

Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China

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Severe acute respiratory syndrome (SARS), now known to be caused by a coronavirus, probably originated in Guangdong province in southern China in late 2002. The first major outbreak occurred in Guangzhou, the capital of Guangdong, between January and March 2003. This study reviews the clinical presentation, laboratory findings and response to four different treatment protocols. Case notes and laboratory findings were analysed and outcome measures were collected prospectively. The SARS outbreak in Guangdong province and the outbreak in Guangzhou associated with hospitals in the city are described, documenting clinical and laboratory features in a cohort of 190 patients randomly allocated to four treatment regimens. Patients were infected by close contact in either family or health-care settings, particularly following procedures likely to generate aerosols of respiratory secretions (e.g. administration of nebulized drugs and bronchoscopy). The earliest symptom was a high fever followed, in most patients, by dyspnoea, cough and myalgia, with 24 % of patients complaining of diarrhoea. The most frequent chest X-ray changes were patchy consolidation with progression to bilateral bronchopneumonia over 5–10 days. Thirty-six cases developed adult respiratory distress syndrome (ARDS), of whom 11 died. There was no response to antibiotics. The best response (no deaths) was seen in the group of 60 patients receiving early high-dose steroids and nasal CPAP (continuous airway positive pressure) ventilation; the other three treatment groups had significant mortality. Cross-infection to medical and nursing staff was completely prevented in one hospital by rigid adherence to barrier precautions during contact with infected patients. The use of rapid case identification and quarantine has controlled the outbreak in Guangzhou, in which more than 350 patients have been infected. Early administration of high-dose steroids and CPAP ventilation appears to offer the best supportive treatment with a reduced mortality compared with other treatment regimens.

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INTRODUCTION

Severe acute respiratory syndrome (SARS) is a novel serious clinical entity involving a febrile upper respiratory illness

Abbreviations: ARDS, adult respiratory distress syndrome; CPAP, continuous positive airway pressure; SARS, severe acute respiratory syndrome.

progressing, in some patients, to a life-threatening pneumonia (WHO, 2003a). Several groups around the world have identified the causative agent of SARS as a new coronavirus (Drosten *et al.*, 2003; Ksiazek *et al.*, 2003; Peiris *et al.*, 2003). Animal inoculation has confirmed the role of coronavirus rather than metapneumovirus or other agents in SARS (A. D. M. E. Osterhaus, quoted in WHO, 2003b). The virus

probably emerged as a human pathogen in late 2002, initially in Fushan and then in other cities in Guangdong province, People's Republic of China, when clusters of cases of atypical pneumonia were noted. A major cluster of cases then occurred in Guangzhou in January/February 2003, following the transfer of a patient who had visited Zhongshan. It was postulated that SARS spread from the Guangzhou cluster to Hong Kong (Tsang *et al.*, 2003). These cases in Hong Kong were shown to fit the WHO criteria for SARS (WHO, 2003c).

We describe here the clinical features and epidemiology of the Guangzhou outbreak, together with results of a randomized treatment trial in 190 patients with presumed SARS.

METHODS

Description of the outbreak. The first patient in Guangdong province thought to have SARS was reported on 19 November 2002 in Fushan city, where no medical staff were infected. He was a 46-year-old government official, and three members of his family suffered from SARS at the same time. Subsequently, cases of SARS were noted in Heyuan, Zhongshan, Jianmen, Shengzhen and Zhaoqing between November 2002 and January 2003; the locations of these cities are shown in Fig. 1. A major cluster of cases then occurred in Guangzhou, following the transfer of a patient from Zhongshan.

The index patient for the Guangzhou outbreak was a 46-year-old male fish merchant who travelled to Zhongshan city, where the first recorded outbreak of SARS was occurring, during the middle of January 2003. He denied any close contact with SARS-infected patients and never went to the local hospitals there. On 26 January 2003, the patient attended the local clinic in Guangzhou after the onset of fever (later investigation found no medical staff were infected in that clinic). He was transferred to the respiratory department of the Second Affiliated Hospital of Sun Yet-San Medical University, Guangzhou, on 30 January 2003 because of worsening dyspnoea and then transferred to the Third Affiliated Hospital of the same medical university on 1 February 2003. He deteriorated further due to the onset of adult respiratory distress

syndrome (ARDS) and was ventilated, being transferred to the Eighth Municipal People's Hospital of Guangzhou on 8 February 2003. He recovered from a critical condition after symptomatic treatment and was discharged from hospital after 30 days of hospitalization with partial pulmonary fibrosis.

While the patient was hospitalized in the Second Affiliated Hospital for 2 days, he infected 28 medical staff in the respiratory department (located on the 12th floor) of that hospital, including the ambulance driver who transferred him to the Third Affiliated Hospital. The driver died of SARS 2 weeks later, his wife being infected as well. The outbreak spread rapidly from the respiratory ward, which is located on the 12th floor, to the 13th and 15th floors on the same building; in all, a further 65 medical and nursing staff were affected, as well as 10 in-patients. These floors shared the same central air-conditioning system. A total of 23 medical staff became infected in the Third Affiliated Hospital. Between 30 January and 9 February 2003, 18 individuals became infected after visiting patients, among them the parents-in-law of the index patient, who both died of SARS. Four medical staff who intubated the index patient in the Third Affiliated Hospital of Sun Yet-San Medical University became infected from the index patient. The time-course for the index patient is shown in Fig. 2. The disease spread in family groups, but not all were infected within a group. There was no evidence of a community outbreak of the disease except amongst those living with or visiting infected patients. In excess of 200 patients were identified as probable SARS cases and 190 patients fulfilling the criteria (Table 1) were allocated randomly to one of four treatment protocols.

Definitions. The Guangdong prophylaxis and treatment group for atypical pneumonia produced a working case definition (Table 1). A total of 120 cases satisfy all five criteria and the other 70 cases satisfy criteria 2-5. With regard to criterion (2), subcriteria (i) and (iii) had to be present for criterion (2) to be positive.

Patients with pneumonia of bacterial or fungal aetiology confirmed by laboratory investigation were excluded. Patients with lung neoplasm, non-inflammatory pulmonary interstitial diseases, pulmonary oedema and atelectasis, pulmonary thrombosis, eosinophilic pneumonitis or pulmonary vasculitis were also excluded.

ARDS was defined according to accepted criteria (Bernard *et al.*, 1994).

Case selection. A total of 190 infected patients who satisfied the case definition were included in the treatment study. There were 70 males



Fig. 1. Location of cities in which SARS cases occurred in Guangdong province, southern China. The cities involved in the earlier outbreak are underlined.

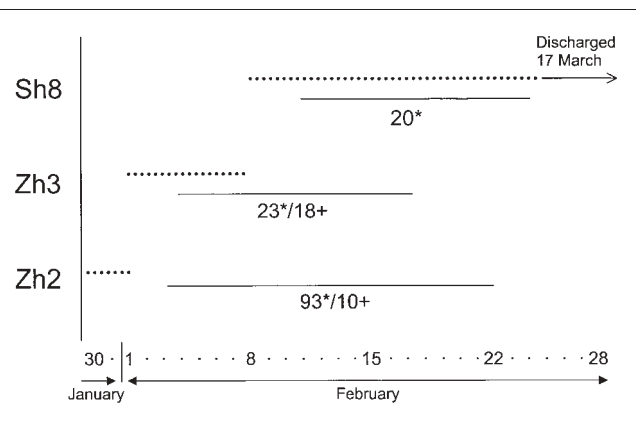


Fig. 2. Time lines of index patient (dotted lines) and for numbers of medical/nursing staff (*) and patients/relatives (+) (solid lines) infected at the three hospitals to which the index patient was admitted (Sh8, Eighth Municipal People's Hospital of Guangzhou; Zh2 and Zh3, Second and Third Affiliated Hospitals of Sun Yet-San Medical University).

Table 1. Clinical characteristics for case definition of SARS used in Guangzhou

Criterion
1. History of recent (≤ 20 days) close contact with symptomatic patients
2. Clinical symptoms and signs: <ol style="list-style-type: none"> i. Acute onset of pyrexia (≥ 38.0 °C), with or without chills ii. Headache, arthralgia, myalgia, fatigue or chest pain iii. Cough, with or without sputum iv. Clinical signs of pulmonary infection (crepitations or consolidation) v. Dyspnoea vi. ARDS
3. Leucopenia/lymphopenia
4. Chest X-ray or CT changes consistent with various degrees of patchy or speckled pneumonia, i.e. infiltrate or interstitial changes in lung
5. No response to antibiotic treatment for typical/atypical pneumonia

and 120 females, aged 16–84 years (mean 28.6 ± 10.3). Of these, 60 cases were medical staff, who had been infected with an apparent incubation period of 2–15 days following contact with symptomatic patients (mean incubation period 3 ± 4 days).

Laboratory investigations. Bacterial cultures of throat swabs and sputum were carried out. Serological detection of antibodies for influenza A and B in 120 patients was undertaken; in addition, 60 patients were tested for antibodies to H5N1 using an ELISA method in the laboratories of the Guangdong Centre for Disease Control. Sera from 60 patients were checked for antibodies to mycoplasma, chlamydia, legionella, adenovirus, coxsackievirus, respiratory syncytial virus (RSV) and cytomegalovirus (CMV).

Treatment

We distributed all patients admitted between 2 and 14 February 2003 randomly to groups A, B and C. After 14 February, the next 60 patients were allocated to group D. Although age, sex and severity were not formally controlled, inspection of the patient records revealed the groups to be broadly the same.

Group A. Forty cases, treated routinely with ribavirin i.v. 0.4–0.6 g day⁻¹ and cefoperazone/sulbactam 2.0 g b.i.d., oxygen by mask 3–5 l min⁻¹. Those patients with a blood oxygen saturation (SaO₂) < 92% were supported with non-invasive continuous positive airway pressure (CPAP). If CPAP failed (SaO₂ < 90%), mechanical ventilation was used by tracheal intubation.

Group B. Thirty cases, treated with a fluoroquinolone plus azithromycin i.v. 0.4 g day⁻¹, combined with recombinant interferon- α (IFN- α) i.m. 3 000 000 U day⁻¹ and restricted use of steroids. Groups A and B received no steroids during the first 14 days of treatment. If steroids were subsequently used, the dose of methyl prednisolone was 80–160 mg day⁻¹. Indications for mechanical ventilation were the same as for group A.

Group C. Sixty cases, treated with a quinolone plus azithromycin i.v. 0.4 g day⁻¹. Some patients were given recombinant IFN- α i.m. 3 000 000 U day⁻¹. Steroids were added (methyl prednisolone 80–160 mg day⁻¹ for 2–3 days) when symptoms worsened or pulmonary infiltrates increased. Indications for mechanical ventilation were the same as for group A.

Group D. Sixty cases, treated with levofloxacin 0.2 g b.i.d. plus azithromycin 0.6 g day⁻¹ i.v. drip. Forty-five patients were given recombinant IFN- α i.m. 3 000 000 U day⁻¹. If patients failed to respond (continuing high fever), with pulmonary infiltrates involving more than one pulmonary segment or expanding area of consolidation, they were treated with high-dose methyl prednisolone for 5–14 days (160–1000 mg day⁻¹ depending on symptoms and X-ray results). Oxygen 3–5 l min⁻¹ was given by mask if SaO₂ < 95% or, if patients felt short of breath, non-invasive CPAP was used. If CPAP failed (SaO₂ < 90%), mechanical ventilation was used.

Patients were treated with appropriate broad-spectrum antibiotics if a bacterial infection was confirmed by culture. Immunoglobulins, thymic peptides or recombinant human thymus proteins were given to 120 critically ill patients in all groups. Patients who had a normal temperature for 7 days after withdrawal of steroid with resolution of pulmonary infiltrates were discharged home.

Histopathology. Needle biopsy of lung was only performed in those cases that died (post-mortem).

Statistical analysis. SPSS 8.0 software for differential analysis and χ^2 test were used.

RESULTS

Clinical features

The clinical features of the 190 patients included in this study are listed in Table 2. Most of the patients were found to have normal respiratory sounds on clinical examination; some patients (24) had coarse respiratory sounds with bronchial breathing. Very few patients had fine crepitations. Electrocardiogram changes included tachycardia or bradycardia, some with ventricular ectopics, atrial fibrillation and changes in the ST and T waves. A few patients had oral blisters on mucosal surfaces.

Table 2. Clinical features of presumed SARS patients in Guangzhou

Clinical symptom	n (%)
Fever	190 (100)
Continued	38 (20)
Remittent	68 (36)
Irregular	84 (44)
Fatigue	179 (94)
Cough	175 (92)
Shortness of breath	175 (92)
Headache	116 (61)
Myalgia	113 (60)
Palpitation	98 (52)
Chills/rigor	89 (47)
Dizziness	89 (47)
Diarrhoea	46 (24)
Chest pain	41 (22)
Blood-stained sputum	23 (12)

Chest X-ray findings

Most patients had a normal X-ray at onset of fever and progressed to interstitial changes or speckled/patchy exudates within 1 week. These involved unilateral or bilateral lung fields becoming larger patchy exudates in 2–3 days with exacerbation of shortness of breath. Of the cases, 23 had infiltrates localized in one pulmonary segment (12%), 26 localized in one lobe (13.7%), 32 cases had signs in one pulmonary field (16.8%) and 93 cases involved both lungs (48.9%). Diffuse damage was seen in 36 cases; 16 cases only showed interstitial changes.

Laboratory findings

On admission, white blood cell counts of $4.0\text{--}10 \times 10^9 \text{ l}^{-1}$ were found in 144 cases, $< 4.0 \times 10^9 \text{ l}^{-1}$ in 46 cases and $< 2.0 \times 10^9 \text{ l}^{-1}$ in 26 cases. Platelets were $< 10 \times 10^{12} \text{ l}^{-1}$ in 25 cases (13.2%), with one case of $2.5 \times 10^{12} \text{ l}^{-1}$. One case had neutropenia, lymphopenia and thrombocytopenia. Elevated levels of glutamate pyruvate transaminase (GPT) and glutamate oxaloacetate transaminase (GOT) (normal range $< 40 \text{ U l}^{-1}$ for both tests) were seen in 126 cases, with the highest up to 500 U l^{-1} , mean $94 \pm 12 \text{ U l}^{-1}$; 50 cases had elevated levels of lactate dehydrogenase (LDH) and creatine phosphokinase (CPK). Some 95 cases were seriously ill, with pulmonary infiltrates involving more than two lobes and a significant decrease in T lymphocyte subgroups, especially affecting CD4^+ , with levels of only $0.03 \times 10^9 \text{ l}^{-1}$, mean $0.085 \pm 0.02 \times 10^9 \text{ l}^{-1}$, which comprised 10–20% of total T lymphocytes (normal value is 24–40%), giving a $\text{CD4}^+/\text{CD8}^+$ ratio of < 1 .

Bacterial cultures of sputum yielded no significant pathogens. Cultures for *Mycoplasma* spp. from nasopharyngeal secretions or sputum in 46 cases were also negative. Serum antibody tests for adenovirus, coxsackievirus, RSV and CMV all failed to demonstrate an acute infection. Sera tested for influenza A and B, influenza A and (H5N1) all failed to

demonstrate an acute infection. Sixty cases tested using ELISA for the detection of mycoplasma, chlamydia and legionella antibodies detected 10 positive sera at 1:80 dilution, but no increase was seen in paired sera. In addition, 20 patients initially suspected of SARS in whom second sera showed a fourfold increase in antibodies to one of the pathogens after 1 week of onset, and also responded well to at least 3 days of treatment with a quinolone plus azithromycin, were excluded from the study cohort of 190 patients. These patients were also found to lack a history of close contact with known cases.

Treatment group outcomes

The responses of the four treatment groups are summarized in Table 3. Patients admitted in the early stages of the outbreak were treated using the group A protocol. All the cases had no early resolution of pyrexia. Within 7–10 days, most of the patients had pulmonary infiltrates and increased shortness of breath. Twelve of the 40 cases had $\text{SaO}_2 < 92\%$ and $\text{PaO}_2 < 90 \text{ mmHg}$ and needed CPAP; of them, three received mechanical ventilation and two died of severe ARDS. After a change of the regimen to the use of quinolone and azithromycin as well as methyl prednisolone $80\text{--}160 \text{ mg day}^{-1}$, the rest of the group A patients had resolution of fever at day 10–14, together with improvement in respiratory symptoms and SaO_2 .

The 30 patients in group B had little reduction in temperature until day 10–16, eight cases needed CPAP and two cases received mechanical ventilation, but there were only two deaths. After adding methyl prednisolone $80\text{--}160 \text{ mg day}^{-1}$ into the therapy, the remaining group B patients improved within 3–5 days and were discharged after 20–30 days of illness. The 60 patients in group C also failed to show temperature reduction and improvement in respiratory symptoms until methyl prednisolone was administered. Of them, 20 cases needed CPAP; eight of these 20 received mechanical ventilation and required an increased dose of

Table 3. Summary of outcomes of four treatment groups for SARS

Treatment regimens A–D are described in Methods.

Factor	A (n = 40)	B (n = 30)	C (n = 60)	D (n = 60)
Age (years)	33.6 ± 13.9	32.4 ± 12.4	32.5 ± 12.1	30.5 ± 12.3
Male : female	15 : 24	11 : 19	22 : 44	22 : 45
Resolution of pyrexia (days)	9.4 ± 3.6	6.7 ± 1.9	7.2 ± 2.8	3.0 ± 1.4 ^{a*}
Respiratory improvement (days)	10.9 ± 7.3	9.8 ± 5.1	7.8 ± 3.9	5.9 ± 2.6 ^a
Resolution of pulmonary infiltrates (days)	15.6 ± 5.3	14.1 ± 3.4	13.6 ± 4.4	7.5 ± 3.1 ^a
Cases on nasal oxygen supply using CPAP (n)	10	8	20	24†
Cases requiring mechanical ventilation (n)	3	2	8	0
Deaths (n)	2	2	7	0
Cases with unabsorbed pulmonary infiltrates (n)	12	11	13	4 ^b
Mean time to discharge (days)	24.8 ± 5.5	24.8 ± 6.4	22.4 ± 5.9	20.7 ± 4.6

*Statistical significance of differences is indicated by: a, $P < 0.001$; b, $P = 0.003$.

†Not compared, due to inconsistency in indications for CPAP for the groups.

methyl prednisolone from 480–1000 mg day⁻¹. Two of the eight cases improved. Seven of 60 cases in group C died of severe ARDS.

The 60 cases in group D were treated with methyl prednisolone if fever did not resolve within 3 days. Dosage for the steroid was chosen according to the area of pulmonary infiltrates: 160 mg day⁻¹ if one lobe was involved, 320 mg day⁻¹ if more than one lobe was involved. A substantial proportion of cases (36/60) had temperature resolution within 1–3 days after starting treatment. Fifteen of 60 needed an increased dosage of the steroid from 160 to 320–720 mg day⁻¹ to maintain respiratory physiological parameters and to control temperature. None of the group D patients needed mechanical ventilation and all of them recovered and were discharged from the hospital.

Follow-up

Side effects of the steroid were minimal, as methyl prednisolone was used in combination with Omelazone 40 mg b.i.d., i.v. during treatment. No case had upper gastrointestinal tract bleeding. One case developed oral candidiasis and elevation of plasma glucose. No rebound phenomena were experienced during sudden withdrawal of the steroid either after 5–14 days of clinical use or after a two-stage dosage reduction protocol.

Most of the discharged patients still had palpitation and shortness of breath within the first week, especially those with incomplete resolution of pulmonary infiltrates. In most cases, continuing use of methyl prednisolone 40–80 mg day⁻¹ for 1 week helped to relieve the symptoms.

Histopathology

Eleven of the 190 patients died, all of ARDS, four females and seven males. Eight cases were >70 years old, the remaining cases being 36, 40 and 45 years old. Three of the dead patients had needle biopsies of the lung performed. Inflammatory infiltration was found in interstitial tissue of the lung. Congestion with dilation, bleeding and deformation of capillaries was seen. Exfoliations of the pulmonary alveolar epithelia were extensive. Hyaline changes in some pulmonary alveoli were noted with proliferation and fibrosis of connective tissue in the pulmonary alveolar interstitial space.

DISCUSSION

Atypical pneumonia is pneumonia caused by mycoplasma, chlamydia, legionella, rickettsia or viruses in which the clinical features are inconsistent with the chest X-ray findings (Saikku, 1997; Lee *et al.*, 2002). With the exception of viral infections, atypical pneumonia can usually be treated successfully with macrolides or tetracycline antibiotics. Atypical pneumonia is not normally life-threatening and seldom develops into ARDS. The pulmonary infection described in this outbreak was highly contagious, mainly through close contact, and often progressed to ARDS and death. At the time that this outbreak occurred, the aetiological agent had not

been identified. It was strongly suspected to be a virus and, very recently, several groups have reported the presence of a novel coronavirus in cases of SARS (Ksiazek *et al.*, 2003). Clusters of SARS in Hong Kong have recently been described (Tsang *et al.*, 2003; Poutanen *et al.*, 2003) and can be traced to an index patient who was a member of the medical staff from the Second Affiliated Hospital of Sun Yet-San Medical University in Guangzhou and who stayed in a hotel in Hong Kong during February 2003. The subsequent outbreaks in Canada can also be traced to a couple, staying in the hotel at the same time as the index patient (the physician from Guangzhou), who then returned to Canada (Poutanen *et al.*, 2003). The speed with which SARS spread and the distances involved prompted a unique multinational response coordinated by the WHO (<http://www.who.int>) that has made rapid progress in identifying the agent and attempting control.

The striking features of this outbreak of SARS were: (i) a highly contagious pneumonia spread mainly through close contact, unlike influenza, which predominately causes outbreaks in the community; (ii) presentation with fever, usually of sudden onset; (iii) no obvious respiratory symptoms such as cough, shortness of breath or chest X-ray changes at the beginning of the infection, with little or no sputum produced. The patients deteriorated rapidly after 3–7 days of illness, with exacerbation of shortness of breath and increase of lung infiltrates, usually bilateral. In our experience, if not treated early, some patients easily developed ARDS, especially older patients. Early use of high-dose steroids appeared to help recovery from SARS. Some patients were left with pulmonary fibrosis after recovery. This outbreak was reminiscent of the outbreak of influenza type H5N1 in Hong Kong in 1997, when 18 patients were infected and six of them died of ARDS (Chan, 2002; Yuen *et al.*, 1998). The difference between these two outbreaks is that there was no person-to-person transmission in the H5N1 outbreak.

Comparing the clinical outcomes of the different therapies, the group D therapy gave the best results. This favourable outcome may have been influenced by inconsistencies in the number of patients in each group given CPAP ventilation. No particular advantage in using ribavirin was seen; this contrasts with the advantages we found in the early use of steroids and non-invasive respiratory support. This approach reflects the opinion expressed by workers treating patients in Canada (Poutanen *et al.*, 2003), who suggested adopting a lung-protective strategy for ventilation. The disease did not respond to antibiotic treatment, and the combined use of interferon and large dose of immunoglobulins had no obvious effect. The early use of high-dose steroids in combination with a quinolone plus azithromycin gave the best outcome, with improvement of clinical symptoms and signs, a decreased incidence of ARDS and mechanical ventilation as well as mortality. The steroids may help by reducing the damaging effect of the local inflammatory response (Peers & Flower, 1990; Williams & Yarwood, 1990). We chose a quinolone plus azithromycin as the baseline regimen for treating atypical pneumonia and

applied it to this outbreak. Although the coronavirus would not be sensitive, there may have been a protective effect on the development of secondary infections. Another important finding is that most patients, especially young patients, responded well to non-invasive nasal CPAP, which the patients received when (i) respiration rate was >30 times min^{-1} , (ii) SaO_2 was $< 95\%$ or (iii) patients developed respiratory distress. CPAP was carried out with an air pressure of 5–15 cm H_2O and was not discontinued for more than 15 min at a time. If patients failed on CPAP ($\text{SaO}_2 < 90\%$), or were intolerant of CPAP, they were intubated and ventilated using CPAP or positive end-expiratory pressure (PEEP).

At the First Municipal People's Hospital of Guangzhou, the following cross-infection precautions were taken for medical and nursing staff. Two isolation gowns were worn, one over the other, and two 12-layer cotton-yarn face masks were worn for all contact with patients. A face visor was also worn before undertaking intubation and sputum aspiration. Gloves were worn at all times and changed frequently. Patients were nursed in either two- or four-bedded rooms, and completely separate areas were provided for the medical staff office and rest area on a different floor of the building. The wards used natural ventilation instead of the central air-conditioning system. By using these precautions, no cases of transmission to the medical and nursing staff of this hospital occurred during the outbreak.

This series represents the largest and earliest group of SARS patients treated so far; previously, 138 patients in Hong Kong were described (Lee *et al.*, 2003). Our clinical and laboratory findings are very similar to those and other, much smaller published series. This paper summarizes our experience up to 10 March 2003. During the last month (to 23 April 2003), there have been 160 more new cases of SARS admitted to our hospitals, aged between 16 and 89. All of them have been treated with the group D protocol; 135 of them have now been discharged, and three patients died (aged 89, 76 and 53). The combined mortality for the 350 treated cases has been 4%. At the time of writing, the SARS outbreak in Guangzhou is under control, with an incidence of new cases of $1-2 \text{ day}^{-1}$. Because the response of different groups of patients to different therapeutic regimens has been documented, we are able to suggest that the early and aggressive use of steroids combined with non-invasive ventilatory support should offer the best hope for a favourable outcome. Until more antiviral and vaccine protection becomes available, optimizing supportive therapy is crucial to reducing mortality from SARS.

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