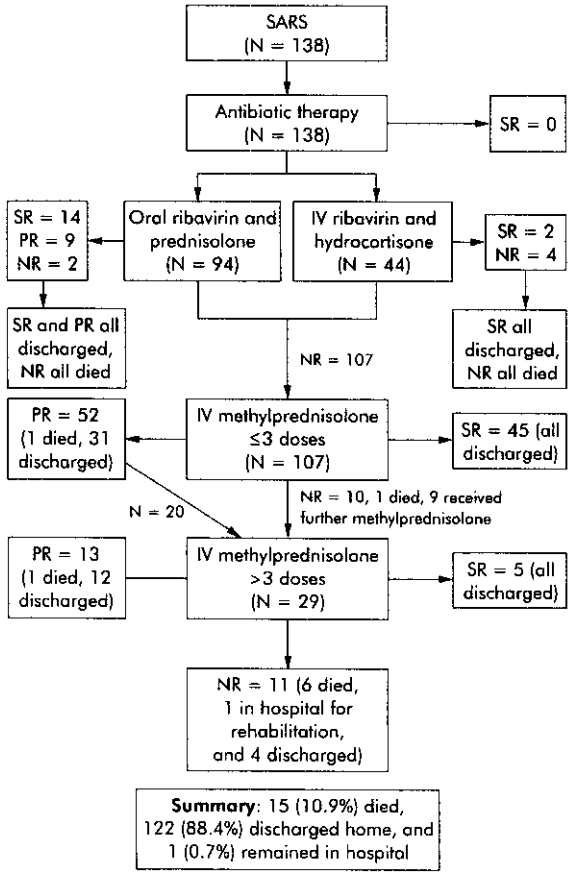
RESULTS

In the 2 week period from 11 March to 25 March 2003 a total of 156 patients were admitted to the Prince of Wales Hospital with SARS, of whom 138 were identified as either secondary or tertiary cases stemming from our index patient. The demography of this cohort has been described in detail in a previous report.[1] Briefly, there were 66 men and 72 women with a mean (SD) age of 39.3 (16.8) years. The duration between onset of symptoms and admission ranged from 0 to 11 days (median 3 days). Of these 138 cases, 124 subsequently showed seroconversion to SARS CoV while two had negative SARS CoV serology. For the remaining 12, convalescent serum was not obtained but eight had SARS CoV isolated from the nasopharyngeal aspirate (n = 3) or necroscopic lung and/or intestinal tissues (n = 5). Thus, only in four patients was SARS CoV infection status not established.

None of the 138 cases responded to antibiotics. Fever persisted in all and lung consolidation progressed in the majority of patients. Ninety four patients received oral ribavirin and prednisolone, of which 14 were sustained

responders and nine were partial responders. These 23 patients were discharged uneventfully. Two patients died in the early phase of the disease before additional treatment could be given. Forty four patients received intravenous ribavirin and hydrocortisone, two of whom had a sustained response and four died. The remaining 107 patients showed no appreciable response to this combination treatment: 11 had persistent fever, 51 had radiological deterioration and developed respiratory insufficiency, and 45 had both fever and respiratory deterioration (fig 2). Overall, 25 patients (18.1%) responded to ribavirin and low dose corticosteroid treatment alone (table 1).

Intravenous pulse methylprednisolone was given to 107 patients who did not respond to ribavirin and low dose corticosteroid therapy. After three infusions of 0.5 g per dose of methylprednisolone, 45 patients (42.1%) showed a sustained response with recovery from the disease and 52 (48.6%) had a partial response. Thirty one of those with a partial response recovered and were discharged from hospital, one died, and 20 required further pulses of high dose methylprednisolone. There were 10 non-responders, one of whom died. Among the partial responders and non-responders, 29 received further doses of intravenous methylprednisolone up to 3 g in total. A sustained response was observed in five and a partial response in 13. Eleven patients (median age 55 years, range 33–82) failed to show any response after more than three pulses of high dose methylprednisolone (fig 2). Of these, six died, one (who has required invasive mechanical ventilation for 3 months) remains in hospital for rehabilitation, and four were discharged on a course of oral prednisolone at 0.5 mg/kg after 3 weeks of hospitalisation. The overall success rate of high dose methylprednisolone treatment was 88.8%.



SR: sustained response, PR: Partial response, NR: No response

Figure 2 Clinical outcome of 138 patients with SARS (at 28 July 2003).

As of 28 July 2003, there were 15 deaths (mortality rate 10.9%). The median age of these 15 patients was 69 years (range 44–82). Two (aged 68 and 69 years) had an unremarkable past history while 13 had at least one chronic medical co-morbidity (including ischaemic heart disease, rheumatic heart disease, congestive heart failure, myelodysplastic syndrome with malignant transformation, alcoholic liver cirrhosis, reactivation of viral hepatitis B infection, chronic renal impairment, and diabetes mellitus).

We have noted a typical clinical course of SARS. Fever subsides after patients receive ribavirin and low dose corticosteroid in the first week. While some patients remain in remission, almost 80% of patients have recurrence of fever with radiological progression by the second week. This is accompanied by the development of respiratory symptoms and hypoxaemia. Intravenous high dose methylprednisolone usually controls the fever and results in resolution of lung shadows and improvement in oxygenation. Biochemical parameters and blood counts take 2–3 weeks to return to normal (fig 3).

Hyperglycaemia (plasma spot glucose $\geq$11.0 mmol/l) was detected in 23 of the 107 patients and hypokalaemia (plasma potassium level $\leq$3.0 mmol/l) in 16. These metabolic derangements were reversed when intravenous high dose methylprednisolone was discontinued. Two patients developed transient confusion, delusion, and anxiety. CT scanning and MR imaging of the brain revealed no abnormalities, and the EEG and cerebrospinal fluid analysis were also normal. The symptoms gradually subsided after discontinuation of steroid.

The 25 patients who responded to ribavirin and low dose steroid were compared with the 113 patients who did not respond and needed further treatment with pulse methylprednisolone (table 2). Initial platelet count, initial LDH, systolic blood pressure, and initial CRP level reached statistical significance by univariate analysis. Multivariate analysis showed that a higher initial level of CRP (odds ratio per 10 mg/dl, 2.18; 95% confidence interval 1.12 to 4.25; $p = 0.02$) was the only independent risk factor for the use of pulse methylprednisolone. Among the parameters recorded during treatment, those who failed to improve after ribavirin and low dose steroid had a significantly lower nadir lymphocyte count and higher peak LDH and CRP levels.

Thirty seven patients (26.8%) were admitted to the ICU. Of these, 21 (15.2%) required endotracheal intubation and mechanical ventilation. Barotrauma was noted in eight patients (21.6% of ICU admissions). Pneumomediastinum with subcutaneous surgical emphysema was seen in three cases and pneumothorax in five. In one case the pneumothorax occurred within 24 hours of the insertion of a central venous catheter in the internal jugular vein. Nosocomial infection was diagnosed in 17 of the 37 patients admitted to the ICU.[9 10] In six the diagnosis of nosocomial infection was made before high dose methylprednisolone administration. Infections included pneumonia in 10 patients (MRSA in six, *Stenotrophomonas maltophilia* in two, *Candida albicans* in one, and polymicrobial in one), urinary tract infections in two patients (*Escherichia coli* in one and *Enterococcus* spp in one), and bacteraemia with no clearly identified site in five patients (MRSA in three, *Enterococcus* spp in one, and *Candida albicans* in one). *Clostridium difficile* toxin was identified in one patient with diarrhoea. Sepsis induced organ failure was considered to have contributed to death in five cases.

Table 1 Clinical response to treatment

	Broad spectrum antimicrobial* (n=138)	Ribavirin + corticosteroid† (n=138)	IV methylprednisolone‡ (n=107)
Sustained response	0 (0)	16 (11.6%)	50 (46.7%)
Partial response	0 (0)	9 (6.5%)	45 (42.1%)
No response	138 (100%)	113 (81.9%)	12 (11.2%)

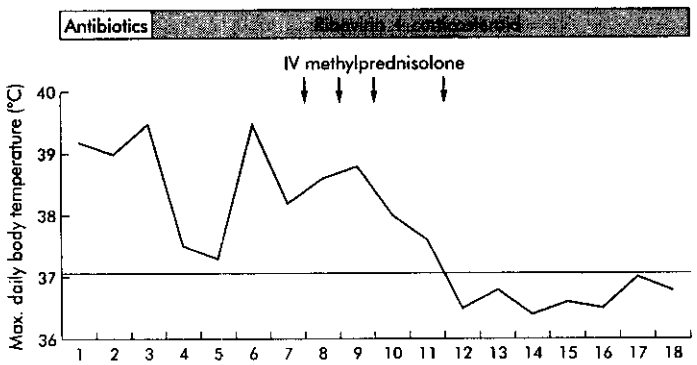
*Antimicrobials included cefotaxime and clarithromycin (or levofloxacin) + oseltamivir.
†Ribavirin (oral or intravenous) + oral prednisolone or intravenous hydrocortisone.
‡Intravenous methylprednisolone up to 3 g in total.
Clinical outcome definitions: (1) afebrile (daily peak temperature <37.5°C) for at least 4 consecutive days; (2) resolution of chest radiograph consolidation by >25% (comparing film of maximal consolidation and that on the 4th afebrile day); (3) oxygen independence (SaO_2 ≥95% on room air) on the 4th afebrile day.
Sustained response = 1+2+3; partial response = 1+2 or 3; no response = failure to fulfil criteria of sustained response and partial response.

After 2 weeks of treatment with ribavirin, 82 patients (59%) had a fall in haemoglobin of more than 2 g/dl from baseline while 39 (28%) experienced a fall of more than 3 g/dl. Two weeks after initiation of ribavirin therapy haemoglobin concentrations ranged from 7.2 to 13.2 g/dl. Evidence of haemolytic anaemia was documented in 49 patients (36%) with a rise of bilirubin (>20 μmol/l) and/or reticulocyte count (>1%). No patients developed overt cardiac toxicity or renal toxicity with ribavirin.

DISCUSSION

SARS is a serious infection with a formidable morbidity and mortality. Of the 138 patients admitted to our hospital during the major outbreak, 113 (81.9%) failed to improve after ribavirin and low dose corticosteroid. High dose methylprednisolone was used in 107 patients and 95 (88.8%) responded favourably. Thirty seven patients (26.8%) required treatment in the ICU, of whom 21 (15.2%) required invasive mechanical ventilation. A high CRP level on admission was the only independent predictor for use of high dose methylprednisolone. As of 28 July 2003 (4 months from the outbreak onset), 122 patients (88.4%) had been discharged and one remained in hospital for rehabilitation. The overall mortality was 10.9%, most with significant co-morbidities.

Similar to the description by Peiris *et al*,[11] the clinical course of our SARS patients appears to follow a typical pattern. Phase 1 is clinically characterised by fever, myalgia, and other systemic symptoms that generally improve after a few days. Phase 2 is characterised by recurrence of fever, oxygen desaturation, and radiological progression of pneumonia. The clinical progression during phase 2 has also been observed by others[11 12] and appears to be related to immunopathological damage.[11] Most of our patients improved during this phase with a combination of ribavirin and intravenous methylprednisolone, but 15.2% progressed into acute respiratory distress syndrome (ARDS) necessitating ventilatory support. Reports from several other series have also suggested that a substantial number of cases develop respiratory failure and



Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
SaO_2 (%)	95	95	96	98	97	96	95	94	91	91	92	95	98	97	96	97	99	99
O_2 supplement (l)	0	0	0	0	0	0	0	2	2	3	5	4	3	2	1	0	0	0
Neutrophil ($\times 10^9$)	7.5	7.7	9.0	9.8	9.0	8.8	16.0	15.1	19.8	29.8	23.2	18.3	17.3	17.2	16.6	-	-	16.3
Lymphocyte ($\times 10^9$)	1.7	1.1	1.1	1.0	0.9	0.7	0.5	0.6	0.7	0.8	0.5	0.5	0.7	0.6	0.5	-	-	0.6
Platelet ($\times 10^3$)	193	179	209	199	196	172	196	215	196	259	261	263	269	268	262	-	-	291
Creatinine (μmol/l)	85	92	79	75	82	98	76	77	77	71	69	62	61	60	68	-	-	79
ALT (mmol/l)	18	18	16	21	19	16	23	31	40	40	60	73	68	62	86	-	-	54
CPK (U/l)	222	461	392	258	445	593	592	230	171	147	132	109	68	73	116	-	-	49
LDH (U/l)	171	193	196	200	229	267	488	445	593	278	377	369	319	315	236	-	-	220
CRP (mg/l)	4.4	11.9	7.8	37.4	60.7	81.6	83.7	111	76.7	42.6	19.9	-	-	-	-	-	-	0.3

Figure 3 Clinical, biochemical, and haematological response of a patient to infusions of methylprednisolone.

Table 2 Univariate analyses of clinical and laboratory parameters associated with the use of intravenous pulse methylprednisolone

	Not responding to ribavirin+low dose steroid (n=113)*	Responding to ribavirin+low dose steroid (n=25)*	Odds ratio (95% CI)	p value
Parameters at presentation				
Age (years)	39.9 (16.4)	37.5 (17.8)	1.01 (0.98 to 1.04)	0.5
Male sex (%)	48.7%	44.0%	1.21 (0.51 to 2.88)	0.7
Duration between onset of symptom and treatment (days)	5.4 (2.7)	6.1 (2.8)	0.91 (0.77 to 1.07)	0.2
Platelet ($\times 10^9$/l)	146 (58)	175 (64)	0.92 (0.86 to 0.99)‡	0.03
Neutrophil count ($\times 10^9$/l)	4 (2)	3 (1)	1.30 (0.98 to 1.74)	0.1
Lymphocyte count ($\times 10^9$/l)	1 (1)	1 (1)	0.82 (0.45 to 1.48)	0.5
Activated partial thromboplastin time (s)	42.3 (7.3)	40.4 (10.4)	1.04 (0.97 to 1.11)	0.3
Sodium (mmol/l)	135.5 (3.5)	136.0 (2.5)	0.95 (0.83 to 1.09)	0.5
Urea (mmol/l)	4.8 (5.4)	4.4 (1.1)	1.02 (0.91 to 1.14)	0.7
Creatinine (μmol/l)	101 (118)	86 (22)	1.01 (0.98 to 1.03)	0.4
Alanine transferase (IU/l)	28.8 (30.1)	62.8 (158.1)	1.01 (0.99 to 1.03)	0.1
Creatinine kinase (U/l)	390.1 (675.1)	219.3 (272.3)	1.08 (0.95 to 1.23)†	0.2
Lactate dehydrogenase (U/l)	370.4 (196.5)	262.4 (114.4)	1.56 (1.07 to 2.25)†	0.02
Systolic blood pressure (mm Hg)	117 (18)	109 (11)	1.36 (1.02 to 1.83)‡	0.04
Diastolic blood pressure (mm Hg)	62 (11)	61 (11)	1.07 (0.72 to 1.59)‡	0.7
Pulse rate/min	94 (14)	92 (13)	1.15 (0.84 to 1.57)‡	0.4
C-reactive protein (mg/dl)	51.9 (57.2)	9.6 (10.3)	2.18 (1.12 to 4.25)‡	0.02
Parameters during treatment				
Peak D-dimer (ng/ml)	1184 (1201)	1247 (2119)		0.3
Lymphocyte count (nadir) ($\times 10^9$/l)	0.3 (0.2)	0.6 (0.4)		<0.001
Creatinine kinase (peak) (U/l)	515.7 (761.4)	246.4 (268.8)		0.1
Lactate dehydrogenase (peak) (U/l)	468.6 (251.5)	279.0 (109.5)		0.001
Systolic blood pressure (nadir) (mm Hg)	95 (9)	94 (16)		0.6
Diastolic blood pressure (nadir) (mm Hg)	48 (7)	49 (8)		0.7
Pulse rate/min (peak)	107 (15)	99 (11)		0.01
C-reactive protein (peak) (mg/dl)	82.6 (83.8)	13.1 (15.7)		<0.001

*Values are mean (SD).
†Per 100 units increase.
‡Per 10 units increase.

ARDS, with 17–30% of patients requiring admission to the ICU,[11–13] whereas the 21 day mortality was reported to be 3.6%[1] and 6.5%,[13] respectively. Necroscopic examination revealed evidence of diffuse alveolar damage, pulmonary oedema with hyaline membrane formation, and haemophagocytosis in the lungs.[1 14]

To date there has been no consensus on the treatment of SARS. Ribavirin, a broad spectrum antiviral agent previously shown to be efficacious against both RNA and DNA viruses, has been used.[1 3 11–13] Previous studies have shown that, in acute viral respiratory infections, large amounts of early response cytokines such as interferon-α, tumour necrosis factor α, interleukin (IL)-1 and IL-6 are produced. These cytokines mediate antiviral activities but, at the same time, may contribute to tissue injury.[15 16] Ribavirin can inhibit viral induced macrophage production of proinflammatory cytokines and Th2 cytokines.[17] Nevertheless, it has subsequently been reported to have no significant in vitro activity against the CoV believed to be responsible for SARS.[18]

High dose pulse corticosteroids have been used by several groups with a favourable response.[1 11 19–22] Corticosteroids have been used because CT scans of the thorax have shown radiographic features of bronchiolitis obliterans organising pneumonia (BOOP)[1 19 22 23] which is a steroid responsive condition suggestive of an immunological phenomenon.[24] The use of high dose pulse methylprednisolone treatment aims to suppress the cytokine induced lung injury (phase 2).[1 11 21 22] A retrospective study has shown that cases receiving pulse methylprednisolone had a lower oxygen requirement, better radiographic outcome, and were less likely to require further rescue pulse steroid.[22] In addition, macrophages are the prominent leucocytes in the alveoli of patients with fatal SARS, with evidence of haemophagocytosis in the lungs.[14] Haemophagocytosis has been attributed to cytokine dysregulation,[25] and intervention with steroids might modulate this cytokine response and prevent a fatal outcome, as has been proposed for other causes of ARDS.[14 26] Understandably, there are concerns about using high dose methylprednisolone in an emerging infectious disease.

In this study the treatment protocol was developed during a rapid major outbreak. The use of a relatively large dose of oral ribavirin (loading dose 2.4 g followed by 3.6 g daily) was based on the fact that the oral bioavailability of ribavirin is only 36–52%.[27 28] High dose methylprednisolone was used only when ribavirin and low dose corticosteroid failed to stop the inflammatory process, which was evident by continuing radiological progression and hypoxaemia. Twenty five patients (18%) responded favourably to ribavirin and low dose corticosteroid treatment. Of these, 23 received oral ribavirin and two received intravenous ribavirin; the numbers were too small to allow a meaningful comparison between them. With the dosage of ribavirin used we observed a modest degree of anaemia in most patients (in 59% the haemoglobin fell by 2 g/dl), probably the result of haemolysis. A much higher dose of ribavirin, based on dosage for treatment of haemorrhagic fever viruses,[29] has been reported to be associated with more significant toxicity including haemolysis (in 76%) and a decrease in haemoglobin of 2 g/dl (in 49%), raised transaminases (in 40%), and bradycardia (in 14% of SARS patients).[13]

Despite the combination of ribavirin and low dose corticosteroid, most of the patients continued to deteriorate during the second week of the illness. High dose methylprednisolone was then used in 107 patients, 95 (88.8%) of whom recovered from the progressive lung disease. Following high dose methylprednisolone treatment, rapid resolution of lung opacity was usually followed by an improvement in hypoxaemia. Most patients responded after receiving three doses of methylprednisolone (up to 1.5 g in total). Less than 30% of cases required additional doses. The timing of

administration of high dose methylprednisolone is important. It was administered only during phase 2 when radiological progression of consolidation and increasing hypoxaemia were documented.[1 11 21] In most cases high dose methylprednisolone was started towards the end of the first week with the first pulse administered on day 8 (median) from fever onset. We have avoided using high dose methylprednisolone in the early phase of SARS[11] as viral clearance by host immunity might be hampered. It must be emphasised that high dose methylprednisolone should not be used only to control fever. In some patients the lung opacities continued to deteriorate even after defervescence. In these patients the benefit of high dose methylprednisolone in reversing radiological progression was also seen. While we recognise that the benefit of high dose methylprednisolone[1 11 19–22] cannot be confirmed without a control group, the use of high dose corticosteroid in the treatment of SARS warrants further investigation.

Our analysis indicated that patients with thrombocytopenia, high LDH, and high CRP levels at presentation were more likely to have uncontrolled inflammation requiring high dose corticosteroid therapy. Of these, a high CRP level at presentation was the only independent factor of non-response to ribavirin and low dose corticosteroid. During treatment with ribavirin and low dose corticosteroid the non-responders also had more severe lymphopenia, a higher peak LDH, and a higher peak CRP level. While a high peak LDH is a poor prognostic marker[1] and is most likely the result of immune mediated lung injury in severe cases of SARS,[11] serial measurements of CRP may be useful in monitoring response to treatment and detecting complications in patients with secondary infections.[30 31]

In those patients admitted to the ICU the predominant feature was isolated respiratory failure. All other recorded organ failure was either pre-existing or could be attributed to nosocomial infections. Despite low volume, low pressure mechanical ventilation, the incidence of barotrauma (21.6% of our ICU admissions) was surprisingly high. Chest radiographs and CT scans did not indicate excessive hyperinflation or bullous lung disease and, at present, we can offer no explanation for this observation other than poor lung compliance.[23] Prone ventilation as salvage therapy appears to have benefited some patients, but its use is controversial in view of the lack of evidence supporting any benefit on mortality.[32] The unusually high rate of nosocomial infection, particularly pneumonia, may have been the consequence of corticosteroid treatment. More serious complications such as disseminated fungal disease have been reported elsewhere.[33]

This report provides an account of a stepwise approach to the treatment of SARS. The use of ribavirin has led to a significant degree of haemolytic anaemia and the lack of in vitro antiviral activity of ribavirin against SARS CoV[18] has rendered its role doubtful in the treatment of SARS. The use of high dose methylprednisolone during clinical progression, on the rationale of preventing immunopathological lung injury,[1 11 14 21 22 26] appeared to be effective in our cohort but the limitation of interpreting uncontrolled data should be noted. Randomised controlled studies will be required to evaluate the efficacy and best timing for high dose methylprednisolone treatment. It is hoped that the availability of the genome sequence of the SARS CoV[34–36] will facilitate efforts to develop new and rapid diagnostic tests, antiviral agents, and vaccines in the long run.

ACKNOWLEDGEMENTS

The authors would like to thank all the healthcare workers who have participated in the battle against SARS. In addition, they would like to thank Ms MY Yung and Mr Michael Chung for helping with data entry and analysis.

Authors' affiliations

J J Y Sung, A Wu, N Lee, C S Cockram, V W Wong, D S C Hui, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong
G M Joynt, Department of Anesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong
K Y Yuen, Department of Microbiology, The University of Hong Kong, Hong Kong
P K S Chan, Department of Microbiology, The Chinese University of Hong Kong, Hong Kong
A T Ahuja, Department of Diagnostic Radiology and Organ Imaging, The Chinese University of Hong Kong, Hong Kong
L M Yu, Center for Clinical Trial and Epidemiological Research, The Chinese University of Hong Kong, Hong Kong

REFERENCES

1 **Lee N**, Hui DS, Wu A, *et al.* A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003;**348**:1986–94.
2 Update: outbreak of severe acute respiratory syndrome—worldwide 2003. *MMWR Morb Mort Wkly Rep* 2003;**52**:241–8.
3 **Kuiken T**, Fouchier RA, Schutten M, *et al.* Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. *Lancet* 2003;**362**:263–70.
4 **Drosten C**, Gunther S, Preiser W, *et al.* Identification of a novel Coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003;**348**:1967–76.
5 **Ksiazek TG**, Erdman D, Goldsmith CS, *et al.* A Novel Coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003;**348**:1953–66.
6 **Centers for Disease Control and Prevention**. Severe acute respiratory syndrome (SARS) updated interim U.S. case definition. http://www.cdc.gov/ncidod/sars/casedefinition.htm (accessed 20 April 2003).
7 Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001;**163**:1730–54.
8 **The Acute Respiratory Distress Syndrome Network**. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;**342**:1301–8.
9 **American Thoracic Society**. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement. *Am J Respir Crit Care Med* 1995;**153**:1711–25.
10 **Garner JS**, Jarvis WR, Emori TG, *et al.* CDC definitions for nosocomial infections. *Am J Infect Control* 1988;**16**:128–40.
11 **Peiris JS**, Chu CM, Cheng VC, *et al.* Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003;**361**:1767–72.
12 **Hsu LY**, Lee CC, Green JA, *et al.* Severe acute respiratory syndrome in Singapore: clinical features of index patient and initial contacts. *Emerg Infect Dis* 2003;**9**:713–7.
13 **Booth CM**, Matukas LM, Tomlinson GA, *et al.* Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* 2003;**289**:2801–9.
14 **Nicholls JM**, Poon LL, Lee KC, *et al.* Lung pathology of fatal severe acute respiratory syndrome. *Lancet* 2003;**361**:1773–8.
15 **Cheung CY**, Poon LL, Lau AS, *et al.* Induction of proinflammatory cytokines in human macrophage by influenza A (H5N1) virus: a mechanism for the unusual severity of human disease? *Lancet* 2002;**360**:1831–7.
16 **Van Reeth K**, Van Gucht S, Pensaret M. In vivo studies on cytokines involvement during acute viral respiratory infection of swine: troublesome but rewarding. *Vet Immun Immunopathol* 2002;**87**:161–8.
17 **Ning Q**, Brown D, Parodo J, *et al.* Ribavirin inhibits viral-induced macrophage production of TNF, IL-1, the procoagulant fg12 prothrombinase and preserves Th1 cytokine production but inhibits Th2 cytokine response. *J Immunol* 1998;**160**:3487–93.
18 **Cyranoski D**. Critics slam treatment for SARS as ineffective and perhaps dangerous. *Nature* 2003;**423**:4.
19 **Tsang KW**, Ho PL, Ooi GC, *et al.* A cluster of cases of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003;**348**:1977–85.
20 **So LK**, Lau AC, Yam LY, *et al.* Development of a standard treatment protocol for severe acute respiratory syndrome. *Lancet* 2003;**361**:1615–7.
21 **Nhong NS**, Zeng GQ. Our strategies for fighting severe acute respiratory syndrome. *Am J Respir Crit Care Med* 2003;**168**:7–9.
22 **Ho JC**, Ooi GC, Mok TY, *et al.* High dose pulse versus non-pulse corticosteroid regimens in severe acute respiratory syndrome. *Am J Respir Crit Care Med* 2003, Epub ahead of print URL: http://ajrccm.atsjournals.org/cgi/reprint/200306-766OCv1.pdf.
23 **Wong KT**, Antonio GE, Hui DS, *et al.* Thin section CT of severe acute respiratory syndrome: evaluation of 73 patients exposed to or with the disease. *Radiology* 2003;**228**:395–400.
24 **Epler GR**. Bronchiolitis obliterans organizing pneumonia. *Arch Intern Med* 2001;**161**:158–64.
25 **Fisman DN**. Hemophagocytic syndrome and infection. *Emerg Infect Dis* 2000;**6**:60–8.
26 **Lai KN**, Leung JC, Metz CN, *et al.* Role for macrophage migration inhibitory factor in acute respiratory distress syndrome. *J Pathol* 2003;**199**:496–508.

27 **Laskin OL**, Longstreth JA, Hart CC, *et al*. Ribavirin disposition in high-risk patients for acquired immunodeficiency syndrome. *Clin Pharm Ther* 1987;**41**:543–55.
28 **Roberts RB**, Laskin OL, Laurence J, *et al*. Ribavirin pharmcodynamics in high-risk patiens for acquired immunodeficiency syndrome. *Clin Pharm Ther* 1987;**42**:365–73.
29 **Borio L**, Inglesby T, Peters CJ, *et al*. Hemorrhagic fever viruses as biological weapons: medical and public health management. *JAMA* 2002;**287**:2391–405.
30 **Hansson LO**, Lindquist L. C-reactive protein: its role in the diagnosis and follow-up of infectious diseases. *Curr Opin Infect Dis* 1997;**10**:196–201.
31 **Gabay C**, Kushner I. Mechanisms of disease: acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999;**340**:448–54.
32 **Gattinoni L**, Tognoni G, Pesenti A, *et al*. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001;**345**:568–73.
33 **Wang H**, Ding Y, Li X, *et al*. Fatal aspergillosis in a patient with SARS who was treated with corticosteroids. *N Engl J Med* 2003;**349**:507–8.
34 **Rota PA**, Oberste MS, Monroe SS, *et al*. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. *Science* 2003;**300**:1394–9.
35 **Marra MA**, Jones SJ, Astell CR, *et al*. The genome sequence of the SARS-associated coronavirus. *Science* 2003;**300**:1399–404.
36 **Ruan YJ**, Wei CL, Ee LA, *et al*. Comparative full-length genome sequence analysis of 14 SARS coronavirus isolates and common mutations associated with putative origins of infection. *Lancet* 2003;**361**:1779–85.

LUNG ALERT

Chronic occupational exposure to nitrogen dioxide is associated with decline in lung function

▲ Bakke B, Ulvestad B, Stewart P, Eduard W. Cumulative exposure to dust and gases as determinants of lung function decline in tunnel construction workers. *Occup Environ Med* 2004;**61**:262–9

Six hundred and fifty one Norwegian male construction workers were followed for a mean of 6 years with spirometric measurement and assessment of their occupational exposure to total dust, respirable dust, α-quartz, volatile organic compounds, oil vapour, oil mist, formaldehyde, nitrogen dioxide, and carbon monoxide. Compared with a low exposure reference group of outdoor (non-tunnel) workers, tunnel workers showed a decrease in lung function between the first and last spirometric assessments. The excess annual decline in forced expiratory volume in 1 second (FEV_1) in non-smoking tunnel construction workers was 26 ml for drill and blast workers, 31 ml in tunnel concrete workers, and 21 ml in shotcreters. The decrease in FEV_1 was found to be significantly associated with all exposures. Multiple linear regression modelling for decline in FEV_1 showed that cumulative exposure to nitrogen dioxide had the strongest association of all the agents.

This study demonstrates a decline in lung function in tunnel construction workers exposed to nitrogen dioxide and other agents over a 6 year period. It highlights a need for decreasing occupational exposure to nitrogen dioxide, and also to respirable dust and α-quartz, which could be achieved by reducing diesel exhaust emissions and deployment of respiratory devices to protect workers.

R Johns
MRC Clinical Research Fellow, University College, London, UK;
r.johns@ucl.ac.uk

Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study

*J S M Peiris, C M Chu, V C C Cheng, K S Chan, I F N Hung, L L M Poon, K I Law, B S F Tang, T Y W Hon, C S Chan, K H Chan, J S C Ng, B J Zheng, W L Ng, R W M Lai, Y Guan, K Y Yuen, and members of the HKU/UCH SARS Study Group**

Summary

Background We investigated the temporal progression of the clinical, radiological, and virological changes in a community outbreak of severe acute respiratory syndrome (SARS).

Methods We followed up 75 patients for 3 weeks managed with a standard treatment protocol of ribavirin and corticosteroids, and assessed the pattern of clinical disease, viral load, risk factors for poor clinical outcome, and the usefulness of virological diagnostic methods.

Findings Fever and pneumonia initially improved but 64 (85%) patients developed recurrent fever after a mean of 8·9 (SD 3·1) days, 55 (73%) had watery diarrhoea after 7·5 (2·3) days, 60 (80%) had radiological worsening after 7·4 (2·2) days, and respiratory symptoms worsened in 34 (45%) after 8·6 (3·0) days. In 34 (45%) patients, improvement of initial pulmonary lesions was associated with appearance of new radiological lesions at other sites. Nine (12%) patients developed spontaneous pneumomediastinum and 15 (20%) developed acute respiratory distress syndrome (ARDS) in week 3. Quantitative reverse-transcriptase (RT) PCR of nasopharyngeal aspirates in 14 patients (four with ARDS) showed peak viral load at day 10, and at day 15 a load lower than at admission. Age and chronic hepatitis B virus infection treated with lamivudine were independent significant risk factors for progression to ARDS (p=0·001). SARS-associated coronavirus in faeces was seen on RT-PCR in 65 (97%) of 67 patients at day 14. The mean time to seroconversion was 20 days.

Interpretation The consistent clinical progression, shifting radiological infiltrates, and an inverted V viral-load profile suggest that worsening in week 2 is unrelated to uncontrolled viral replication but may be related to immunopathological damage.

Lancet 2003; **361:** 1767–72. Published online May 9, 2003
http://image.thelancet.com/extras/03art4432web.pdf

*Members listed at end of paper
Departments of Microbiology and Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong, Special Administrative Region, China (Prof J S M Peiris DPhil, V C C Cheng MRCP, I F N Hung MRCP, L L M Poon DPhil, B S F Tang MB, K H Chan PhD, Y Guan PhD, B J Zheng PhD, Prof K Y Yuen MD); **Department of Medicine, Intensive Care, Radiology, and Pathology, United Christian Hospital, Hong Kong** (C M Chu MRCP, K S Chan FRCP, K I Law MRCP, T Y W Hon FRCP, C S Chan FRCP, J S C Ng MB, W L Ng MRCP, R W M Lai FRCPA)

Correspondence to: Prof K Y Yuen, Department of Microbiology, University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong, Special Administrative Region, China
(e-mail: kyyuen@hkucc.hku.hk)

Introduction

Severe acute respiratory syndrome (SARS) is a new emerging disease that has affected many countries, with more than 3500 cases reported. A novel virus, the SARS-associated coronavirus, has been identified as the causal agent.[1–4] The clinical, radiological, and other investigative findings at initial presentation have been previously described,[5–7] but the temporal progression is unclear. The routes and duration of viral shedding and the best clinical samples for diagnosis at different stages of the illness are also largely unknown. From March 24, 2003, a major outbreak of SARS involving 321 patients occurred in Amoy Gardens, a high-rise housing estate in Hong Kong. Epidemiological investigations suggested a point-source outbreak, which was linked to a faulty sewage system, initially contaminated by the excreta of the index case who visited the housing block on March 14 and 19.[8] The first 75 adult patients, belonging to 57 households, were admitted with a clinical diagnosis of SARS to one hospital. We did a prospective study on the clinical, haematological, radiological, and microbiological findings of these 75 patients over a period of 24 days, and correlated these findings with treatment[9,10] and with viral load in the nasopharyngeal aspirate to elucidate the pathogenesis and the impact of treatment. We report the usefulness of different clinical samples for virological diagnosis and its importance in transmission.

Patients and methods

Patients

Between March 24 and 28, 2003, we included 75 patients admitted to the United Christian Hospital from the Amoy Gardens housing estate who fulfilled the modified WHO definition of SARS.[3] Briefly, the case definition is: fever 38°C or higher, cough or shortness of breath, new pulmonary infiltrates on chest radiography or high-resolution CT in the absence of an alternative diagnosis to explain the clinical presentation. Patients were nursed in an isolation ward with other SARS patients.

Methods

The study was approved by the ethics committee of the United Christian Hospital, Hong Kong. We entered on a predesigned database the daily clinical findings based on history and physical examination, oximetric measurement, and haematological, biochemical, radiological, and microbiological investigations. We collected nasopharyngeal aspirates and clotted blood for virological studies from all patients at presentation and on day 14 after the onset of illnesses. Anteroposterior chest radiography was done daily for each patient. All chest radiographs were jointly reported by specialist radiologists and respiratory physicians. We did high-resolution CT of the thorax for patients who had apparently normal, equivocal, or atypical chest radiographs. For patients who developed acute respiratory distress syndrome (ARDS) with partial arterial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) less than 26·6 kPa,[11] and recorded acute physiology and chronic health evaluation II (APACHE II) scores,[12]

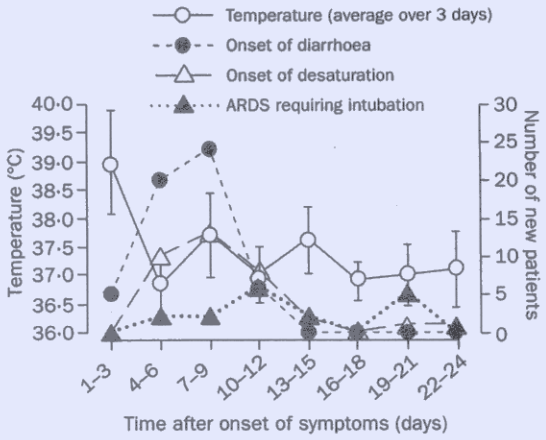


Figure 1: **Temporal clinical profiles in 75 patients with SARS**
Mean (SD) are presented.

From 20 patients in whom SARS-associated coronavirus RNA was detected by reverse-transcriptase (RT) PCR in the initial nasopharyngeal aspirate samples, we collected further nasopharyngeal aspirates, urine, and faecal samples every 3 days. In 14 of these patients, quantitative PCR was done on the nasopharyngeal aspirates collected on days 5, 10, and 15 after onset of symptoms. The nasopharyngeal aspirates on admission were assessed by rapid immunofluorescent antigen detection for influenza A and B, parainfluenza types 1, 2, and 3, respiratory syncytial virus, and adenovirus, and were cultured for conventional respiratory pathogens on Mardin Darby Canine Kidney, LLC-Mk2, RDE, Hep-2, MRC-5, and fetal rhesus kidney (FRhK-4) cell lines. RT-PCR for SARS coronavirus was done directly on all clinical samples. Briefly, total RNA from clinical samples was reverse transcribed with random hexamers and cDNA was amplified with primers 5′TACACACCTCAGCGTTG-3′ and 5′-CACGAAC GTGACGAAT-3′.[3] For real-time quantitative PCR assays, cDNA was amplified in an SYBR Green I fluorescence reactions (Roche, Mannheim, Germany) as described.[13] Briefly, 20 μL reaction mixtures containing 2 μL cDNA, 3·5 mmol/L magnesium chloride, and 0·25 μmol/L of the same forward and reversed primers as the reaction mixtures were thermal-cycled by a Light cycler (Roche, Mannheim; 95°C, 10 min followed by 50 cycles of 95°C, 10 min; 57°C, 5 s; 72°C, 9 s). Plasmids with the target sequence were used to generate the standard curve. At the end of the assay, PCR products (182 bp) were subjected to a melting curve analysis (65–95°C, 0·1°C/s) to find out the specificity of the assay. The acute and convalescent sera were tested in parallel for SARS-associated coronavirus IgG, with SARS-associated-coronavirus-infected Vero cells fixed in acetone in an indirect immunofluorescent format.

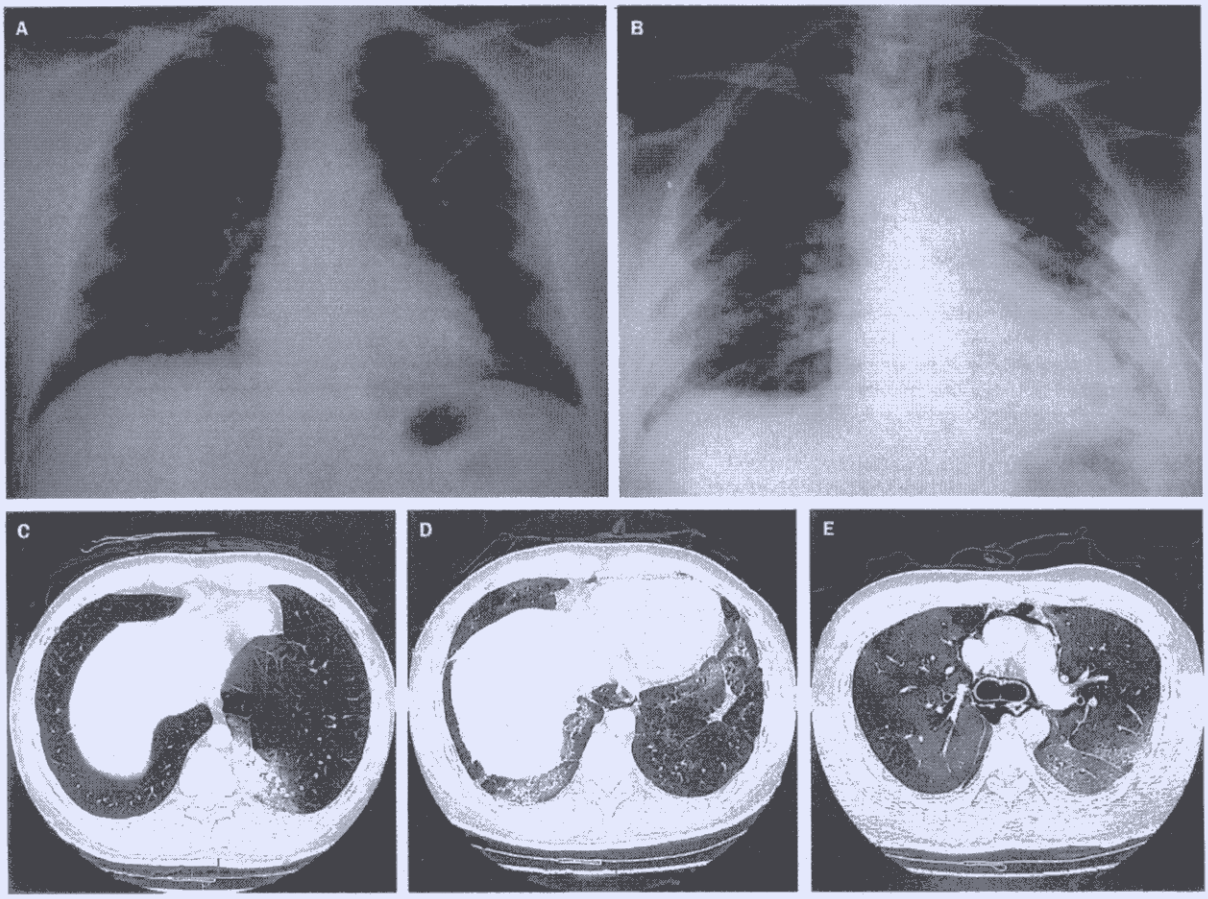


Figure 2: **Chest radiographs and high-resolution CT scans from two SARS patients**
A Man aged 34 years admitted for high fever and cough. A: Consolidation seen in left upper and middle zones, which progressed maximally at day 7. B: At day 20, resolution of consolidation in the left upper and middle zones but new widespread air-space opacities noted; those in left lung base were confluent. Man aged 32 years, presented with fever, chills, rigors and myalgia, with clear chest radiograph at admission. C: High-resolution CT of thorax shows peripheral subpleural consolidation in medial basal segment of left lower lobe. D: Resolution of original left lower-lobe consolidation at day 18. E: Disease complicated by spontaneous pneumomediastinum.

We investigated blood, sputum or endotracheal aspirates, and urine bacteriologically, as clinically indicated. All patients had sepsis work up on admission and if fever recurred. Stools were sent for routine bacteriological culture, *Clostridium difficile* cytotoxin assay, and examined for parasites in selected patients.

All patients were treated with 1·2 g intravenous amoxicillin-clavulanate every 8 h, and 500 mg oral azithromycin daily. In patients with a known penicillin allergy, we administered 500 mg oral levofloxacin every 24 h. As soon as the diagnosis of SARS was established, 8 mg/kg intravenous ribavirin every 8 h for 14 days, and a tailing regimen of hydrocortisone (starting dose 200 mg intravenously every 8 h) over 10 days, followed by oral prednisolone for 11 days (1 mg/kg for 5 days, 0·5 mg/kg for 3 days, and 0·25 mg/kg for 3 days) were given. We used pulses of methylprednisolone 500 mg intravenously daily for two or three doses if patients worsened, with increasing shortness of breath, oxygen desaturation, and radiological worsening. All HBsAg-positive patients were given 100 mg oral lamivudine daily while taking corticosteroids.

Statistical analysis

We compared risk factors associated with the development of ARDS by Fisher's exact test for categorical variables and Student's *t* test for continuous variables. Significant risk factors identified on univariate analyses were further analysed by multiple logistic regressions to identify independent risk factors associated with the development of ARDS. We took $p<0·05$ to be significant. We used SPSS (version 11.0) for all analyses.

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

Of the 75 patients, 71 (95%) were ethnic Chinese, and the remainder were Filipino. The male-to-female ratio was one to 0·92, and mean age was 39·8 (SD 12·2) years. Five patients were smokers. Underlying diseases were identified in 13 patients, including nine patients positive for HBsAg with no stigmata of chronic liver disease and normal liver function tests. The clinical symptoms on admission included fever in 75 (100%) patients, chills in 49 (65%), rigors in 42 (56%), myalgia in 51 (68%), cough in 22 (29%), sore throat in eight (11%), shortness of breath in three (4%), headache in 11 (15%), dizziness in three (4%), and diarrhoea in one (1%).

Initial chest radiograph was abnormal in 53 (71%) patients; involvement was confined to one lung zone in 37 (49%) and was multizonal in 16 (21%). Lower-zone infiltrates or consolidation occurred in 45 (60%) patients. Initial high-resolution CT was done in 33 (44%) patients in whom the initial chest radiographs were normal, equivocal, or atypical. Of these 33 patients, 18 (55%) had abnormalities confined to one lobe. Multilobar involvement was seen in 15 (46%) patients. Focal ground-glass opacification was the only type of abnormality in eight (24%) patients. 12 (36%) patients had consolidation only, and 13 (39%) had both types of infiltrates.

On haematological and biochemical investigation, anaemia was detected in six (8%), leucopenia in five (7%), severe lymphopenia of less than 1×10^9/L in 56 (75%), and thrombocytopenia in 28 (37%). Raised values were seen for alanine aminotransferase (42–343 U/L), aspartate aminotransferase (39–302 U/L), and creatinine kinase (176–1466 U/L) in 22 (29%), 24 (32%), and 27 (36%) patients, respectively. The median lymphocyte counts decreased from $0·8\times10^9$/L (IQR 0·6–1·1) on admission to $0·6\times10^9$/L (0·5–0·9), $0·4\times10^9$/L (0·3–0·5), and $0·4\times10^9$/L (0·3–0·6) at days 7, 14, and 21, respectively.

In terms of disease progression, all except one patient became afebrile within 48 h with the standard treatment protocol, but the fever recurred in 64 (85%) patients at a mean of 8·9 days (SD 3·1). Only ten of these patients had positive findings on sepsis work up: three had *Stenotrophomonas maltophilia* bacteraemia, four had clinical evidence of catheter-related sepsis, and three had nosocomial pneumonia due to *Klebsiella pneumoniae* (in two) and *Escherichia coli* (one). All these septic episodes responded to the appropriate antimicrobial treatment and removal of infected catheters. In the remaining 54 patients, fever recurred after a mean of 8·0 (2·1) days, which was unlikely to be caused by hospital-acquired infection. Between days 13 and 15, 17 (23%) patients developed another episode of fever (figure 1).

Watery diarrhoea developed in 55 (73%) patients, with onset at a mean of 7·5 (2·3) days. The rate of diarrhoea peaked at a mean of 8·7 (2·3) days, with a maximum frequency of 6·3 (3·5) times daily (figure 1). Work up for diarrhoeal pathogens, including *C difficile* cytotoxin, was negative in all these patients. The mean duration of diarrhoea was 3·9 (2·3) days. Simultaneous occurrence of fever and diarrhoea occurred in 24 (32%) patients. Concomitant fever, diarrhoea, and radiological worsening occurred in 16 (21%) patients. Improvement of diarrhoea occurred in all patients by day 13.

Radiological worsening was noted in 60 (80%) patients at a mean of 7·4 (2·2) days: 34 (45%) developed shifting of radiological lesions, evidenced by improvement of original lesions followed by the appearance of new lesions (figure 2); worsening of original lesions with or without

	ARDS (n=15)	No ARDS (n=60)	p
Mean (SD) age (years)	48·5 (12·6)	37·3 (11·3)	0·002
Male/female ratio	11/4	25/35	0·042
Underlying illnesses	9 (60%)*	4 (7%)	<0·001†
Chronic hepatitis B virus infection	6 (40%)	3 (5%)	0·001
Mean (SD) duration of symptoms to admission (days)	2·6 (1·1)	2·38 (1·2)	0·51
Mean (SD) initial haemoglobin concentration (g/L)	135 (21)	134 (12)	0·79
Mean (SD) initial total peripheral white blood cell count ($\times10^9$/L)	7·1 (2·1)	6·1 (2·1)	0·09
Mean (SD) initial lymphocyte count ($\times10^9$/L)	1·1 (0·9)	0·9 (0·4)	0·19
Mean (SD) initial platelet count ($\times10^9$/L)	163 (56)	167 (41)	0·77
Mean (SD) initial creatinine (μmol/L)	94·5 (11·1)	86·1 (14·6)	0·004
Mean (SD) initial ALT (U/L)	47·8 (27·5)	35·9 (45·2)	0·33
Mean (SD) initial CPK	327·1 (367·7)	161·5 (125·9)	0·11
Mean (SD) initial LDH	482·6 (242·9)	384·8 (119·8)	0·25
NPA RT-PCR positive at diagnosis	5 (33%)	19 (31·7%)	0·77
Mean (SD) day of antibody seroconversion after onset of symptoms	20·0 (5·5)	19·9 (4·9)	0·94
Apparently normal chest radiograph on admission‡	4 (27%)	18 (30%)	1·0
Multilobar involvement on chest radiograph on admission	5 (33%)	11 (18%)	0·29
Diarrhoea	12 (80%)	43 (72%)	0·75
Recurrent fever	13 (87%)	41 (68%)	0·21

ALT=alanine aminotransferase. CPK=creatinine phosphokinase. LDH=lactic dehydrogenase. NPA=nasopharyngeal aspirate. *Three patients had chronic active hepatitis B, one had uterine fibroid. †SARS established by clinical features plus high-resolution CT findings. ‡Six patients had chronic active hepatitis B infection, one had carcinoma of ovary, one had diabetes mellitus, and one had asthma.

Table 1: **Risk factors associated with development of ARDS requiring ventilatory support and intensive care**

	Adjusted odds ratio (95% CI)	p
Independent predictive factors		
Age-groups (years)		
21–40	1·0	..
41–60	4·3 (0·9–20·0)	0·06
61–80	28·0 (3·1–253·3)	0·003
HBsAg-positive patients	18·0 (3·2–101·3)	0·001

Table 2: **Independent risk factors predicting development of ARDS by multivariate analysis**

development of new lesions was noted in the remaining 26 (35%) patients. Overall, 46 (61%) patients subsequently improved, 11 (15%) had remained static at the time of writing, and 18 (24%) further progressed into a diffuse ground-glass appearance at a mean of 12·0 (4·4) days. Of the 18 patients with diffuse ground-glass changes, 15 developed ARDS. Among all 75 patients, nine (12%) developed spontaneous pneumomediastinum during follow-up. The characteristic shifting of radiological changes is illustrated in figure 2.

33 (44%) patients developed arterial oxygen desaturation of less than 90% at room air, at a mean of 9·1 (4·2) days after onset of symptoms (figure 1). 24 (32%) patients required intensive care at a mean of 11·0 (6·4) days, among whom 19 had to be intubated at a mean of 12·9 (6·4) days. 15 (20%) patients progressed to ARDS and required mechanical ventilation. On day 1 of mechanical ventilation for ARDS, the mean PaO_2-to-FiO_2 ratio was 14·7 kPa (10·8) and the mean APACHE II score was 22·3 (5·8). Time to occurrence of ARDS showed a bimodal pattern, with one peak at 11·0 days and another peak at 20·0 days (figure 1). Seven patients developed hospital-acquired infection during their stay in the intensive-care unit, including hospital-acquired pneumonia in three, meticillin-resistant *Staphylococcus epidermidis* bacteraemia in one, and clinical sepsis in three, without positive cultures.

On univariate analysis, the risk factors associated with ARDS requiring ventilatory support and intensive care were age, male sex, chronic hepatitis B virus carriage, raised creatinine, and recurrence of fever (table 1). Lymphocyte counts of ARDS patients on days 7, 14, and 21 did not differ significantly from those in non-ARDS patients. On multivariate analysis, only age and chronic hepatitis B virus infection were significant risk factors (table 2).

The mean length of stay for 75 patients was 22·1 (3·1) days, whereas for the 15 patients who developed ARDS, the mean length of stay was 26·8 days at the time of writing. Five patients died during the study period, of whom two, aged 79 and 64 years, had succumbed to acute myocardial infarction on days 13 and 17, respectively. One patient died of clinical sepsis on day 23. Another two patients died of clinical sepsis and ARDS on days 24 and 25, respectively. 27 (36%) of patients were discharged home or transferred to a rehabilitation facility. One patient was transferred to a specialised obstetric unit for urgent delivery of a baby at 32 weeks' gestation. For the 42 patients who remained in the hospital, 13 were treated in intensive care for ARDS (table 3).

IgG seroconversion was documented

	n=75
Outcome	
Death*	5 (7%)
Convalescence at home or at rehabilitation facility	27 (36%)
Transfer to special obstetric unit	1 (1%)
Hospital admission	
In general ward	29 (39%)
In intensive-care unit for ARDS	13 (17%)

*Two patients died of acute myocardial infarction, one of clinical sepsis, and two of clinical sepsis and ARDS

Table 3: **Outcomes in SARS patients at the time of writing**

in 70 (93%) patients at mean of 20 (5·1) days (figure 3). SARS-associated coronavirus RNA was detected in nasopharyngeal aspirates by RT-PCR in 24 (32%) of 75 patients at initial presentation (mean 3·2 [1·3] days after onset) and in 51 (68%) at day 14. In stool samples collected later in the illness (a mean of 14·2 [2·2] days after onset), viral RNA was detected in 65 (97%) of 67. Similarly, viral RNA was detected in 31 (42%) of 74 urine samples collected at a mean of 15·2 (1·7) days after onset of symptoms.

The 20 patients initially documented to have SARS-associated coronavirus RNA in the nasopharyngeal aspirates on RT-PCR were serially followed up with sequential samples; the virological profile is shown in table 4. Quantitative RT-PCR of the nasopharyngeal aspirates showed an inverted V pattern, with mean geometric viral loads of $2·3\times10^5$ copies per mL, and $1·9\times10^7$ copies per mL, and $9·8\times10^4$ copies per mL on days 5, 10, and 15, respectively, after onset of symptoms (figure 4).

Discussion

Studies on SARS have generally been retrospective or limited to the description of the initial clinical, haematological, radiological and microbiological findings. The patients we studied, however, were residents of a housing estate placed under closed surveillance by the Department of Health soon after identification of the outbreak. All residents underwent frequent health checks, and symptomatic patients were admitted to hospital soon

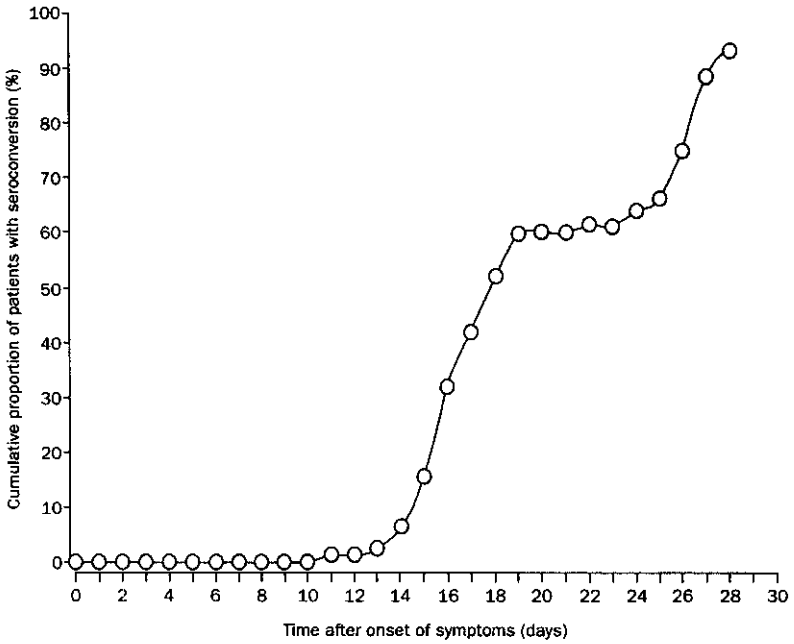


Figure 3: **Kinetics of IgG seroconversion to SARS-associated coronavirus**
Cumulative data on earliest time to seroconversion is presented.

	Time after onset of symptoms (days; n=20)				
	10	13	16	19	21
Sample (positivity rate)					
Nasopharyngeal aspirate	19 (95%)	18 (90%)	18 (90%)	15 (75%)	9 (47%)*
Stool	20 (100%)	20 (100%)	19 (95%)	12 (80%)†	10 (67%)†
Urine	10 (50%)	9 (45%)	7 (35%)	6 (30%)	4 (21%)*

*In 19 patients. †In 15 patients

Table 4: **Subsequent analysis of clinical samples of 20 patients with initial RT-PCR-positive nasopharyngeal aspirates and antibody seroconversion to SARS-associated coronavirus**

after the onset of symptoms and, thus, were admitted early in the course of the illness. Therefore, we were able to do a prospective study in a large cohort of patients infected in one community outbreak of SARS who were epidemiologically linked, and of whom most had virologically confirmed SARS-associated coronavirus.

The clinical progression of SARS was mostly uniform in our cohort, with a tri-phasic pattern. Week 1 was characterised by fever, myalgia, and other systemic symptoms that generally improve after a few days. The increasing viral load during this phase suggests that the symptoms are largely related to the effect of viral replication and cytolysis. As the disease progressed into week 2, the patients frequently had recurrence of fever, onset of diarrhoea, and oxygen desaturation. Strikingly, nearly half the patients had shifting radiographic shadows. If viral-induced damage was the primary pathological mechanism, such a flitting pattern of radiological change is difficult to explain. The timing of the IgG seroconversion, which starts on day 10, seems to correlate with falls in viral load, which occurs from between day 10 and 15, despite the use of pulse methylprednisolone. Severe clinical worsening also occurs at this time, which cannot be explained by uncontrolled viral replication. This finding is supported by the progressive decrease in rates of viral shedding from nasopharynx, stool, and urine from day 10 to 21 after onset of symptoms in the 20 patients who underwent prospective follow-up with RT-PCR. Taken together, these findings suggest that the lung damage at this phase is related to immunopathological damage as a result of an overexuberant host response, rather than uncontrolled viral replication. 20% of patients in this cohort progressed to the third phase, characterised by ARDS necessitating ventilatory support. Inevitably, several patients developed nosocomial sepsis during this phase of end-organ damage and severe lymphopenia.

In terms of pathogenesis, in pulmonary reovirus infection in athymic mice, a lower plaque-forming value of 10^6 is associated with pathological changes of bronchiolitis obliterans organising pneumonia, whereas a higher inoculum of 10^7 is associated with ARDS.[14] To lessen the risk of progression to the chronic phase of ARDS, an effective antiviral to reduce the viral load may be important. At the time of writing, no antiviral is reported to be clinically effective for the treatment of this novel coronavirus. Ribavirin has broad-spectrum antiviral activities and is effective for the treatment of fulminant hepatitis in mice caused by the mouse hepatitis coronavirus.[15] Although the inhibitory activity of ribavirin against mouse hepatitis coronavirus is weak, ribavirin can decrease the release of proinflammatory cytokines from the macrophages of mice. It also switched the immune response of the mice from a T-helper-2 to a T-helper-1 response. Thus, irrespective of its antiviral role, ribavirin may act as an immunomodulator. An effective antiviral agent is needed because decreasing the initial cytolytic damage and viral load in the first phase may in turn result in decreased immunopathological damage during the second phase. Since a notable proportion of our patients developed ARDS, the role of immunologically directed strategies, such as corticosteroids, intravenous immunoglobulin, IgM-enriched immunoglobulin, convalescent plasma, and the antitumour necrosis factor thymosin, deserve further investigation.

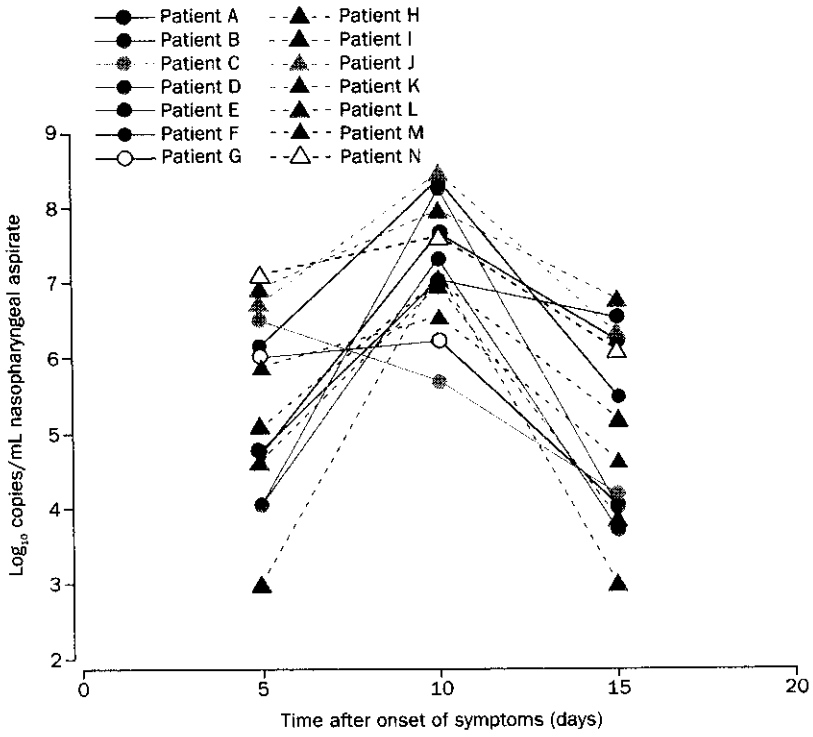


Figure 4: **Sequential quantitative RT-PCR for SARS-associated coronavirus in nasopharyngeal aspirates of 14 SARS patients**

Unexpectedly, chronic hepatitis B infection was an important independent risk factor for progression to ARDS. This finding may also explain a higher rate of death among young Chinese patients because of the high rate of chronic hepatitis B infection in Southern China. The finding is important because in all our patients, lamivudine was given as prophylaxis while the patients were taking corticosteroids. We did not assess the viral load for hepatitis B virus DNA since the liver function tests were normal with no clinical stigmata of chronic liver diseases. Thus these patients' poor

outcome cannot be explained by uncontrolled hepatitis activity. An unknown immune defect in chronic hepatitis B carriers may account for their poor ability to control the coronavirus infection or the associated immunopathological damage. Co-infection with SARS coronavirus in hepatitis B carriers may predict a worse prognosis. The option of prophylaxis with intranasal interferon alfa could be investigated in household contacts and health-care workers, especially in those with chronic hepatitis B virus carriage, because this approach is effective in other human coronavirus infections.[16]

The case definition of SARS is clinical and rather non-specific in the absence of epidemiological history of contact. We showed that IgG seroconversion has 93% sensitivity at day 28, even despite corticosteroid treatment. In this case, IgG isotype-specific antibody to the SARS coronavirus was tested for. If antibody to all immunoglobulin classes is assayed for, seroconversion will probably be detected earlier. Although viral RNA detection in the nasopharyngeal aspirate has a sensitivity of only 32% at presentation, testing of multiple nasopharyngeal and faecal samples increased the sensitivity of the RT-PCR assay.

The presence of virus in the stool is an important finding because it suggests the possibility of oral-faecal transmission. The epidemiological investigation of the Amoy Gardens SARS outbreak suggested that the outbreak was caused by a faulty sewage system.[8] Diarrhoea seemed more prominent in our cohort of patients than previously reported,[3,7] and the severe watery diarrhoea in these patients presented a challenge to health-care workers for infection control. Whether this apparent change in the clinical presentation is related to the difference in the route of infection or a mutation in the virus is still conjectural. Importantly, the mortality rate of 6·7% we reported is higher than the previously reported figure of 3·5% at day 21.[6]

We noted the absence of a relation between the high rate of spontaneous pneumomediastinum unrelated to intubation and positive-pressure ventilation. This phenomenon is rarely reported in advanced cytomegalovirus pneumonia,[17] and influenza bronchiolitis,[18] whereas spontaneous pneumothorax is commonly reported in *Pneumocystis carinii*, and *Staphylococcus aureus* pneumonia. The initial radiographic lesions in SARS were pleural based.[6] In patients in whom the initial consolidation is abutting on to the mediastinum, adhesions and cyst formation might occur at the interface between the mediastinal pleura and the pulmonary pleura. Any rupture of these cysts will result in spontaneous pneumomediastinum. Alternatively, a diffuse peripheral pneumonic changes followed by pleural adhesion may occur over the parietal pleura of the chest walls, which leaves the mediastinal sites as the area in which rupture of cyst can occur. This will also create the necessary setting for spontaneous pneumomediastinum to occur without spontaneous pneumothorax.

RT-PCR on respiratory and faecal samples, together with serology, can confirm the diagnosis of SARS-associated coronavirus infection in most SARS patients. The progression of the disease to respiratory failure might not be associated with uncontrolled viral replication, but may, in fact, be immunopathological in nature.

Contributors

J S M Peiris and K Y Yuen are co-principal investigators, jointly wrote the report, and supervised the virological and clinical component of the study. C M Chu, V C C Cheng, K S Chan, I F N Hung, K I Law, B Y F Tang, J S C Ng, and W L Ng were involved in collection and analysis of the clinical data. C S Chan and T Y W Hon were involved in radiological analysis. L L M Poon, K H Chan, and Y Guan did the quantitative PCR and other virology assays. R W M Lai coordinated the microbiological investigations in United Christian Hospital.

Members of the HKU/UCH SARS Study Group

S W Kwan, K F Lo, A M Y Fung, I M T Chu, W T Hui, H K Leung, W H Seto, Department of Microbiology, Queen Mary Hospital; S Y Lam, P C Y Woo, S K P Lau, W Luk, H Y Ng, L J Zhang, C Y Cheung, O K Wong, W Cheung, G Tse, Department of Microbiology, University of Hong Kong; P W Ng, T C Sim, L S Lau, V Chan, W S Leung, J T M Chan, K L Lee, Y S Poon, E Chow, C Y Leung, F L Lau, W L Tsoi, A C H Choi, C N C Chan, M F Leung, C Y Tse, United Christian Hospital.

Conflict of Interest statement

None declared.

Acknowledgments

We thank E K Yeoh of the Hong Kong Government for facilitating this study; Klaus Stöhr and WHO for initiating and coordinating the information exchange between members of the WHO SARS Laboratories network; and the staff of the Department of Microbiology, Queen Mary Hospital, and of the Department of Medicine and Intensive Care Unit, United Christian Hospital, for technical assistance and management of patients. Research funding was received from from the National Institute of Allergy and Infectious Diseases, USA (public health research grant A195357), the Wellcome Trust (grant GR067072/D/02/Z), University of Hong Kong and the Hospital Authority of Hong Kong.

References

1 Severe Acute Respiratory Syndrome (SARS): multi-country outbreak—update 34. http://www.who.int/csr/don/2003_04_19/en/ (accessed May 5, 2003).
2 Centers for Disease Control and Prevention. SARS coronavirus sequencing. http://www.cdc.gov/ncidod/sars/sequence.htm (accessed May 5, 2003).
3 Peiris JSM, Lai ST, Poon LLM, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; **361:** 1319–25.
4 Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. http://content.nejm.org/cgi/reprint/NEJMoa030781v3.pdf (accessed at May 5, 2003).
5 Poutanen SM, Low DE, Henry B, et al. Identification of severe acute respiratory syndrome in Canada. http://content.nejm.org/cgi/reprint/NEJMoa030634v3.pdf (accessed May 5, 2003).
6 Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. http://content.nejm.org/cgi/reprint/NEJMoa030685v2.pdf (accessed May 5, 2003).
7 Tsang KW, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. http://content.nejm.org/cgi/reprint/NEJMoa030666v3.pdf (accessed May 5, 2003).
8 Atypical pneumonia. http://www.info.gov.hk/dh/ap.htm (accessed May 5, 2003).
9 Ho W. Guideline on management of severe acute respiratory syndrome (SARS). *Lancet*; 2003; **361:** 1313–15.
10 HA guidelines on severe acute respiratory syndrome. http://www.ha.org.hk/sars/guidelines/index.html (accessed May 5, 2003).
11 Bernard GR, Artigas A, Brigham KL, et al. The American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; **149:** 818–24.
12 Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13:** 818–29.
13 Poon LLM, Wong OK, Luk W, et al. Rapid diagnosis of a coronavirus associated with severe acute respiratory syndrome (SARS). http://www.clinchem.org/cgi/content/full/49/4/DC1 (accessed May 5, 2003).
14 Majeski EI, Harley RA, Bellum SC, et al. Differential role for T cells in the development of fibrotic lesions associated with reovirus 1/L-induced bronchiolitis obliterans organizing pneumonia versus acute respiratory distress syndrome. *Am J Respir Cell Mol Biol* 2003; **28:** 208–17.
15 Ning Q, Brown D, Parodo J, et al. Ribavirin inhibits viral-induced macrophage production of TNF, IL-1, the procoagulant fgl2 prothrombinase and preserves Th1 cytokine production but inhibits Th2 cytokine response. *J Immunol* 1998; **160:** 3487–93.
16 Turner RB, Felton A, Kosak K, et al. Prevention of experimental coronavirus colds with intranasal alpha-2b interferon. *J Infect Dis* 1986; **154:** 443–47.
17 Olliff JF, Williams MP. Radiological appearances of cytomegalovirus infections. *Clin Radiol* 1989; **40:** 463–67.
18 Tutor JD, Montgomery VL, Eid NS. A case of influenza bronchiolitis complicated by pneumomediastinum and subcutaneous emphysema. *Pediatr Pulmonol* 1995; **19:** 393–95.

Nephrol Dial Transplant (2003) 18: 2178–2181
DOI: 10.1093/ndt/gfg454

Nephrology
Dialysis
Transplantation

Case Report

Severe acute respiratory syndrome in haemodialysis patients: a report of two cases

Hon Lok Tang[1], Au Cheuk[1], Kwok Hong Chu[1], William Lee[1], Sze Ho Wong[1], Yuk Lun Cheng[2], Alex Wai Yin Yu[2], Ka Shun Fung[1], Wai Kay Tsang[1], Hilda Wai Han Chan[1] and Kwok Lung Tong[1]

[1]Division of Nephrology, Department of Medicine and Geriatrics, Princess Margaret Hospital, Hong Kong and [2]Renal Unit, Department of Medicine, Alice Ho Miu Ling Nethersole Hospital, Hong Kong, China

Keywords: end-stage renal failure; haemodialysis; pulse methylprednisolone; ribavirin; SARS; severe acute respiratory syndrome

Introduction

In March 2003, an outbreak of severe acute respiratory syndrome (SARS) occurred in Hong Kong. As of July 10, 2003, the World Health Organization has reported 1755 cases of SARS in Hong Kong and 8437 cases worldwide [1]. Outbreaks and case clusters have been reported in the literature in recent months [2–5]. The first known case of SARS in Hong Kong was a physician working in a hospital in Guangdong Province who travelled to Hong Kong on February 21, 2003 [3]. A novel coronavirus has been identified as a possible cause of SARS [6,7]. SARS can occur in both healthy individuals and those with chronic illness including end-stage renal failure. Clinical information of SARS on renal dialysis patients is lacking. We describe here two end-stage renal failure patients, both receiving chronic haemodialysis, who acquired the disease after contact with SARS patients and had different outcomes.

Cases

Patient 1

A 49-year-old male, who had end-stage renal failure and was receiving chronic haemodialysis twice weekly, was admitted to the Princess Margaret Hospital on April 6, 2003, because of fever, chills, rigors and cough for 1 day. He also had myalgia, malaise, anorexia, headache and dizziness (Table 1). He had a history of contact with SARS patients. From March 31 to April 2, 2003, he was hospitalized in a medical ward of the Alice Ho Miu Ling Nethersole Hospital, where there was an outbreak of SARS, for haemophilus influenzae pneumonia. Four days after discharge from that hospital (day 1), he began to run a fever and was admitted into the Princess Margaret Hospital the following day (day 2). After admission, serial chest radiographs from days 2 to 6 showed no consolidation (Figure 1A). His laboratory data at presentation revealed lymphopaenia with a normal total white cell count, mild thrombocytopaenia and an elevated C-reactive protein level (Table 2). Other laboratory results are shown in Table 2. His liver enzymes, lactate dehydrogenase and creatine phosphokinase were normal. After admission, he was started on broad-spectrum antibiotic therapy with levofloxacin. However, his fever persisted with a highest temperature of 39.5°C. In view of his contact history with SARS patients, he was put on anti-viral therapy with i.v. ribavirin on day 5. He was given 900 mg (20 mg/kg) as a loading dose, followed by 450 mg (10 mg/kg) every 24 h. In view of the negative chest radiographs, a high-resolution CT scan of the thorax was performed on day 7 (Figure 1B), which revealed patchy consolidation predominantly over the superior and posterior left lower lobe, small areas of consolidation and ground-glass shadowing over the left lingular lobe, anterior, posterior and lateral right lower lobe. His chest radiograph then began to deteriorate to a maximum degree on day 11 with involvement of the right lower zone, left middle zone and left lower zone (Figure 1C and D), associated clinically with dyspnoea. The patient was started on i.v. pulse methylprednisolone on day 7 after a CT scan of the thorax revealed bilateral involvement of the lungs.

Correspondence and offprint requests to: Dr Hon Lok Tang, MRCP, Division of Nephrology, Department of Medicine and Geriatrics, Princess Margaret Hospital, 2–10 Princess Margaret Hospital Road, Lai Chi Kok, Kowloon, Hong Kong, China. Email: pmhrenal@hotmail.com

Methylprednisolone 0.5 g daily was given from days 7 to 9, then 1 g daily was given on days 10, 12 and 13. A total of 4.5 g of methylprednisolone was given over 7 days. His fever began to subside on day 13 and his lung condition improved with a decreasing intensity of consolidation (Figure 1E). Intubation was not required even during maximum deterioration of his pneumonia. The reverse-transcriptase polymerase chain reaction (RT–PCR) assay for coronavirus of his throat and nasal swabs and stool specimens were all positive. He was discharged on day 25 after recovering from SARS. Eighteen days of ribavirin and 26 days of steroids including methylprednisolone were given during the course of his illness. The patient's serum coronavirus antibody titre showed a >8-fold rise during the convalescent phase at 5 weeks (from <1/25 to 1/200).

Table 1. Symptoms of two haemodialysis patients with SARS at presentation

Symptoms	Patient 1	Patient 2
Fever >38°C	+	–
Chills or rigors	+	–
Cough	+	–
Sputum	–	–
Haemoptysis	–	–
Shortness of breath	–	–
Myalgia	+	–
Malaise	+	–
Anorexia	+	–
Diarrhoea	–	–
Headache	+	–
Runny nose	–	–
Sore throat	–	–
Dizziness	+	–

Patient 2

An 86-year-old male, who had end-stage renal failure secondary to diabetic nephropathy, had been receiving chronic haemodialysis thrice weekly for 3 years. He had other co-morbid diseases including diabetes mellitus, hypertension, ischaemic heart disease, a history of cerebral infarction and thalassaemia minor. He was admitted to the Princess Margaret Hospital on March 31, 2003. He had a history of close contact with SARS

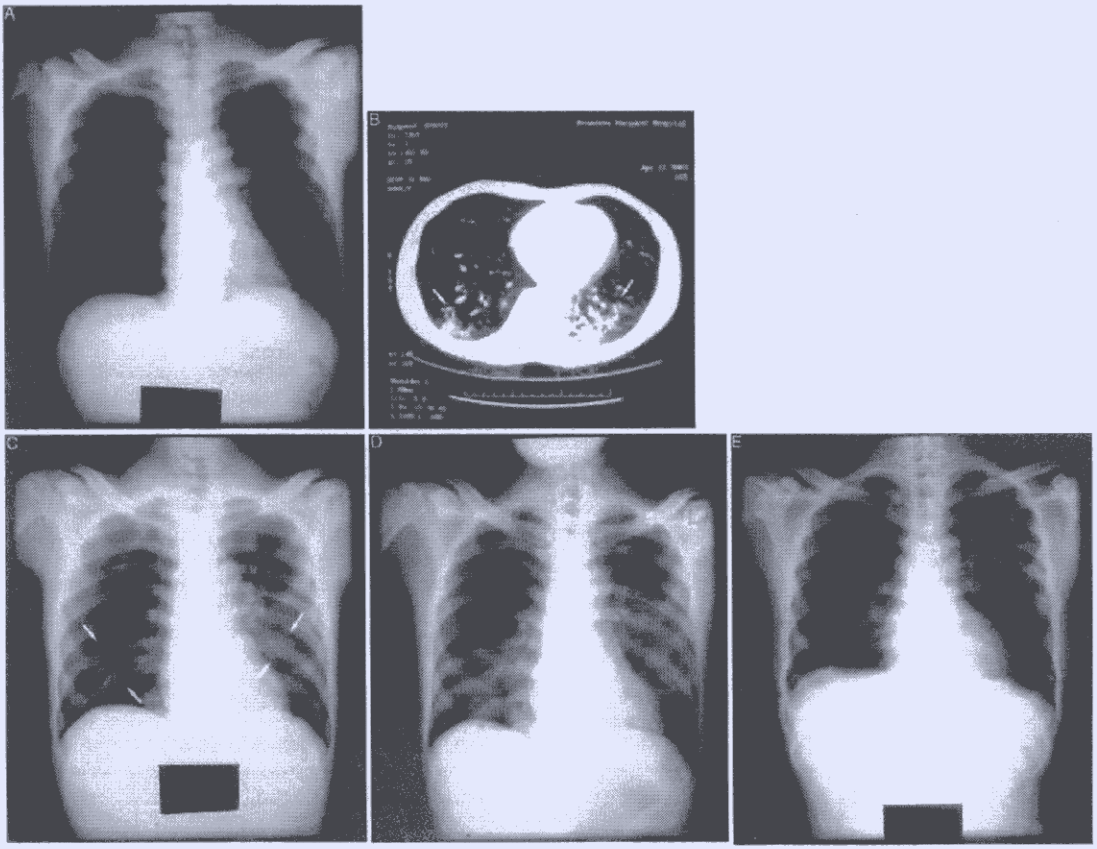


Fig. 1. Radiographic images of patient 1. **(A)** Chest radiograph on day 6 after onset of symptoms showed no consolidation. **(B)** High-resolution CT scan of the thorax on day 7 showing patchy consolidation and ground-glass shadowing in both the left and right lower lobes. **(C)** Chest radiograph on day 9 began to reveal air-space shadowing over the left middle zone and right lower zone. **(D)** Chest radiograph during maximum deterioration (day 11) showing extensive pulmonary infiltrates over bilateral lung fields. **(E)** Chest radiograph on day 20 showing improvement of lung shadows after therapy.

Table 2. Laboratory data of two haemodialysis patients with SARS at presentation

Laboratory test	Patient 1	Patient 2
Total white cell count ($\times 10^9$/l)	7.6	7.4
Lymphocyte count ($\times 10^9$/l)	0.6	0.3
Neutrophil count ($\times 10^9$/l)	6.2	6.8
Platelet count ($\times 10^9$/l)	130	211
Haemoglobin (g/dl)	9.3	9.9
Sodium (mmol/l)	130	133
Potassium (mmol/l)	4.3	6.4
Urea (mmol/l)	20.9	17.2
Creatinine (μmol/l)	967	892
Albumin (g/l)	39	37
Globulin (g/l)	33	32
Total Bilirubin (μmol/l)	7	12
Alkaline phosphatase (U/l)	50	83
Alanine aminotransferase (U/l)	9	14
Lactate dehydrogenase (U/l)	130	280
Creatine phosphokinase (U/l)	74	–
C-reactive protein (mg/l)	34.1	–

patients, his two Fhilipino maids, who took care of the patient. Ten days before his admission, his two maids were admitted into the hospital because of high fever and were later confirmed to have SARS. One day after admission (day 1), the patient began to develop a low-grade fever of 37.6°C. Apart from the low-grade fever, he had no chills, rigors, cough, sputum, haemoptysis, shortness of breath, myalgia, malaise, diarrhoea or headache (Table 1). Laboratory data revealed lymphopaenia with a normal total white cell count and an elevated lactate dehydrogenase level (Table 2). Other laboratory results are shown in Table 2. His chest radiograph on day 1 showed mild right upper zone haziness. He was covered with broad-spectrum antibiotic therapy with levofloxacin. In view of the strong contact history, he was started on i.v. ribavirin 400 mg (6.5 mg/kg) every 24 h on day 2. Despite ribavirin treatment, the patient ran a persistently low-grade fever and a chest radiograph on day 21 revealed new shadows over the right lower zone. The antibiotic was then changed to imipenem. A chest radiograph taken on day 26 showed new consolidation over the left middle zone. I.v. hydrocortisone 100 mg every 6 h was started on the same day. However, 2 days later (day 28) the patient developed cardiac arrest and succumbed. Throughout his course in hospital, the patient's fever was low grade, with a highest temperature of 38°C. The RT–PCR assay for coronavirus of his throat and nasal swabs was negative on day 14 but a second specimen taken on day 24 became positive. The patient's serum coronavirus antibody titre checked on days 14 and 24 showed no rise (both titres were $< 1/25$). However, the two serum specimens were taken only 11 days apart.

Discussion

We report two cases of SARS occurring in end-stage renal failure patients. Both patients were receiving chronic haemodialysis. Apart from renal failure, patient 2 also had other multiple co-morbid diseases. The incubation period for SARS in patient 1 was 4–7 days, while that in patient 2 was ~11 days. Patient 1 had typical presentation of SARS with high fever (temperature > 38°C), cough, chills, rigors, myalgia, malaise and headache. However, patient 2 was totally asymptomatic except for a low-grade fever of 37.6°C at presentation. The maximum temperature throughout his stay in hospital was only 38°C. The diagnosis of SARS was based on his strong contact history, chest radiograph shadows and the second RT–PCR assay for coronavirus of his throat and nasal swabs on day 24. Both cases had lymphopaenia with a normal total white cell count at presentation. Patient 1 had a positive RT–PCR assay for coronavirus of the throat and nasal swabs. The RT–PCR assay of his stool specimen was also positive, despite the absence of diarrhoea. The first throat and nasal swabs of patient 2 for coronavirus RT–PCR assay on day 14 was negative, while a second specimen on day 24 was positive. This may be due to the fact that throat and nasal swabs contain considerably less viral RNA than sputum, and the virus may escape detection [7]. Patient 1 demonstrated a > 8-fold rise in coronavirus antibody titre during the convalescent phase, confirming a recent coronavirus infection.

Both patients had been treated with i.v. ribavirin, which was used as anti-viral therapy. The dose of ribavirin used ranged from 6.5 to 10 mg/kg every 24 h. However, the optimal dose for treating SARS in patient with end-stage renal failure and in those undergoing haemodialysis is not known. The use of i.v. pulse methylprednisolone during the phase of deterioration seemed to benefit our first patient, leading to improvement of pulmonary infiltrates. The total dose of methylprednisolone used was 4.5 g. Pulse methylprednisolone was not given in patient 2 in view of his advanced age and multiple co-morbidities. The first patient recovered after a maximum deterioration 11 days from the onset of symptoms, whereas the second patient died as a result of SARS.

In summary, the experiences in our two cases show that SARS, in end-stage renal failure patients, may have an atypical presentation. They can present with minimal symptoms, e.g. low-grade fever only, leading to diagnostic difficulty. The optimal ribavirin dose for treating SARS in patients with end-stage renal failure and in those receiving haemodialysis is unknown. Further studies are warranted to clarify these. I.v. pulse methylprednisolone given at the phase of deterioration seems to be of benefit. One patient died of SARS and the other recovered from the disease.

Acknowledgement. We would like to thank all of the medical and nursing staff in our departments for their dedicated care of the SARS patients.

Conflict of interest statement. None declared.

References

1. World Health Organization. Cumulative number of reported probable cases of SARS. http://www.who.int/csr/sars/country/2003_06_19/en (accessed July 11, 2003)
2. Lee N, Hui D, Wu A *et al.* A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003; 348: 1986–1994
3. Tsang KW, Ho PL, Ooi GC *et al.* A cluster of cases of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003; 348: 1977–1985
4. Poutanen SM, Low DE, Henry B *et al.* Identification of severe acute respiratory syndrome in Canada. *N Engl J Med* 2003; 348: 1995–2005
5. Peiris JSM, Chu CM, Cheng VCC *et al.* Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003; 361: 1767–1772
6. Peiris JSM, Lai ST, Poon LLM *et al.* Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; 361: 1319–1325
7. Drosten C, Gunther S, Preiser W *et al.* Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003; 348: 1967–1976

Received for publication: 11.7.03
Accepted in revised form: 17.7.03

Clinical Presentation and Outcome of Severe Acute Respiratory Syndrome in Dialysis Patients

Ping-Nam Wong, MRCP(UK), Siu-Ka Mak, FRCP(Edin), Kin-Yee Lo, MRCP(UK), Gensy M.W. Tong, MRCP(UK), Yuk Wong, MRCP(UK), Chi-Leung Watt, FANZCA(A & NZ), and Andrew K.M. Wong, FRCP(London)

• **There was a major outbreak of severe acute respiratory syndrome (SARS) affecting more than 300 patients occurring in a private housing estate in Hong Kong, in which an infected renal patient was suspected to be the primary source. It is unknown whether renal patients would represent a distinct group of patients who share some characteristics that could predispose them to have higher infectivity. In this context, we have encountered 4 dialysis patients contracting SARS in a minor outbreak, which involved 11 patients and 4 health care workers, in a medical ward of a regional hospital. Of these 4 dialysis patients, 1 patient was receiving hemodialysis while the other 3 patients were on continuous ambulatory peritoneal dialysis. Fever and radiological changes were their dominant presenting features. All were having positive results for SARS-associated coronavirus ribonucleic acid by reverse transcriptase–polymerase chain reaction performed on their nasopharyngeal aspirates or stool samples. It appeared that treatment with high-dose intravenous ribavirin and corticosteroids could only resolve the fever, but it could not stop the disease progression. All 4 patients developed respiratory failure requiring mechanical ventilation on days 9 through 12. At the end, all of the patients died from sudden cardiac arrest, which was associated with acute myocardial infarction in 2 cases. From this small case series, it appeared that dialysis patients might have an aggressive clinical course and poor outcome after contracting SARS. However, a large-scale study is required to further examine this issue, and further investigation into the immunologic abnormalities associated with the uremic state in this group of patients is also warranted.** ***Am J Kidney Dis*** **42:1075-1081.**

INDEX WORDS: Severe acute respiratory syndrome (SARS); dialysis; presentation; outcome.

MANY COUNTRIES in the world have been seriously affected by the outbreaks of severe acute respiratory syndrome (SARS) since March 2003.[1] It is a new emerging infectious disease with a novel coronavirus being identified as the causative agent.[2,3] Hong Kong has been one of the most severely affected areas.[4,5] Of the 1,755 cases reported in Hong Kong so far, 321 cases originated from a major outbreak in Amoy Gardens, a high-rise and densely populated private estate.[6] An epidemiological investigation has linked the outbreak to a faulty sewage system. The system was probably contaminated by the excreta of an index case who was a patient with chronic renal disease on dialysis. While the exact spreading mechanism remains uncertain, it has been speculated that a patient having renal failure might carry an extraordinarily high viral load, which could lead to a large outbreak. It would also be interesting to know whether the clinical course and outcome of a renal patient having SARS would be different from that of other SARS patients. In this regard, we have encountered a minor SARS outbreak occurring in a ward of a regional hospital involving 11 patients and 4 health care workers. All of the cases fulfilled the modified World Health Organization (WHO) definition of SARS.[2] Of these 11 patients, 4 were on dialysis. We have therefore taken the opportunity to examine the clinical courses and outcomes of these patients to see whether they represent a distinct patient group.

PATIENTS AND RESULTS

Setting

Kwong Wah Hospital is a major regional acute hospital in Hong Kong with over 1,200 beds. The SARS outbreak occurred in 1 of the general medical wards. The medical ward involved comprises 56 medical beds and a hemodialysis facility (Fig 1). The 56 medical beds spread over 9 rooms

From the Department of Medicine and Geriatrics and Intensive Care Unit, Kwong Wah Hospital, Hong Kong SAR, China.

Received June 13, 2003; accepted in revised form August 19, 2003.

Address reprint requests to Ping-Nam Wong, MRCP(UK), Renal Unit, Department of Medicine and Geriatrics, Kwong Wah Hospital, 25 Waterloo Road, Kowloon, Hong Kong SAR, China. E-mail: apnwong@yahoo.com

0272-6386/03/4205-0029$30.00/0
doi:10.1053/S0272-6386(03)01084-9

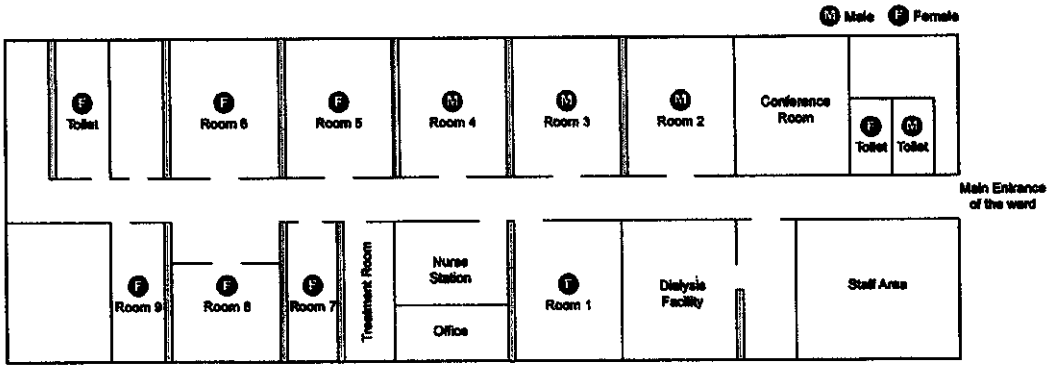


Fig 1. Diagram showing the floor plan of the ward where the SARS outbreak occurred.

(6 for women and 3 for men). Each room could accommodate 4 to 10 patients. Common patient areas in the ward include the main corridor and toilet facilities (1 for men and 2 for women). All of the rooms share a common ventilation system with the ventilation duct outputs located at the ceiling (Fig 2). During the outbreak, the ventilation facility was providing 6 air changes per hour (ACH) with no high-efficiency particulate air (HEPA) filter in use.

Case Descriptions

The outbreak involved 11 female patients and 4 women health care workers. All of the SARS patients fulfilled the modified WHO definition of SARS. The mean age of the 11 patients was 66.3 ± 13.5 years (median, 68 years).

The First SARS Patient

The first SARS patient, a 57-year-old woman with no known contact with SARS patients, was admitted to room 8 of the ward on March 23, 2003, for some minor respiratory symptoms and fever. At that time, droplet precautions and contact precautionary measures were already implemented in the ward. The patient was subsequently transferred to the isolation ward on March 25, 2003, for suspected SARS infection. Her 6 roommates were then cohorted as suspected SARS contacts. The cohorting was intended to last for 10 days, during which time no new patients would be admitted to the same room or transferred out to another room and ward. During that period, anyone who developed suspicious symptoms of SARS was transferred to the isolation ward immediately. At the end, 4 of her 6 roommates and 2 health care workers having contact with the patient developed SARS (Fig 3). The 4 roommates who developed SARS were 46, 74, 81, and 87 years old, respectively. In addition, the first SARS patient probably also infected patient 1, who at that time was staying in room 6, through contact in the common patient areas.

Patient 1

Patient 1 was a 44-year-old diabetic woman who was newly diagnosed to have end-stage renal failure. She was admitted to room 6 of the ward because of uremic symptoms in February 2003. After staying in the hospital for about 1 month, she was stabilized with regular hemodialysis and was discharged on March 26, 2003. During the hospitalization, none of her roommates in room 6 suffered from SARS, but the first SARS patient was admitted to room 8 3 days

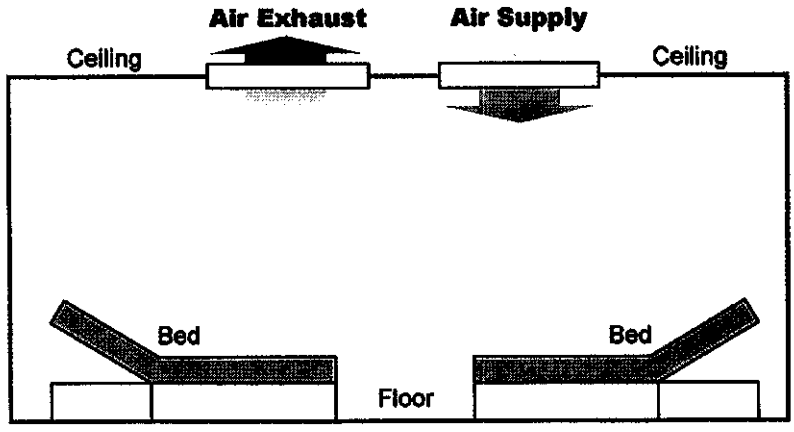


Fig 2. Cross-sectional view of rooms 6 and 8 showing the locations of ventilation ducts.

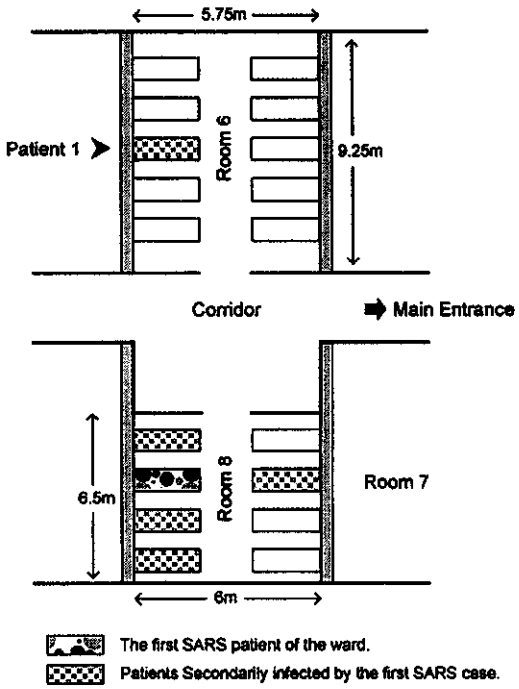


Fig 3. Diagram showing the dimensions of rooms 6 and 8 and the bed locations of the SARS cases related to the first SARS patient.

before patient 1 was discharged from the hospital. Two days after her discharge from the hospital, she was readmitted to room 6 again because of fever, chills, and rigors. On admission, she was advised to put on a surgical mask, although she showed no symptom of upper respiratory tract infection other than fever. Her initial chest radiograph revealed an ill-defined right lower zone air-space opacity, which rapidly worsened after admission. She was then transferred to the isolation ward after staying in the original ward for 46 hours. Her 7 roommates were then cohorted for suspected SARS contacts. At the end, she (patient 1) was confirmed to have SARS, and 5 of her 7 roommates were also found to have SARS (Fig 4). The ages of these 5 patients varied from 60 to 74 years. Of these 5 cases, 3 were renal patients receiving chronic ambulatory peritoneal dialysis (CAPD) who had stayed in the same room with patient 1 for 12, 46, and 45 hours, respectively. Their times to first development of symptoms of SARS after the last exposure varied from 4 to 8 days. In addition, another 2 health care workers who had been exposed to patient 1 subsequently also developed SARS.

Infection Control Measures

After the outbreak, the movement of patients in the ward was stopped. All of the patients in the ward were closely monitored for clinical features of SARS. No visitors to the ward were allowed. A list of potential SARS contacts related to that ward was generated, and it was sent to the Department of Health of the Government for contact tracing and monitoring. All staff of the ward were required to monitor themselves for SARS, and all clinical staff were reminded to look out for suspected SARS cases to facilitate early identification and isolation. Infection control precautions were stepped up to the level of airborne precautions. Disposable gowns, caps, and gloves were used for direct patient care. Rooms 6 and 8 were thoroughly cleansed. Additional exhaust fans were installed for all patient rooms in the ward, after which the airflow rates of these patient rooms were increased to greater than 12 ACH.

After being diagnosed with SARS, patient 1 was hemodialyzed in an isolated area within the dialysis facility where the ventilation could provide 12 ACH. The hemodialyzers were not reused. Because the 3 CAPD patients were too weak to perform the CAPD exchanges themselves, they were switched to twice weekly intermittent peritoneal dialysis (IPD) using automated peritoneal dialysis machines (Home choice; Baxter Healthcare, McGraw Park, IL) to minimize staff exposure to the patients. Each IPD comprised 30 1-hour cycles of 2-L exchanges of 1.5%, 2.5%, or 4.25 % dextrose solution, depending on the hydration status of the patients.

Although we had not sent the spent dialysate for SARS-associated coronavirus study, all the body fluids of suspected or confirmed SARS-infected dialysis patients including the spent dialysate were regarded as potentially infectious and were handled with special precautions. The staff members who needed to handle or dispose the spent dialysate and those who conducted the CAPD exchanges or hemodialysis procedures for suspected or confirmed patient were protected with N95 respirators, eye shields, and disposable gowns, caps, and gloves. To minimize transport of potential infectious material, the drainage bags of spent peritoneal dialysate were emptied into the sink of the sluice room of the ward where the patients stayed. All the disconnected drainage bags were recapped to avoid leakage and were kept in a

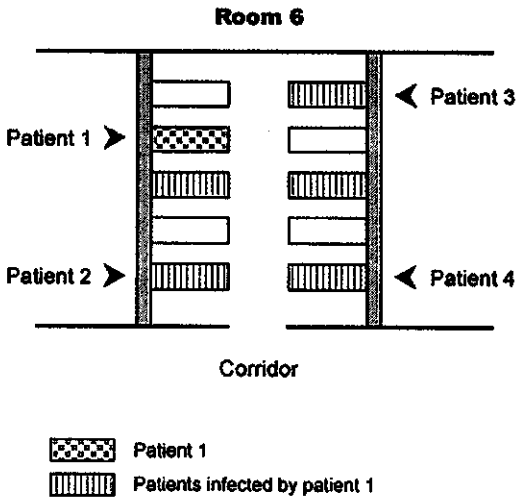


Fig 4. Diagram showing the bed locations of the SARS patients related to the readmission of patient 1 in room 6.

Table 1. Individual Profiles and Clinical Features of the 4 Dialysis Patients Having SARS

	Patient			
	1	2	3	4
Age (y)	44	67	73	71
Sex (M/F)	F	F	F	F
Mode of dialysis	HD	CAPD	CAPD	CAPD
Duration on dialysis (mo)	1	12	104	28
Significant comorbidity other than renal failure	DM	DM, tuberculous lymphadenitis	DM	–
Duration of exposure (h)	Index case of room 6	12	46	45
Time to the onset of symptom (d)	Index case of room 6	4	5	8
Clinical features				
Fever	+	+	+	+
Chills/rigors	+	–	–	+
Myalgia	–	–	–	–
Dyspnea	–	–	–	–
Cough	–	–	–	+
Laboratory findings before treatment with steroids and ribavirin				
Neutrophil count ($\times 10^9$/L)	2.6	9.7	10.3	7.0
Lymphocyte count ($\times 10^9$/L)	0.7	0.6	0.7	2.3
Platelet count ($\times 10^3/\mu$L)	165	189	309	230
Serum LDH (U/L)*	383	263	503	223
Serum ALT (U/L)†	17	40	5	14
Initial chest radiograph findings	Right lower zone opacity	Left upper zone opacity	Left middle zone opacity	Bilateral lower zone opacities

NOTE. To convert platelets in $\times 10^3/\mu$L to $\times 10^9$/L, multiply by 1.
Abbreviations: DM, diabetic; LDH, lactic dehydrogenase; ALT, alanine aminotransferase; HD, hemodialysis.
*Normal range, 94 to 250 U/L.
†Normal range, 1 to 30 U/L.

covered container while pending disposal. For IPD, the pails used to receive and hold the spent dialysate were previously filled with 500 mL of hypochlorite solution. Extra precautions were also taken to avoid splashing during the emptying process, after which a large amount of hypochlorite solution was poured into the sink and left for 15 minutes before flushing. There were no more local transmission of SARS reported in the ward after the implementation of these measures.

Clinical Courses and Outcomes

Finally, 6 of the 11 patients (54.5%) involved in the outbreak died, while all 4 health care workers (27 to 55 years of age) survived and recovered. The 6 deceased patients included the 4 dialysis patients from room 6 and 2 patients from room 8. The 2 deceased patients from room 8 included the first SARS patient, who subsequently died of secondary sepsis and multiorgan failure following acute respiratory distress syndrome, and the 74-year-old woman, who died of superimposed severe bacterial pneumonia. With the exception of the first SARS patient who developed acute renal failure as a part of the manifestations of multiorgan failure, there had not been any significant change observed in the renal function of the SARS-affected individuals not on dialysis throughout their courses of illness.

The 4 SARS-affected dialysis patients all fulfilled the modified WHO definition of SARS. Fever was their dominant symptom (Table 1). They were all ethnic Chinese women ranging from 44 to 73 years of age. All were patients on CAPD, except for patient 1. Their durations of dialysis ranged from 1 to 104 months. Three were diabetic. None of them had a known history of ischemic heart disease, and they were all hepatitis B surface antigen negative. They were all nonsmokers. Patient 2 was originally admitted for vomiting after taking medications for the treatment of tuberculous lymphadenitis. Patient 3 was admitted for the treatment of CAPD peritonitis, which resolved during the cohorting period before she developed SARS. Patient 4 was admitted for mild hyperkalemia after an excessive ingestion of fruits. They all had fever >38°C as the only initial presenting symptom of SARS, except for patient 4, who also complained of cough and sputum on presentation. None of them complained of myalgia or headache. Nevertheless, 3 patients

(patients 1, 2, and 3) developed watery diarrhea up to 6 times per day 2 to 9 days after the onset of fever.

All of their initial chest radiographs showed localized air-space infiltrate or consolidation on presentation. There were 2 different patterns of radiological progression observed. While patient 1 showed progressive worsening and increasing in the air-space opacities, patients 2, 3, and 4 demonstrated another distinct pattern in their radiological changes. These 3 patients (patients 2, 3, and 4) also started with focal air-space consolidations on day 1 corresponding to the onset of fever (Fig 5A). Nevertheless, there was complete or partial resolution of the initial shadows on day 3, even before the commencement of specific antiviral and corticosteroid therapy (Fig 5B). The improvement, however, rapidly reversed afterwards, with worsening of the initial lesions, appearance of new opacities, and relentless progression to diffuse bilateral air-space opacification simulating acute respiratory distress syndrome (ARDS) (Fig 5C).

We treated all 4 patients with corticosteroids, ribavirin, and antibacterial agents, which was the prevalent standard treatment for SARS in Hong Kong at that time. They were treated initially with a combination of broad-spectrum antibiotics (intravenous meropenam or amoxycillin/clavulanate, plus levofloxacin or a second-generation macrolide), which was then followed by intravenous corticosteroids (hydrocortisone or methylprednisolone) and ribavirin therapy.

Prior to the commencement of corticosteroids and ribavirin, 3 patients had lymphopenia (0.6 to 0.7 $\times$ 10^9/L). No thrombocytopenia was observed. Their pretreatment serum lactate dehydrogenase ranged from 223 U/L (223 IU/L) to 503 U/L (503 IU/L), and only patient 2 had a slight increase in serum alanine aminotransferase level. No bacterial, fungi, mycoplasma, chylamdia, or common respiratory viruses were detected by the laboratory investigations. SARS-associated coronavirus ribonucleic acid (RNA) was detectable using reverse transcriptase–polymerase chain reaction (RT-PCR) in nasopharyngeal aspirate samples in all 4 patients on days 2 through 5 and in fecal samples in 3 patients (patients 1, 2, and 4) on days 2 through 9. All of the specimens were collected and sent fresh to a local government laboratory for analysis on the same day. The details of the methodology of the test had been described in a previous report,[2] and the turnaround time was about 1 to 2 days. In addition, patient 1 also showed a more than 4-fold increase in the antibody titer for the SARS-associated coronavirus.

Regardless of the dosing and timing of administration, the clinical responses of the 4 renal patients to the combination therapy with ribarivin and corticosteroids had been consistently poor (Table 2). The treatment had been started between days 2 and 8. Two different dosing regimens of ribavirin were tried. Two patients (patients 1 and 2) received 4 mg/kg ribavirin thrice daily while the other 2 patients (patients 3 and 4) received 8 mg/kg ribavirin thrice daily. Patients 3 and 4 also received a higher daily dose of corticosteroids (4 mg/kg hydrocortisone every 4 hours or 15 mg/kg methylprednisolone daily) compared with patients 1 and 2 (4 mg/kg hydrocortisone every 6 hours). Although they all had their fever completely resolved within 48 hours, there had been no parallel response in the other clinical parameters, including radiological shadows and oxygen saturation. They all required endotracheal intubation for mechanical ventilation by days 9 through 12. There had been no obvious adverse event attributable to the treatment. Finally, all of the patients died with sudden cardiac arrest between days 11 and 33 of the onset of SARS. Death was preceded in 2 patients (patients 1 and 4) by acute myocardial infarction occurring within the same day.

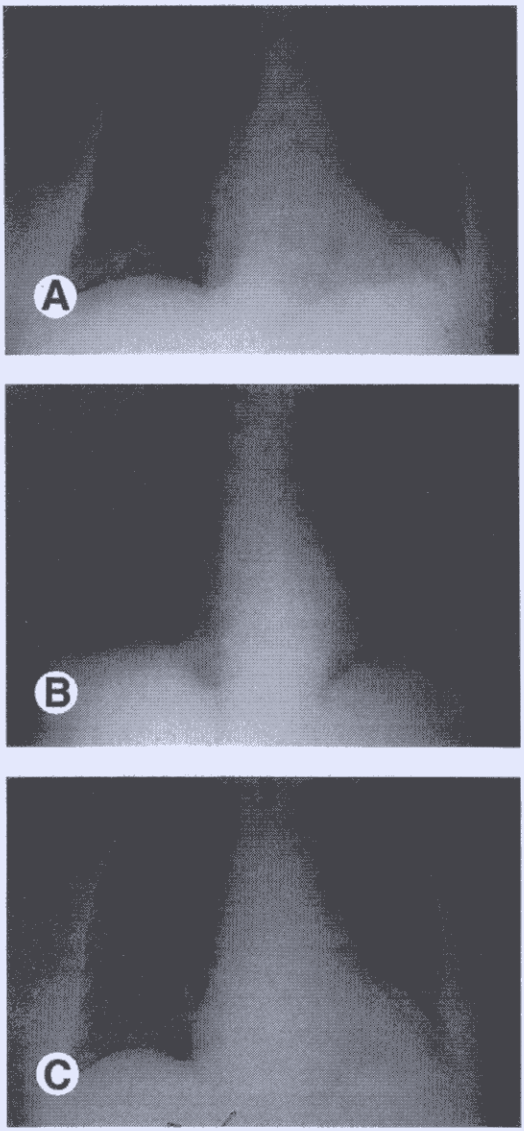


Fig 5. Serial chest radiographs of patient 4, who presented with fever and cough. (A) Ill-defined air-space opacities over bilateral lower zones on day 1 of presentation. (B) Apparent resolution of initial presenting lung opacities on day 3. (C) Subsequent reappearance of bilateral lower zones opacities.

Table 2. Treatment Regimens and Outcomes of the 4 Dialysis Patients Having SARS

	Patient			
	1	2	3	4
Treatment				
Ribavirin				
Daily dose	4 mg/kg every 8 h	4 mg/kg every 8 h	8 mg/kg every 8 h	8 mg/kg every 8 h
Hydrocortisone				
Starting dose	4 mg/kg every 6 h	4 mg/kg every 6 h	4 mg/kg every 4 h	—
Methylprednisolone				
Starting dose	—	—	—	15 mg/kg daily
Outcome				
Resolution of fever	Day 9	Day 3	Day 7	Day 7
Intubation	Day 11	Day 11	Day 9	Day 12
Death	Day 33	Day 11	Day 10	Day 13

DISCUSSION

Based on a 75-patient cohort study, the clinical progression of SARS has been observed to show a triphasic pattern.[7] It was speculated that the tissue damage in patients having SARS was caused mainly by an unchecked cytokine storm occurring during the second phase. Because the uremic state is associated with a wide range of impairment in the lymphocyte and granulocyte functions,[8] it is plausible that the abnormalities in their immune system could predispose them to a modified response to SARS-associated coronavirus infection.

All our dialysis patients had fever on presentation as the dominant symptom, whereas other systemic symptoms, such as myalgia and malaise, were inconspicuous. In addition, while the yield of the novel coronavirus RNA by RT-PCR in the early phase of the disease was reported to be modest in other nonselected series,[7,9] it was readily detectable in the nasopharygneal and stool samples of the 4 patients on days 2 through 8. In addition, there was interesting transient complete or partial resolution of the initial lung opacities on day 3 for the 3 CAPD patients. While the underlying pathogenetic mechanism remains unknown, the 3 CAPD patients (patients 2, 3, and 4) were apparently older in age and had undergone dialysis for much a longer time than had the hemodialysis patient (patient 1).

In addition, their responses to the combination treatment with ribarivin and corticosteroids were poor. Despite an apparent success in resolving the fever, the treatment had not been able to change the course of the disease and prevent the patients from developing respiratory failure. Because we had not serially monitored the viral load in the blood and the other body fluids of these patients, it is unknown whether the poor outcomes were related to uncontrolled viral infection, possibly predisposed by the underlying immunologic abnormalities and steroid treatment, or due to an overwhelming immune response.

In this report, the 4 dialysis patients showed extremely poor outcomes after contracting SARS. Nevertheless, with a small number of patients in this report, most of whom were old, were diabetic, and had significant comorbidities, it remains unclear whether dialysis patients actually belong to a specific clinical group carrying a particularly poor prognosis when contracted with SARS. A large-scale comparative study, therefore, would be helpful to further examine this issue.

ACKNOWLEDGMENT

The authors thank Herman Chan for his help in the preparation of the illustrations.

REFERENCES

1. Severe Acute Respiratory Syndrome (SARS): Multi-country outbreak-update 34—Unanswered questions: A critical point in the evolution of SARS (http://www.who.int/csr/sars/archive/2003_04_19/en/). Accessed: May 21, 2003

2. Peiris JS, Lai ST, Poon LL, et al: Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 361:1319-1325, 2003

3. Ksiazek TG, Erdman D, Goldsmith CS, et al: A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 348:1953-1966, 2003

4. Tsang KW, Ho PL, Ooi GC, et al: A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med 348:1977-1985, 2003

5. Lee N, Hui D, Wu A, et al: A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 348:1986-1994, 2003

6. Atypical pneumonia (http://www.info.gov.hk/dh/diseases/ap.htm) Accessed: August 1, 2003

7. Peiris JS, Chu CM, Cheng VC, et al: Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: A prospective study. Lancet 361:1767-1772, 2003

8. Pesanti EL: Immunologic defects and vaccination in patients with chronic renal failure. Infect Dis Clin North Am 15:813-832, 2001

9. Hon KL, Leung CW, Cheng WT, et al: Clinical presentations and outcome of severe acute respiratory syndrome in children. Lancet 361:1701-1703, 2003