Development of a standard treatment protocol for severe acute respiratory syndrome


A series of 31 patients with probable SARS, diagnosed from WHO criteria, were treated according to a treatment protocol consisting of antibacterials and a combination of ribavirin and methylprednisolone. Through experience with the first 11 patients, we were able to finalise standard dose regimens, including pulsed methylprednisolone. One patient recovered on antibacterial treatment alone, 17 showed rapid and sustained responses, and 13 achieved improvement with step-up or pulsed methylprednisolone. Four patients required short periods of non-invasive ventilation. No patient required intubation or mechanical ventilation. There was no mortality or treatment morbidity in this series.

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Severe acute respiratory syndrome (SARS) is an emerging infectious disease associated with a novel coronavirus and causing worldwide outbreaks. In two large series, the clinical, laboratory, radiological, and microbiological findings have been analysed. Treatment strategies remain diverse and experimental without uniform effectiveness. We describe, from our continuing prospective study, the development of a standard treatment protocol and its preliminary outcome.

Between March 9, and March 29, 2003, 31 clinically compatible SARS patients were admitted to Pamela Youde Nethersole Eastern Hospital, Hong Kong, among whom 16 could be traced to an index case admitted on March 2 and who died on March 16. Our case definitions were: fever 38°C or higher at presentation or in the previous 2 days, with or without chills or rigor; influenza-like symptoms; new radiological infiltrates compatible with pneumonia; and contact history. Exclusions were pre-existing infective lung disorders, aspiration, or hospital-acquired bacterial pneumonia. All cases fulfilled the WHO criteria for probable SARS cases current at that time.

Laboratory investigations included haematological (complete blood counts with differentials and clotting profile), biochemical (electrolytes, liver and renal function, creatine kinase, lactate dehydrogenase), and microbiological tests to exclude other causative pathogens (bacterial cultures of blood, sputum, and urine, serologies by microagglutination for mycoplasma and legionella, serologies by direct immunofluorescence for chlamydia, influenza, parainfluenza, and respiratory syncytial and adenoviruses, nasopharyngeal aspirates for viral cell cultures, and direct sputum smear for Pneumocystis carinii by silver stain). All chest radiographs were semiquantified by separating each lung into six sections (upper, middle, and lower zones and medial and lateral divisions) and scoring them on a four-point scale: 0 clear, 1 subtle haziness or mild infiltrates, 2 ground-glass appearance or prominent infiltrates, and 3 confluent or dense opacities. Three respirologists scored chest radiographs independently, with consensus decided between themselves in case of discordance.

We launched the initial protocol on March 12, 2003, consisting of combination treatment with a broad-spectrum antiviral and an immunomodulating agent. Antibacterials were instituted before exclusion of recognised pathogens. Acute viral infection may produce damage to host cells by cytolysis or immunopathological damage. In the early stage, cytolysis is accompanied by viral amplification, such that

### Standard treatment protocol for SARS (suspected and probable) in adult patients

#### Antibacterial treatment
- Start levofloxacin 500 mg once daily intravenously or orally
- Or clarithromycin 500 mg twice daily orally plus co-amoxiclav (amoxicillin and clavulanic acid) 375 mg three times daily orally if patient <18 years, pregnant, or suspected to have tuberculosis

#### Ribavirin and methylprednisolone
Add combination treatment with ribavirin and methylprednisolone when:
- Extensive or bilateral chest radiographic involvement
- Or persistent chest radiographic involvement and persistent high fever for 2 days
- Or clinical, chest radiographic, or laboratory findings suggestive of worsening
- Or oxygen saturation <95% in room air

#### Standard corticosteroid regimen for 21 days
- Methylprednisolone 1 mg/kg every 8 h (3 mg/kg daily) intravenously for 5 days
- Then methylprednisolone 1 mg/kg every 12 h (2 mg/kg daily) intravenously for 5 days
- Then prednisolone 0–5 mg/kg twice daily (1 mg/kg daily) orally for 5 days
- Then prednisolone 0–5 mg/kg daily orally for 3 days
- Then prednisolone 0–25 mg/kg daily orally for 3 days
- Then off

#### Ribavirin regimen for 10–14 days
- Ribavirin 400 mg every 8 h (1200 mg daily) intravenously for at least 3 days (or until condition becomes stable)
- Then ribavirin 1200 mg twice daily (2400 mg daily) orally

#### Pulsed methylprednisolone
- Give pulsed methylprednisolone if clinical condition, chest radiograph, or oxygen saturation worsens (at least two of these), and lymphopenia persists
- Give as methylprednisolone 500 mg twice daily intravenously for 2 days, then back to standard corticosteroid regimen

#### Ventilation
- Consider non-invasive ventilation or mechanical ventilation if oxygen saturation <96% while on >6 L per min oxygen or if patient complains of increasing shortness of breath
antivirals may be important in treatment. In the later stage, when adaptive immune response is mounted, viral clearance can be accompanied by severe inflammatory damage, especially with high viral burden. An immunomodulating agent, such as a corticosteroid, could reduce tissue damage. As an antiviral we chose ribavirin for its potency against DNA and RNA viruses, and methylprednisolone to achieve immunomodulation.

Dose and weaning schedules of methylprednisolone were modified according to our experiences in treating the first 11 patients and the index case. The index case’s fatal outcome suggested that late administration of combination treatment was probably ineffective. Patients with heavier bodyweights worsened despite intravenous 30 mg methylprednisolone every 12 h. Correction for bodyweight to 1 mg/kg daily resulted in lowering of fever and radiographic improvement in 1–2 days, but in most patients fever worsened again thereafter. We therefore increased the initial methylprednisolone dose to 3 mg/kg daily, but several severe cases continued to worsen and required pulsed methylprednisolone. Finally, since step-down of methylprednisolone dose in 2–3 days resulted in rebound of SARS in some patients, each dose level was continued for 5 days. We finalised our treatment protocol on March 18, 2003 (panel).

We also implemented stringent infection control measures to keep to a minimum droplet spread and possible contact with patients’ secretions, fluids, or excreta. Patients with suspected or probable SARS and convalescent cases were put into isolation cubicles, each accommodating four to six patients, and visits were not allowed. Air change (central air conditioning) was increased to 10–12 changes per h. Two exhaust ventilation fans were installed in each cubicle to achieve negative-pressure airflow. Closed-system suction was used for mechanical ventilators, the tubes of which were fitted with high-efficiency particulate air or similar filters. All health-care workers wore surgical or N-95 masks, protective eye-wear, full-face shields, caps, gowns with full sleeve coverage, surgical gloves, and shoe covers. Advanced barriers, such as the Air-Mate HEPA Powered Air Purifying Respirator System (3M, MN, USA) or T4 Personal Protection System (Stryker Instruments, MI, USA) were stocked in case high-risk procedures, such as endotracheal intubation, were required. Staff washed hands with antiseptic rubs after every contact with patients or contaminated objects and after taking off protective garments. Direct contact of eyes, nose, or mouth with hands before sanitisation was discouraged. Environmental or equipment surfaces were cleaned daily and immediately after use with domestic bleach (1000 ppm hypochlorite solution) for non-metallic items and 70% alcohol for metallic items.

We treated 31 Chinese residents (11 men) with a mean age of 39·6 years (SD 13·3). Four (13%) patients were smokers and one had comorbidities (diabetes mellitus, hypertension, coronary artery disease). Clinical and laboratory features for 12 were described in earlier reports. Overall, presenting symptoms included pyrexia (90%), chills or rigor (71%), malaise (65%), anorexia (65%), cough (52%), myalgia (42%), headache (42%), dyspnoea (29%), and diarrhoea (23%). Mean temperature was 38.5°C (0–8), pulse 97.5 beats per min (11–1), respiratory...
rate 19-7 breaths per min (2-0), and oxygen saturation 94-9% (2-4). Common presenting laboratory findings were lymphopenia (0-91×10^9/L [0-29]) in 58%, thrombocytopenia (165×10^9/L [44]) in 39%, and raised lactate dehydrogenase (242 IU/L [92]) in 68%. All patients had chest-radiograph abnormalities on admission (71% bilateral), with 19%, 74%, 97% in upper, middle, lower zones, respectively, features of subtle haziness in 36%, ground glass appearance in 57%, and dense opacities in 7%. Total mean chest radiography scores were 8-9 (5-9).

We followed up patients for a mean of 18-9 days (4-1). 30 of 31 patients required combination treatment at a mean of 1-7 (1-5) days after admission and 5-5 (2-7) days after symptom onset. One patient, who was seropositive for the novel coronavirus and viral RNA in nasopharyngeal aspirates recovered on levofloxacin alone. Rapid (within 1-2 days) and sustained response to the combination treatment was evident in 17 patients (figure). In the remaining 13, two required step-up of methylprednisolone dose and 11 required step-up of methylprednisolone dose and 11 received pulsed methylprednisolone for severe disease (figure) or rebound after rapid step-down of methylprednisolone dose (figure). 16 patients required oxygen and four required short periods (2–5 days) of non-invasive ventilation at 8–10 cm H₂O inspiratory pressure. No patient required intubation nor mechanical ventilation, and no death has occurred since we started using the treatment protocol. We attribute the death of our index case to late diagnosis and treatment that did not conform to our subsequent standard protocol.

High dose corticosteroids produced no severe complications, although prophylactic antibiotics (piperacillin and tazobactam) had been given to seven patients who had fever and raised white cell counts; all recovered and had negative bacterial cultures. Ribavirin led to no complications, despite its known adverse effects of haemolysis and arthralgia.

In this emerging disease that frequently has rapid deterioration, the inclusion of control patients was not possible or ethical. Future controlled studies may be able to shed more light on the efficacy of our treatment protocol.

Contributors
L K Y So and A C W Lau designed the study. The treatment protocol was developed by A C W Lau, L K Y So, T M T Cheung, and L Y C Yam. Data collection was done by L K Y So, A C W Lau, E Poon, and 30 patients were followed up by L K Y So, L Y C Yam, and E Poon, and data analyses by A C W Lau and L Y C Yam. We recorded mutations in GATA1 in all patients with Down’s syndrome (age 0–24 days) and in all with acute myeloid disorder (n=6). We recorded mutations eliminating exon 2 from GATA1 in all patients with transient myeloid disorder (age 0–24 days) and in all with acute megakaryoblastic leukaemia (age 14–38 months). The range of mutations did not differ between patients with each disorder. Patients with transient myeloid disorder with mutations in GATA1 can regress spontaneously to complete remission, and mutations do not necessarily predict later acute megakaryoblastic leukaemia.

Conflict of interest statement
None declared.

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Acquired mutations in GATA1 in neonates with Down’s syndrome with transient myeloid disorder

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Transient myeloid disorder is a unique self-regressing neoplasia specific to Down’s syndrome. The transcription factor GATA1 is needed for normal growth and maturation of erythroid cells and megakaryocytes. Mutations in GATA1 have been reported in acute megakaryoblastic leukaemia in Down’s syndrome. We aimed to investigate changes in GATA1 in patients with Down’s syndrome and either transient myeloid disorder (n=10) or acute megakaryoblastic leukaemia (n=6). We recorded mutations eliminating exon 2 from GATA1 in all patients with transient myeloid disorder (age 0–24 days) and in all with acute megakaryoblastic leukaemia (age 14–38 months). The range of mutations did not differ between patients with each disorder. Patients with transient myeloid disorder with mutations in GATA1 can regress spontaneously to complete remission, and mutations do not necessarily predict later acute megakaryoblastic leukaemia.

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Transient myeloid disorder is a self-regressing myeloproliferative disorder that arises mainly in babies with Down’s syndrome during the first 4 weeks of life, affecting as many as 10% of all neonates with Down’s syndrome. It could therefore provide valuable insights into cellular mechanisms that could be exploited to control proliferation outside conventional therapeutic approaches.

Wechsler and colleagues noted acquired mutations in the erythroid/megakaryocyte lineage-specific transcription factor GATA1 in genomic DNA samples from six of six patients with Down’s syndrome and acute megakaryoblastic leukaemia, and in none of 92 controls. All mutations were acquired (DNA from remission samples did not have the GATA1 changes) and all resulted in a premature translation termination, eliminating the GATA1 activation domain (encoded by exon 2). Without examination of patients with transient myeloid disorder, we cannot understand if the GATA1 dysfunction is a primary permissive event or a second hit, important for emergence of fully developed leukaemia. Thus, we aimed to investigate GATA1 mutations in tissue samples from patients with Down’s syndrome and transient myeloid disorder.

We analysed exon 2 of GATA1 by reverse transcription PCR (RT-PCR), directly from RNA of presentation samples of patients. Samples were surplus or archived clinical.